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ORIGINAL ARTICLE

An investigation of the relationship between Behçet's disease and tenascin-C

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ABSTRACT

Objectives: The study aimed to investigate serum tenascin-C levels and its relationship with pathogenesis of Behçet's disease (BD) with inflammatory processes.

Patients and methods: This prospective and analytical study included 34 BD patients (19 males, 15 females; mean age: 31.5±8.2 years; range, 18 to 48 years) who met the 2014 International Criteria for Behçet's Disease and had no comorbidities and 37 healthy volunteers (21 females, 16 males; mean age: 29.6±5.3 years; range, 21 to 45 years). Sex, age, age at diagnosis, clinical and laboratory data, medication use, and smoking history of the participants were recorded. Serum tenascin-C levels were measured using a commercially available tenascin-C enzyme-linked immunosorbent assay kit.

Results: There was no significant difference between the groups in terms of age (p=0.262) and sex (p=0.287). Serum tenascin-C levels were significantly lower in the BD group (10,824±7,612 pg/mL) compared to the control group (27,574±14,533 pg/mL, p<0.001). In the receiver operating characteristic analysis performed for the diagnostic value of tenascin-C level in BD, the sensitivity was determined as 79.4% and the specificity as 82.5% (p<0.001). No statistically significant difference was observed in tenascin-C levels in correlation with clinical characteristics, laboratory values, medication use, and smoking in the BD group.

Conclusion: In contrast to other chronic inflammatory diseases, lower levels of tenascin-C were observed in patients with BD than in the healthy individuals, which can be attributed to the absence of prolonged chronic inflammatory course in BD. The fact that tenascin-C levels are high in other rheumatic inflammatory diseases but low in BD may be useful in the differential diagnosis of BD.

Keywords: Behçet's disease, inflammation, tenascin-C.

Behçet's disease (BD) was first described by Dr. Hulusi Behçet in 1937. BD is an inflammatory, multisystemic disease characterized by attacks of oral aphthae and genital ulcers, arthritis, skin lesions, and ocular lesions along with gastrointestinal and central nervous system involvement. Although infectious, genetic, and immunologic factors are thought to be involved in the etiology of BD, a definite cause has not been established yet.[1,2] In addition to genetic factors, environmental factors are thought to affect the regional prevalence of BD globally.[3,4]

Türkiye has the highest number of BD cases in the world, with a prevalence of 20-600 cases per 100,000 people.[5] BD usually occurs in the third or fourth decade of life.[6] Although BD was initially thought to be more common in males, recent studies have reported that the occurrence of BD is independent of sex.[7] Male sex, systemic involvement in the onset of BD, HLA (human leukocyte antigen)-B51 positivity, and early age of onset are associated with a severe course of the disease; BD has a milder course in females.[8]

Unlike other vasculitis subtypes, BD has a unique pathology as it can involve arterial and venous structures of any diameter and localization. Endothelial dysfunction is a characteristic of BD.[9] Studies on the etiopathogenesis of BD report that neutrophils, T cells, and antigen presenting cells are effective in manifesting immunological changes.[10] Although the cause of thrombosis

in BD, which is characterized by vasculitis and thrombosis attacks, is unknown, it has been suggested that dysfunctional procoagulant, anticoagulant, and fibrinolytic factors along with vasculitis and inflammation-induced endothelial damage lead to thrombosis in BD.[11] Studies have found low arterial elasticity and high intima-media thickness in patients with BD.[12]

Tenascin-C is a large hexameric protein present in the extracellular matrix that exhibits limited expression in healthy tissues, but its expression rapidly increases in the case of tissue damage. Expression of tenascin-C is usually limited to the area of damaged tissue. Tenascin-C levels return to normal after tissue repair, and its expression is transient.[13] However, persistent expression of tenascin-C is associated with a wide range of pathological conditions, such as autoimmune, fibrotic, and metabolic diseases and cancer.[14] High expression levels of tenascin-C are observed in malignancy, thrombosis, heart failure, and atherosclerotic processes. It is involved in cell proliferation, angiogenesis, and invasion in carcinogenesis. Karabulut et al.[15] demonstrated that tenascin-C can affect the interaction between cells, as well as cell growth, migration, and differentiation. It has been reported that tenascin-C is effective in detecting the early stages of cellular damage and increase in the degree of inflammation.[16,17] Studies have shown that persistent tenascin-C accumulation occurs in various chronic pathological conditions, including cancer, rheumatoid arthritis (RA), and fibrosis, as well as in cases of chemical or mechanical injury.[18]

Processes such as endothelial proliferation, thrombosis, angiogenesis, cell growth, and migration play an important role in the pathogenesis of BD. As mentioned above, tenascin-C is known to play a role in similar pathologies.[1,3] However, there is no study investigating the possible role of tenascin-C in BD, which is involved in the pathogenesis of rheumatic diseases such as RA and ankylosing spondylitis (AS).[18-20] The aim of the present study was to investigate the possible relationship between serum tenascin-C level and clinical characteristics of BD, an inflammatory disease.

PATIENTS AND METHODS

A total of 34 patients (19 males, 15 females; mean age: 31.5±8.2 years; range, 18 to 48 years) who met the 2014 International Criteria for Behçet's Disease, had no comorbidities, were over 18 years of age, were newly diagnosed or followed up for BD, and were admitted to the outpatient clinics of the Ondokuz Mayıs University Faculty of Medicine, Departments of Rheumatology and General Internal Medicine between January 2021 and January 2022 were included in the this prospective and analytical study. Pregnant or breastfeeding patients and those with diabetes, hypertension, allergies, and active infections were excluded from the study. Thirty-seven healthy volunteers (21 females, 16 males; mean age: 29.6±5.3 years; range, 21 to 45 years) were included in the control group. All participants included in the study were from Samsun and its surrounding provinces and were ethnically Caucasian.

Sex, age, age at diagnosis, clinical findings of skin, pathology test results, medication use, smoking habits, and history of thrombosis, uveitis, oral ulcers, genital ulcers, and arthritis were recorded. Additionally, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), leukocyte, hemoglobin, platelet, urea, creatinine, aspartate aminotransferase, and alanine aminotransferase levels were recorded.

In the BD group, cases who had had at least two of the following signs in addition to oral ulcers and high ESR or CRP levels were interpreted as active: genital ulcers, skin lesions, recent eye involvement, recent vascular involvement, recent neurological involvement, active arthritis, and a positive pathergy test sign.[21]

Levels of tenascin-C were determined by collecting serum samples of the participants in the BD and control groups, which were stored at –80°C, using a commercial enzyme-linked immunosorbent assay kit (HUMAN Tenascin-C ELISA kit, No. 201-12-1415; Sunred Biological Technology Co., Shanghai, China). Enzymatic reactions were measured using an automated microplate photometer. Tenascin-C levels were determined by comparing the optical density of the samples and the standard curve. The measurement range of the kit was

200-60,000 pg/mL. All measurements were made according to the manufacturer's instructions.

Statistical analysis

Data were analyzed using IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Numerical variables were expressed as mean and standard deviation. The number and percentage values of the demographic data and clinical findings of the individuals participating in the study were calculated. The relationship between clinical findings in BD and tenascin-C level was analyzed using Student's t-test and the Mann-Whitney U test for normally and nonnormally distributed variables, respectively. Possible relationships between the variables were analyzed using Pearson's correlation test and Spearman's correlation test for normally and nonnormally distributed variables, respectively. Receiver operating characteristic analysis was performed for the diagnostic value of tenascin-C. A p-value <0.05 was considered statistically significant.

RESULTS

There was no difference between the groups in terms of age and sex (Table 1). ESR was significantly higher in the BD group. However, the increase in CRP values was not statistically significant (Table 1). Tenascin-C levels were significantly lower in the BD group (10,824±7,612 pg/mL) than the control group (27,574±14,533 pg/mL, p<0.001, Figure 1).

In the receiver operating characteristic analysis performed for the diagnostic value of tenascin-C level in BD, the sensitivity was determined as 79.4% and the specificity as 82.5% (area under the curve: 0.826; cut-off according to Youden's index: 11,913.34 pg/mL; p<0.001, Figure 2).

There was no significant correlation between tenascin-C levels and age, ESR, CRP, leukocyte count, hemoglobin, platelets, urea, creatinine, alanine aminotransferase, and aspartate aminotransferase levels in the study groups (p>0.05 for all parameters). No significant correlation was found between tenascin-C levels and clinical manifestations of BD and smoking. Similarly, smoking did not affect tenascin-C levels in healthy volunteers (Table 2). No significant correlation was found between tenascin-C level and the medications used for treating BD (colchicine, steroids, biologic agents, and immunosuppressives; Table 3).

Table 1. Demographic data and laboratory values of the BD and control groups

	Healthy control		Behçet's disease		
	n	Mean±SD	n	Mean±SD	p
Age (year)		29.6±5.3		31.5±8.2	0.262
Sex					0.287
Male	16		19		
Female	21		15		
Erythrocyte sedimentation rate (mm/h)		12.9±8		22.9±15.2	0.001
C-reactive protein (mg/L)		4.9±5.4		10.9±25.4	0.165
Leukocyte (/mm^3)		6,836±1,559		7,977±1,875	0.007
Hemoglobin (g/dL)		14.0±1.7		13.8±1.6	0.547
Platelet (×10^3/mm^3)		266±45		263±67	0.872
Urea (mg/dL)		11±2.5		13.4±3.2	0.001
Creatinine (mg/dL)		0.77±0.13		0.74±0.16	0.333
Aspartate aminotransferase (U/L)		22.6±16		19.5±8.7	0.315
Alanine aminotransferase (U/L)		18.7±13.7		22.7±25.4	0.418
Tenascin-C (pg/mL)		27,574±14,533		10,824±7,612	0.001

BD: Behçet's disease; SD: Standard deviation.

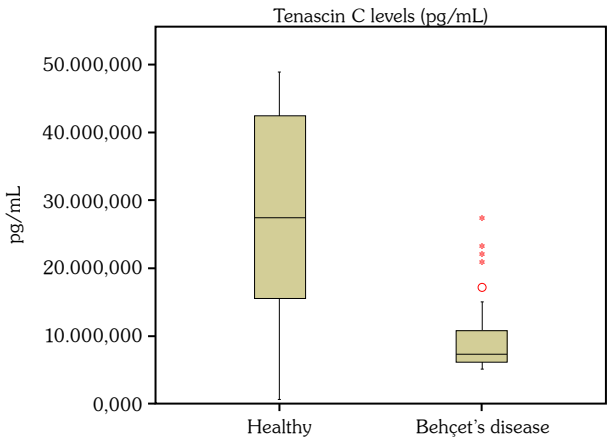

Figure 1. Tenascin-C levels in the Behçet's disease group and the control group.

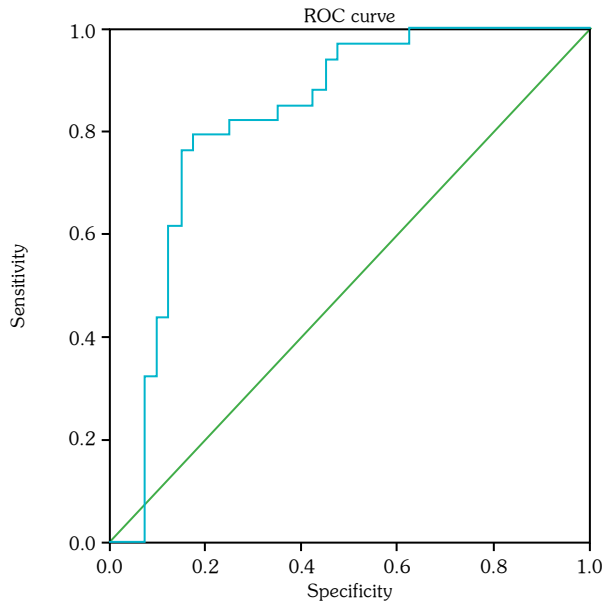

Figure 2. ROC curve of tenascin-C.
ROC: Receiver operating characteristic.

While eight patients in the BD group were in the active phase, the other BD patients were in the inactive phase. Tenascin-C levels were found to be similar in patients with and without active BD.

DISCUSSION

This study was conducted to investigate the possible role of tenascin-C, which was previously shown to be involved in the pathogenesis of few chronic rheumatic inflammatory diseases, in the pathogenesis of BD. Lower levels of serum tenascin-C were seen in the BD group than in the control group. It was found that serum tenascin-C level was not associated with clinical course of BD, medication use, and disease activity. On the other hand, tenascin-C level was found to have a diagnostic value in BD. To the best of our knowledge, this is the first study that investigated serum tenascin-C levels in patients with BD that was characterized by recurrent acute inflammatory attacks.

Serum tenascin-C levels were found to be higher in patients with AS compared to the healthy individuals.[19,20] It was also reported that tenascin-C level is not associated with disease activity, but it may reflect chronic structural spinal damage.[19] In the present study, in contrast to the previous studies, lower serum tenascin-C level was observed in patients with BD that presented with recurrent inflammatory attacks than in the healthy control group. Low tenascin-C level in BD may be attributed to the fact that BD is characterized by inflammation, recurrent attacks, no chronic course, and no structural deformity of the joints, unlike AS that progresses as a chronic disease resulting in fibrosis and chronic structural damage, particularly in the affected vertebrae. Therefore, it can be suggested that tenascin-C may be a biomarker for chronic structural damage in joints.

Chevalier et al.[22] compared tenascin-C expression levels in articular cartilage of patients with osteoarthritis and RA and healthy controls. A higher expression level of tenascin-C was seen in arthritic cartilage than in normal cartilage.[23] A study conducted by Cutolo et al.[24] revealed that tenascin-C levels were correlated with joint erosions in patients with RA. The authors stated that tenascin-C levels could indicate structural cartilage damage in the early period of RA. Based on these findings, it can be inferred that high tenascin-C levels are observed in cases of structural damage that develops in response to chronic inflammation in joints; however, this inference is in contrast to the present study wherein lower tenascin-C levels were seen in patients with BD compared to healthy controls.

Table 2. Association of tenascin-C levels with clinical characteristics in the patient group

Clinical characteristics	n	Tenascin-C level (pg/mL) Mean±SD	*p*
Genital ulcer			0.677
No	7	11,330±9,674	
Yes	27	10,693±7,201	
Erythema nodosum			0.929
No	22	11,012±8,219	
Yes	12	10,482±6,682	
Papulopustular lesion			0.913
No	11	13,978±10,950	
Yes	23	9,316±5,006	
Pathergy			0.467
No	24	11,610±8,059	
Yes	10	8,940±6,393	
Arthritis			0.318
No	31	10,525±7,459	
Yes	3	13,917±10,279	
Vascular involvement			0.466
No	22	9,435±6,380	
Yes	12	13,372±9,229	
Uveitis			0.607
No	19	10,236±6,607	
Yes	15	11,570±8,910	
Smoking			0.763
No	22	10,729±7,062	
Yes	12	10,999±8,864	

SD: Standard deviation.

In a study conducted by Závada et al.[25] involving patients with systemic lupus erythematosus (SLE), no significant difference was found in serum tenascin-C levels between patients with SLE and the control group, but tenascin-C levels were significantly higher in patients with active SLE compared to those without active disease. In addition, Estany et al.[26] investigated the role of tenascin-C in lung diseases and found that higher tenascin-C levels were observed in patients with idiopathic pulmonary fibrosis compared to healthy individuals. In the same study, cases with hypersensitive pneumonitis were divided into two categories: chronic and subacute cases. As compared to the healthy control group in that study, no significant increase was found in tenascin-C levels in subacute cases, whereas significantly high tenascin-C levels were seen in chronic hypersensitive pneumonitis cases. These results suggest that tenascin-C is not involved in acute but chronic inflammation and is associated with fibrosis.

Table 3. Association of tenascin-C levels with the medications used in the patient group

Medication	n	Tenascin-C level (pg/mL) Mean±SD	*p*
Colchicine			0.537
No	19	12,489±8,850	
Yes	15	8,716±5,230	
Steroid			0.368
No	26	9,831±7,164	
Yes	8	14,055±8,618	
Biological agent			0.834
No	21	10,568±7,141	
Yes	13	11,240±8,605	
Azathioprine			0.904
No	20	11,007±8,337	
Yes	14	10,564±6,736	

SD: Standard deviation.

Tenascin-C expressions are high in affected tissue and circulation in patients with

scleroderma.[27,28] An *in vitro* study conducted by Makhluf et al.[29] reported that a high tenascin-C level was observed in the affected tissue of patients with scleroderma due to high levels of interleukin (IL)-4. Upon stimulating normal and scleroderma fibroblasts using IL-4, it was observed that the tenascin-C level increased in the extracellular matrix.[29] In the pathogenesis of systemic sclerosis, toll-like receptors (TLRs) have been found to be crucial in the pathology of persistent organ fibrosis.[30,31] Bhattacharyya et al.[30] reported high tenascin-C levels in the skin tissue and serum of patients with scleroderma and in fibrotic skin tissue of mice. In addition, exogenous tenascin-C administration could induce collagen gene expression and myofibroblast differentiation via TLR4 signaling pathway. They showed that skin and lung fibrosis is attenuated and fibrosis resolution is accelerated in tenascin-C knockout mice, and tenascin-C was crucial for this fibrotic cycle. It has been reported that IL-4 levels do not increase even in the active period of BD.[31] In addition, no end-stage organ failure due to structural damage to the internal organs and specific marked organ fibrosis is seen in patients with BD. In conclusion, the fact that fibroblasts do not play an important role in the pathogenesis of BD may explain the low levels of tenascin-C.

In chronic inflammatory conditions, the balance of proinflammatory and anti-inflammatory cytokines is disturbed in favor of proinflammatory cytokines. In addition, there is a more pronounced cytokine pattern in other rheumatic diseases. For example, while there is a T helper (Th)1 cytokine pattern in RA and a Th2 cytokine pattern in SLE, the inflammatory cytokine response in BD does not show a definite character.[32,33] It has been stated that BD may be a mixture of Th1 and Th2 activity. The cytokine pattern of BD has not been clearly revealed, and it has been stated that cytokine patterns in BD may differ according to the stage of the disease.[34,35] It seems possible that anti-inflammatory cytokines, which appear in response to increased proinflammatory cytokines in the acute attack period and ensure the end of the attack, may decrease the level of tenascin-C. Low tenascin-C levels may be related to this cytokine pattern of BD. We think that the low level of tenascin-C in our study, unlike other rheumatic diseases, may be related to the nature of BD, which does not show a chronic course and progresses with attacks. It is interesting that the tenascin-C level is even lower in BD than in the healthy control group, and new studies are needed to clarify this.

There are certain limitations to the study. The results would have been more comprehensive if a disease group with high tenascin-C levels and fibroblast activity had been examined in addition to patients with BD. Another limitation is that confounding factors thought to affect tenascin-C levels, such as obesity and drug use, were not excluded from the study. Furthermore, evaluation of other fibrotic, proinflammatory, and anti-inflammatory cytokines along with tenascin-C would have provided comprehensive results. However, this is the first study to evaluate tenascin-C levels in patients with BD, and the results show that its low levels in BD contrast with other rheumatic diseases, which is a notable finding. In our study, the number of patients was insufficient to perform subgroup analysis according to clinical features in patients with BD.

In conclusion, the results of our study indicate that tenascin-C levels are of diagnostic importance in BD. However, there is a need for new studies investigating the role of tenascin-C in the pathogenesis of BD and why the tenascin-C level is low in BD.

Ethics Committee Approval: The study protocol was approved by the Ondokuz Mayıs University Clinical Research Ethics Committee (date: 27.10.2021, no: B.30.2.ODM.0.20.08/646-423). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept: H.K.; Design: D.Y.K., M.O; Control/supervision: M.O.; Data Collection and/or processing: H.K.; Analysis and/or interpretation: D.Y.K.; Literature review: M.O.; Writing the article: H.K., D.Y.K.; Critical review: M.O.; References and fundings: M.O.; Materials: D.Y.K.

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