EJR European Journal of Rheumatology

DOI:10.5152/eurjrheum.2023.23007

Original Article

Matrix Metalloproteinase-2 and -3 Levels in Patients with Behçet's Disease and Implication for the Presence of Vascular Aneurysm or Neurologic Involvement

Pinar Talu Erten[1], Gökhan Keser[2], Raika Durusoy[3], Sinem Burcu Kocaer[4], Kenan Aksu[2]

Abstract

Background: Behçet's disease is a systemic vasculitis affecting both arteries and veins, as well as causing recurrent inflammatory multiorgan disease. Vascular involvement is associated with increased mortality and morbidity. Matrix metalloproteinases are released at sites of inflammation and degrade various components of the extracellular matrix. Increased levels of metalloproteinase-9 and metalloproteinase-2 have been previously reported in Behçet's disease.

Methods: In this cross-sectional study, metalloproteinase-2 and metalloproteinase-3 serum levels were investigated in 103 patients with Behçet's disease and 69 healthy controls, using Invitrogen immunoassay human metalloproteinase-2 and metalloproteinase-3 ELISA kits.

Results: Serum metalloproteinase-2 and metalloproteinase-3 levels were significantly higher in the Behçet's disease group compared to healthy controls. Besides, serum metalloproteinase-3 levels were significantly higher in subgroups of Behçet's disease with aneurysmal vascular involvement and with neurological involvement. However, metalloproteinase-2 and metalloproteinase-3 serum levels did not show a positive correlation with disease activity.

Conclusion: Metalloproteinase-2 and -3 may contribute to the complex pathogenesis of Behçet's disease. More importantly, the detection of very high serum levels of metalloproteinase-3 may predict the formation of an aneurysm, or possibly the presence of neurological involvement in Behçet's disease and may lead the clinician to make an earlier diagnosis of these complications in young male patients with high risk.

Keywords: Behçet's disease, matrix metalloproteinase, vascular, aneurysm, neurologic, pathogenesis

ORCID iDs of the authors:
P.T.E. 0000-0002-0697-360X;
G.K. 0000-0001-7289-1816;
R.D. 0000-0003-1041-8462;
S.B.K. 0000-0002-5481-0776;
K.A. 0000-0001-8889-2688.

Cite this article as: Talu Erten P, Keser G, Durusoy R, Kocaer SB, Aksu K. Matrix metalloproteinase-2 and -3 levels in patients with behçet's disease and implication for presence of vascular aneurysm or neurologic involvement. *Eur J Rheumatol.* 2023;10(3):101-106.

[1] Department of Internal Medicine, Medicana International Izmir Hospital, Division of Rheumatology, Izmir, Turkey
[2] Department of Internal Medicine, Ege University, Division of Rheumatology, Faculty of Medicine, Izmir, Turkey
[3] Department of Public Health, Ege University, Faculty of Medicine, Izmir, Turkey
[4] Department of Internal Medicine, Izmir University of Economics, Medical Point Hospital, Division of Rheumatology, İzmir, Turkey

Corresponding author:
Pınar Talu Erten,
E-mail: doktortalu@yahoo.com

Received: January 23, 2023
Accepted: June 28, 2023
Publication Date: August 21, 2023

Introduction

Behçet's disease (BD) is characterized by recurrent oral aphthae and several systemic manifestations, including genital aphthae, ocular disease, skin lesions, gastrointestinal involvement, neurologic disease, vascular disease, or arthritis. Behçet's disease usually starts around the third or fourth decade of life.[1,2] The disease is particularly prevalent in regions along the "Silk Route," extending from Japan to the Middle East and Mediterranean countries and rarely seen in Western countries.[3] Although the pathogenesis of BD remains unclear, it possibly involves complex interactions of genetic, environmental, and immunological factors.

The frequency of vascular involvement in BD has been reported as 2%-46%. It is mostly seen in men and is more likely to be seen in the first 2-5 years of the disease.[4,5] Superficial venous thrombosis (SVT) and deep vein thrombosis (DVT) are the most frequent vascular involvements, affecting 15%-40% of patients with BD[6] altogether. Although there are studies on the role of genetic causes, endothelial dysfunction, and coagulation factor abnormalities in thrombosis of BD, the primary causative pathology seems to be inflammation.[7] Arterial involvement may appear as occlusion or aneurysm and affects only 3%-5% of patients with BD. Aneurysm formation is most common in the aorta and pulmonary arteries. Mortality is reported to be around 50% in patients with BD with pulmonary artery aneurysms.[5,8] In general, these involvements can only be detected when patients are symptomatic, and despite treatment, mortality and morbidity in these patients are high.[9] Although noninvasive imaging techniques are reliable and preferred for detecting thoracic and abdominal aneurysms or thrombi, they cannot be used to screen asymptomatic patients because they are expensive and difficult to reach.

Matrix metalloproteinases (MMPs) are included in the family of zinc metalloendopeptidases that can degrade extracellular matrix components. They are stimulated by inflammatory cytokines and play diverse

roles in many physiological or pathological conditions.[10] Several groups of researchers have previously studied the levels of MMPs in serum samples or in the inflamed tissues of patients, especially with large vessel vasculitis.[10-13] However, data regarding serum levels of MMPs in BD are scarce, and to our knowledge, only a single study investigated the role of MMP-2 and MMP-9 in vascular BD. On the other hand, MMP-9 levels in cerebrospinal fluid (CSF) in neuro-Behçet patients were also studied.

In BD, there is an ongoing search to find a marker to help detect disease activity and severe vascular involvement. In this cross-sectional study, we aimed to investigate whether serum levels of MMP-2 and MMP-3 were elevated in patients with BD, especially in those with aneurysmal vascular involvement. We also aimed to determine whether serum levels of MMPs vary with disease activity.

Material and Methods

This cross-sectional study included 103 patients with BD [M/F: 70/33; mean age: 38 ± 9 (21-61) years]. All of these were followed by the outpatient Department of Rheumatology at Ege University Faculty of Medicine and fulfilling the criteria for diagnosis of BD issued by the International Study Group for BD.[14] None of the patients had additional diseases, including hypertension, diabetes, or malignancy. Sixty consecutive patients with BD with either arterial or venous involvement were enrolled in the vascular Behçet group, irrespective of other findings. Among those 60 patients with vascular involvement, 10 also had aneurysm formation. The remaining 43 consecutive patients with BD, without vascular involvement, formed a heterogeneous group. Those having only oral ulcer, genital ulcer, and skin findings were clustered as a pure mucocutaneous group, while others had any of the other findings, including arthritis, eye involvement, or neurologic involvement (Table 1). All of these 43 patients were defined as the nonvascular group. Age- and sex-compatible 69 healthy controls without systemic diseases were also enrolled in this study. This study was approved by the EgeUniversity Faculty of Medicine Research Ethics Committee (Approval no: B.30.2.EGE.0.01 .00.00/7 BOM /00001668-1398) after reviewing the ethical issues, and written consent was taken from all the patients.

Table 1. Demographic Data and Disease Characteristics of Patients

	Total	Female	Male	MMP-2 (ng/mL)	MMP-3 (ng/mL)
Healthy controls (n, age, years)	69	22	47	360 (±85)	7.5 (±7)
	37.8 (±8)	38 (±8)	37 (±8)		
Patients (n, age, years)	103	33	70	F/M:490/461	F/M:10/40
	38 (±9)	39 (±9)	37 (±9)		
Age of diagnosis	30 (±8.5)	29	31		
Family history of Behcet's disease	20 (19%)	7	13		
Vascular involvement	60 (58.2%)	12	48	478 (±121)	31 (±33)
Peripheral venous	48	8	40	485 (±123)	29 (±31)
Large venous	25	6	19	469 (±107)	38 (±35)
Aneurysm	10	1	9	433 (±39)	49 (±33)
Nonvascular group	43 (41.8%)			460 (±146)	30 (±44)
Pure mucocutaneous	7	7	0	462 (±185)	2.2
Neurologic involvement	15	5	10	451(±121)	47 (±54)
Eye involvement	27	9	18	455 (±138)	30 (±41)
Arthritis	19	11	8	455 (±163)	32 (±46)
Active disease	33 (32%)	16	17	445 (±162)	33 (±46)

MMP-2, matrix metalloproteinase-2; MMP-3, matrix metalloproteinase-3.

Standard case-report forms were prepared, and the data of the patients were recorded on these forms. Demographic data, clinical findings, disease characteristics, number of cutaneous, ocular, neurological, arthritic, and vascular involvements, and treatments of all patients were noted on these forms. In addition, patients with vascular involvement were subdivided based on arterial and venous involvement and the presence or absence of an aneurysm. The same investigator (PTE) filled all of these forms, who also examined the patients, and evaluated disease activity. Behçet's disease activity was assessed using Leeds activity score.[15] Patients with BD were categorized as having active total activity score ≥5 or inactive total activity score <5.

Blood samples were collected at the time of study entry. For MMP enzyme measurement, 10 mL of venous blood was taken from the patients and healthy volunteers; after centrifugation, serum samples were stored at −80°C. At the end of 6 months, serum levels of MMP-2 and MMP-3 were studied using commercially available ELISA kits of Invitrogen immunoassay human MMP-2 and MMP-3. At the time of study entry, erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) levels were also measured.

Statistical Analysis

Data were recorded and analyzed in the Statistical Package for the Social Sciences (SPSS) program version 21.0 (IBM SPSS Corp.; Armonk, NY, USA). Descriptive statistics were performed with frequencies and percentages for nominal data and means and standard deviations or medians and interquartile range for scale-type data, depending on its distribution. The values of MMP2 and MMP3 were compared with Student's *t*-test according to sex and the presence or absence of several disease characteri stics/subtypes, while the Mann–Whitney *U* test was used in conditions where parametric conditions were not met. The chi-square test was used to compare categorical data. Spearman's correlation was used to test if MMP2 and MMP values correlated with the patient's age and disease duration. Receiver operating characteristic (ROC) analysis was conducted to test whether MMP-3 could be a predictor of aneurysm formation among the vascular group.

Main Points

- 1-Metalloproteinase-2 and metalloproteinase-3 play a role in the pathogenesis of Behçet's disease.
- 2-High serum metalloproteinase-3 levels might be useful to predict patients of Behçet's disease with aneurysmal vascular involvement.
- 3-High serum metalloproteinase-3 levels might be also useful to predict patients of Behçet's disease with neurological involvement
- Metalloproteinases serum levels did not show a positive correlation with disease activity.

Results

Both demographic data and disease characteristics of patients with BD are summarized in Table 1. One hundred three patients with BD without hypertension, diabetes, and cancer were included. Twenty patients (19.6%) were found to have a first- or second-degree relative having BD when the family histories were outlined. Some patients had even more than 1 case of BD in their families. Considering the whole group of patients, eye, neurologic and joint involvements were found at similar rates between males and females, with no statistical significance. However, there was male dominance in the vascular Behçet's group (M/F : 5/1). All patients with vascular involvement had venous thrombosis; peripheral venous thrombosis and large vein thrombosis were detected in 48 (80%) and 25 (41%) patients, respectively. Notably, 13 (21%) patients had both peripheral and large vein thrombosis. Additional aneurysm formation in the abdominal aorta or pulmonary arteries was detected in 10 (9.7%) patients (M/F : 9/1).

Matrix Metalloproteinase-2 and Matrix Metalloproteinase-3 Levels in Patients with Behçet's Disease and Healthy Controls

The levels of MMP-2 and MMP-3 were studied in 103 patients with BD and 69 age- and sex-matched healthy volunteers as a control group.

Overall, in patients with BD, both MMP-2 and MMP-3 serum levels were significantly higher than those of healthy controls. However, while serum MMP-2 levels of patients with BD were significantly higher for both sexes, serum MMP-3 levels were significantly higher only in male patients compared to the control group. As expected, vascular Behçet's group also had significantly higher MMP-2 and MMP-3 levels than healthy controls. On the other hand, there was no significant difference between the healthy controls and the pure mucocutaneous subgroup of the nonvascular Behçet's group. However, the rest of the patients with nonvascular BD, after exclusion of the pure mucocutaneous subgroup, also had significantly higher MMP-2 and MMP-3 levels compared to healthy controls.

Matrix Metalloproteinase-2 and Matrix Metalloproteinase-3 Levels in Patients with Behçet's Disease and Healthy Controls

Matrix metalloproteinase-2 and matrix metalloproteinase-3 levels were studied in 103 patients with BD and 69 age- and sex-matched healthy volunteers as a control group.

Both MMP-2 and MMP-3 serum levels of patients with BD were significantly higher than those of healthy controls. Concerning gender, while serum MMP-2 levels of patients with BD were significantly higher for both sexes, serum MMP-3 levels were significantly higher only in male patients compared to the control group. As expected, vascular Behçet's group also had significantly higher MMP-2 and MMP-3 levels than healthy controls ($P < .005$; Figure 1A and B). On the other hand, there was no significant difference between the healthy controls and the pure mucocutaneous

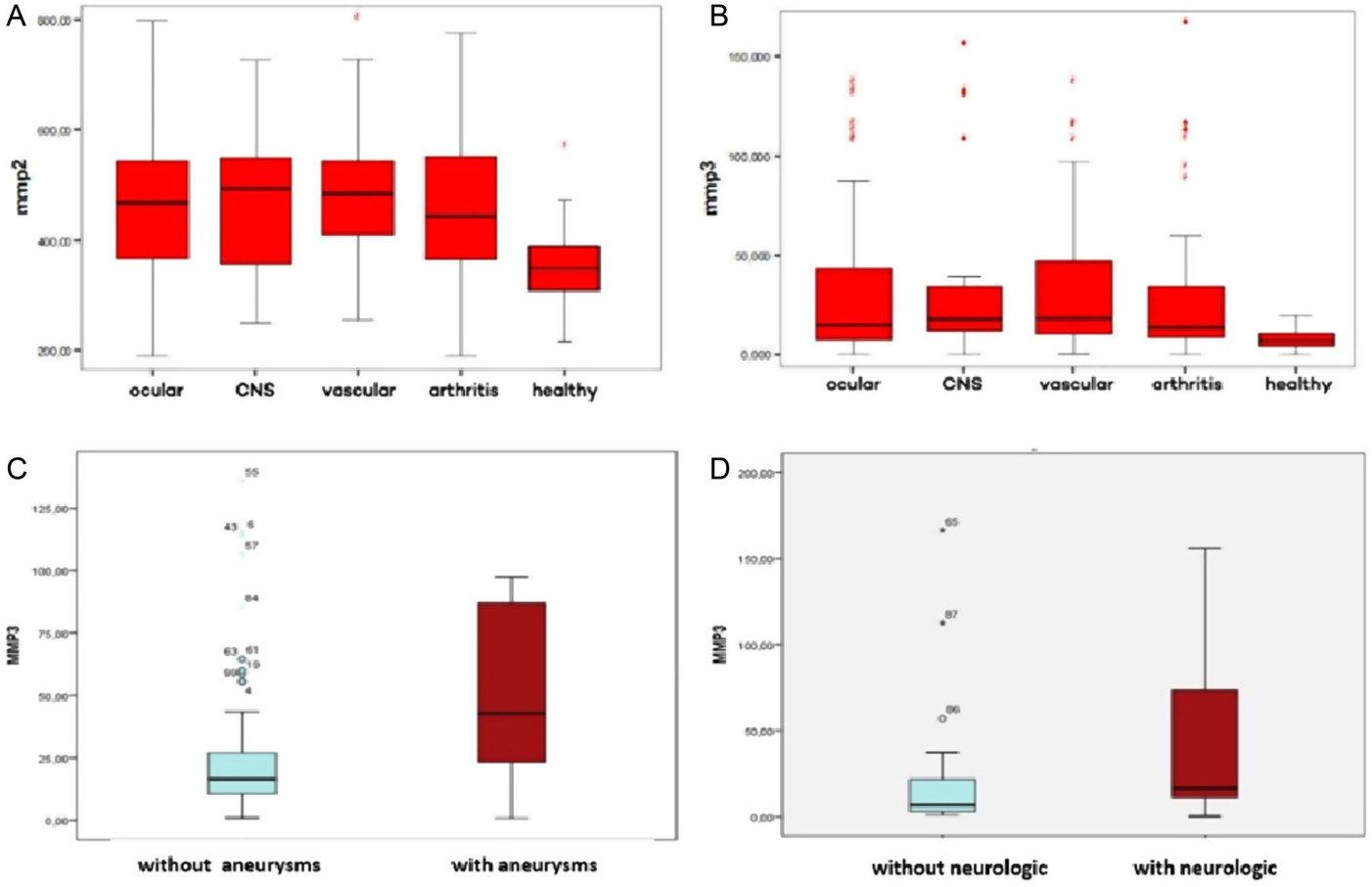

Figure 1. Comparisons of MMP-2 (A) and MMP-3 (B) levels from patients with the ocular, central nervous system, vascular, and arthritis Behçet's disease and healthy controls. Comparison of MMP-3 levels (C) in patients with vascular involvement with and without aneurysm. Comparison of MMP-3 levels (D) in patients with nonvascular Behçet disease with and without neurologic involvement. The values of MMP2 and MMP3 were compared with Student's *t*-test or Mann–Whitney *U* test (where parametric conditions were not met) according to the presence or absence of several disease subtypes. MMP-2, matrix metalloproteinase-2; MMP-3, matrix metalloproteinase-3.

subgroup of the nonvascular Behçet's group. However, after the exclusion of the pure mucocutaneous subgroup, the rest of the patients with nonvascular BD also had significantly higher MMP-2 and MMP-3 levels compared to healthy controls.

Analysis of Serum Matrix Metalloproteinase-2 and Matrix Metalloproteinase-3 Levels in Different Clinical Groups and Subgroups of Patients with Behçet's Disease

Both serum MMP-2 and MMP-3 levels in the vascular Behçet's group were not significantly higher compared to the nonvascular group. However, in the subgroup analysis, serum MMP-3 levels were found to be remarkably high both in the aneurysm subgroup (Figure 1C) of patients with vascular BD and in the subgroup of neurologic involvement (Figure 1D) of patients with nonvascular BD. High serum MMP-3 levels in the aneurysm subgroup were significantly different compared to both the nonvascular group ($P < .05$) and the rest of the vascular group (P .026). Similarly, high serum MMP-3 levels in the subgroup of neurologic involvement reached significance compared to the rest of the nonvascular group (P .041). However, there were no significant differences compared to the whole vascular group or aneurysm subgroup.

On the other hand, serum MMP-3 levels in the pure mucocutaneous subgroup of nonvascular Behçet group were similar to healthy controls.

Receiver operating characteristic analysis was conducted to test whether MMP-3 could predict aneurysm formation among the vascular group (Figure 2). If the cut-off point of serum MMP-3 level is chosen as 22.85 ng/mL to predict aneurysmal patients with BD, the sensitivity and specificity may be determined as 80% and 68%, respectively.

Disease Activity of Patients with Behçet's Disease

Using the Leeds activity index, 33 (32%) patients were clinically active. Some of these cases were recently diagnosed patients whose treatment had not been started yet. Serum MMP-2 and MMP-3 levels were not significantly different between active and inactive patients with BD.

Discussion

In the present study, we found that serum MMP-2 and MMP-3 levels were significantly higher than those of healthy controls. The highest serum MMP-3 levels were detected in patients with aneurysm formation among the vascular Behçet's group and in patients with neurological involvement among the nonvascular Behçet's group. This finding may suggest that high serum MMP-3 levels may predict not only the presence of vascular aneurysms in patients with BD with high risk but also the likelihood of neurological involvement. Strikingly, we found that serum MMP-3 levels in the aneurysm subgroup were significantly higher compared to both the nonvascular group and the rest of the vascular group with venous involvement only. This observation may be useful in clinical practice, leading the physician to search for an aneurysm in young male patients with BD with high serum MMP-3 levels.

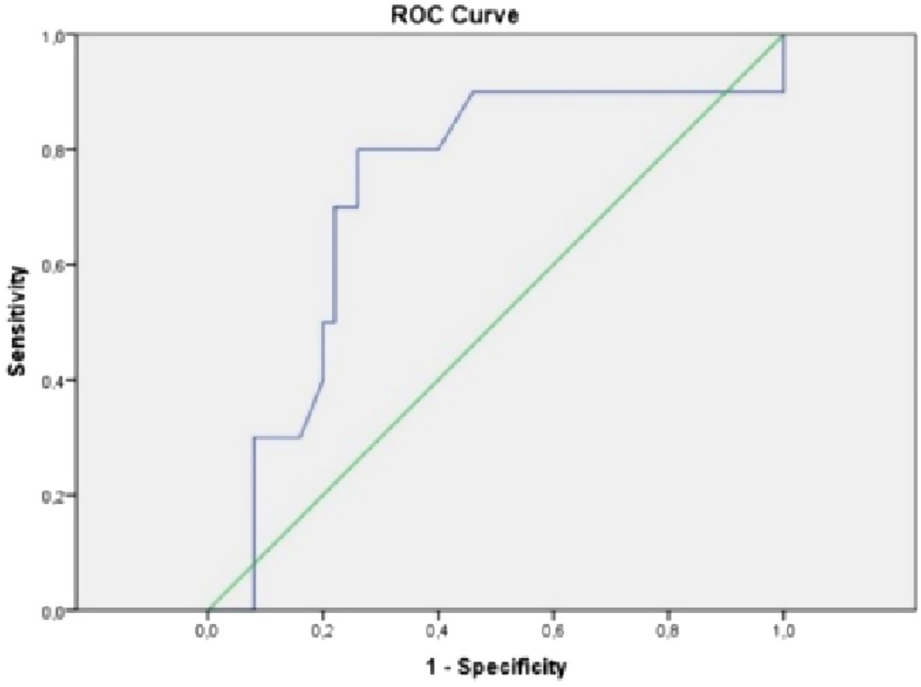

Figure 2. Receiver operating characteristic (ROC) analysis was conducted to test whether MMP-3 could predict aneurysm formation among the vascular group. If the cutoff point of serum MMP-3 level is chosen as 22.85 ng/mL to predict aneurysmal patients with Behçet's disease, the sensitivity and specificity may be determined as 80% and 68%, respectively.

One may wonder why only subgroup with aneurysm but not the whole group of vascular Behçet group reached significance in serum MMP-3 levels compared to patients with nonvascular BD. This finding may be due to the very low rate of disease activity in the whole vascular Behçet's group. Besides, since our center was a referral center where mainly complicated patients with BD are evaluated, the nonvascular group included many severe patients with neurological involvement presenting with very high serum MMP-3 levels. Therefore, we speculate that the presence of cerebral sinus venous thrombosis in some patients with neurological involvement may contribute to high serum MMP-3 levels detected in this subgroup. Among the subgroup of neurological involvement in the nonvascular group, 6 out of 15 patients had cerebral sinus venous thrombosis. On the other hand, the lowest serum MMP-3 levels in the pure mucocutaneous group may implicate that less severe disease does not cause high serum MMP levels.

The frequency of vascular involvement in BD is reported to be 2%-46%.[4] In the literature, few studies investigated the role of MMP-9, MMP-2, and MMP-3 in patients with BD with vascular involvement, as well as in other vasculitic diseases.

Pay et al's study was the first to investigate the relationship of MMP in patients with BD with vascular involvement. They studied serum MMP-2 and MMP-9 levels and found that only serum MMP-9 levels were significantly higher in patients with BD, both in active and inactive disease based on the Leeds index, compared to healthy controls. Besides, they also found that serum MMP-2 levels positively correlated with active patients with vascular BD. They concluded that serum MMP-2 and MMP-9 levels might be used as an activity marker for patients with vascular BD or patients with active BD, respectively. More importantly, they also pointed out that systemic expression of MMP-2 and MMP-9 were strongly associated, especially with aneurysmatic involvement, consistent with our findings.[12]

There are several studies in the literature to analyze the relationship between MMP-2, -9, -12, and tissue inhibitor metalloproteinase-2 (TIMP-2) promoter polymorphisms in the development of BD. In these studies, tissue expressions of MMP-9 detected by immunohistochemistry and serum and thrombocyte levels of MMP-9 were found to be significantly higher in BD. Based on these results, MMP-9 was suggested to be associated with BD susceptibility. On the other hand, MMP-2 results were inconclusive.[16-18] Another study that investigated the effect of single-gene polymorphisms in the MMP-9 gene showed that some polymorphisms increased susceptibility to BD, while others seemed to have a protective effect.[19]

The levels of MMP-9 in CSF of patients with BD with neurological involvement were also investigated in a previous study. This study reported a significantly increased MMP-9/TIMP-1 ratio in CSF in Behçet's group compared to patients with non-inflammatory neurological diseases.[20] This report may support our finding of high serum MMP-3 in the subgroup of neurological Behçet patients.

In another study comparing synovial MMP-3 levels between patients with BD and rheumatoid arthritis (RA), synovial MMP-3 levels were lower in the BD group compared to RA.[21] This observation was explained by the non-erosive character of Behçet arthritis. In our study, serum MMP-3 level in the BD subgroup with arthritis was not different from other BD subgroups.

Other than those limited number of studies investigating MMP-2, MMP-3, and MMP-9 in BD, MMP-3 levels were also studied in other vasculitides with predominant aneurysmal involvement such as Takayasu's arteritis (TA), Giant Cell Arteritis (GCA), and Kawasaki Disease (KD).[10-13] Matsuyama et al[13] investigated serum levels of MMP-2, MMP-3, and MMP-9 in 25 patients with TA. In this study, MMP-2 levels were higher than those of healthy controls in all TA, including patients in remission. In this study, MMP-3 and MMP-9 levels were significant in determining active disease. In another study, IL-2, -6, -8, -12, -18, TNFα, MMP-3, and MMP-9 serum levels were measured in 36 patients with TA and 36 controls. Vascular disease activity was assessed using PET-CT scans in this study. Serum IL-6 and MMP-3 levels were higher in TA patients compared to healthy controls ($P < .001$), but serum MMP-3 levels were not found to be significant in determining active disease.[22]

Overall, there are only a few studies investigating MMP levels and polymorphisms in BD, and previous studies mainly focused on MMP-2 and MMP-9. The present study is notable for focusing mainly on MMP-2 and MMP-3 serum levels in a larger cohort of patients with vascular BD. The role and association of MMP-3 have already been reported in abdominal aortic aneurysm formation due to both vasculitic and non-vasculitic etiologies.[23-26] However, to our knowledge, this is the first study reporting significantly higher serum MMP-3 levels in vasculitic Behçet patients with aneurysm formation, as well as in those with neurologic involvement. In conclusion, the detection of very high serum levels of MMP-3 may predict the formation of an aneurysm, or possibly the presence of neurological involvement in BD, and may lead the clinician to make an earlier diagnosis of these complications in young male patients with high risk.

Ethics Committee Approval: This study was approved by Ethics Committee of Ege University (Approval No: B.30.2.EGE.0.01.00.00/7 BOM /00001668-1398).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - K.A., P.T.E., G.K.; Design - K.A., P.T.E., G.K.; Supervision - K.A., P.T.E., G.K.; Resources - K.A., P.T.E., G.K.; Materials - K.A., P.T.E., G.K.; Data Collection and/or Processing - K.A., P.T.E., G.K., S.B.K., R.D.; Analysis and/or Interpretation - R.D., K.A., P.T.E., G.K., S.B.K.; Literature Search - K.A., P.T.E., G.K., S.B.K., R.D.; Writing - K.A., P.T.E., G.K., S.B.K., R.D.; Critical Review - G.K., P.T.E., K.A.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

References

1. Behçet H. Uber rezidivierende Aphthose, duruch ein Virus verursachte Geschwre am Mund am Auge und an den Genitalien. *Dermatol Wochenschr*. 1937;105:1151.
2. Alpsoy E, Zouboulis CC, Ehrlich GE. Mucocutaneous lesions of Behcet's disease. *Yonsei Med J*. 2007;48(4):573-585. [CrossRef]
3. Sakane T, Takeno M, Suzuki N, Inaba G. Behçet's disease. *N Engl J Med*. 1999;341(17):1284-1291. [CrossRef]
4. Calamia KT, Schirmer M, Melikoglu M. Major vessel involvement in Behçet disease. *Curr Opin Rheumatol*. 2005;17(1):1-8. [CrossRef]
5. Koç Y, Güllü I, Akpek G, et al. Vascular involvement in Behçet's disease. *J Rheumatol*. 1992;19(3):402-410.
6. Nasr H, Scriven JM. Superficial thrombophlebitis (superficial venous thrombosis). *BMJ*. 2015;350:h2039. [CrossRef]
7. Emmi G, Bettiol A, Silvestri E, et al. Vascular Behçet's syndrome: an update. *Intern Emerg Med*. 2019;14(5):645-652. [CrossRef]
8. Uzun O, Akpolat T, Erkan L. Pulmonary vasculitis in Behcet disease: a cumulative analysis. *Chest*. 2005;127(6):2243-2253. [CrossRef]
9. Marzban M, Mandegar MH, Karimi A, et al. Cardiac and great vessel involvement in "Behcet's disease". *J Card Surg*. 2008;23(6):765-768. [CrossRef]
10. Nikkari ST, Höyhtyä M, Isola J, Nikkari T. Macrophages contain 92-kd gelatinase (MMP-9) at the site of degenerated internal elastic lamina in temporal arteritis. *Am J Pathol*. 1996;149(5):1427-1433.
11. Rodríguez-Pla A, Bosch-Gil JA, Rosselló-Urgell J, Huguet-Redecilla P, Stone JH, Vilardell-Tarres M. Metalloproteinase-2 and –9 in giant cell arteritis: involvement in vascular remodeling. *Circulation*. 2005;112(2):264-269.[CrossRef]
12. Pay S, Abbasov T, Erdem H, et al. Serum MMP-2 and MMP-9 in patients with Behçet's disease: do their higher levels correlate to vasculo-Behçet's disease associated with aneurysm formation? *Clin Exp Rheumatol*. 2007;25(4 suppl 45):S70-S75.
13. Matsuyama A, Sakai N, Ishigami M, et al. Matrix metalloproteinases as novel disease markers in Takayasu arteritis. *Circulation*. 2003;108(12):1469-1473. [CrossRef]
14. Criteria for diagnosis of Behçet's disease. International study group for Behçet's disease. *Lancet*. 1990;335(8697):1078-1080.
15. Bhakta BB, Brennan P, James TE, Chamberlain MA, Noble BA, Silman AJ. Behçet's disease: evaluation of a new instrument to measure clinical activity. *Rheumatol (Oxf Engl)*. 1999;38(8):728-733. [CrossRef]
16. Park KS, Min Y, Park SR, et al. Matrix metalloproteinase-2, –9, –12, and tissue inhibitor of metalloproteinase 2 gene polymorphisms and cutaneous expressions in patients with Behçet's disease. *Tissue Antigens*. 2012;79(5):333-339. [CrossRef]
17. Lee YJ, Kang SW, Baek HJ, et al. Association between matrix metalloproteinase 9 promoter polymorphisms and Behçet's disease. *Hum Immunol*. 2010;71(7):717-722. [CrossRef]
18. Fernández Bello I, Álvarez MT, López-Longo FJ, et al. Platelet soluble CD40L and matrix metalloproteinase 9 activity are proinflammatory mediators in Behçet disease patients. *Thromb Haemost*. 2012;107(1):88-98. [CrossRef]
19. Naouali A, Kaabachi W, Tizaoui K, Amor AB, Hamzaoui A, Hamzaoui K. Association of MMP-9 gene polymorphisms with Behçet's disease risk. *Immunol Lett*. 2015;164(1):18-24. [CrossRef]
20. Hamzaoui K, Maître B, Hamzaoui A. Elevated levels of MMP-9 and TIMP-1 in the cerebrospinal fluid of neuro-Behçet's disease. *Clin Exp Rheumatol*. 2009;27(2 suppl 53):S52-S57.
21. Pay S, Erdem H, Pekel A, et al. Synovial proinflammatory cytokines and their correlation with matrix metalloproteinase-3 expression in Behçet's disease. Does interleukin-1beta play a major role in Behçet's synovitis? *Rheumatol Int*. 2006;26(7):608-613. [CrossRef]

22. Arraes AE, de Souza AW, Mariz HA, et al. (18)F-Fluorodeoxyglucose positron emission tomography and serum cytokines and matrix metalloproteinases in the assessment of disease activity in Takayasu's arteritis. *Rev Bras Reumatol Engl Ed*. 2016;56(4):299-308. [CrossRef]
23. Newman KM, Jean-Claude J, Li H, et al. Cellular localization of matrix metalloproteinases in the abdominal aortic aneurysm wall. *J Vasc Surg*. 1994;20(5):814-820. [CrossRef]
24. Carrell TW, Burnand KG, Wells GM, Clements JM, Smith A. Stromelysin-1 (matrix metalloproteinase-3) and tissue inhibitor of metalloproteinase-3 are overexpressed in the wall of abdominal aortic aneurysms. *Circulation*. 2002;105(4):477-482. [CrossRef]
25. Saratzis A, Bown MJ, Wild B, et al. Association between seven single nucleotide polymorphisms involved in inflammation and proteolysis and abdominal aortic aneurysm. *J Vasc Surg*. 2015;61(5):1120-8.e1. [CrossRef]
26. McColgan P, Peck GE, Greenhalgh RM, Sharma P. The genetics of abdominal aortic aneurysms: a comprehensive meta-analysis involving eight candidate genes in over 16,700 patients. *Int Surg*. 2009;94(4):350-358.