Adel *et al.*
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Evaluation of calprotectin and ischemia-modified albumin serum levels as biomarkers to measure disease activity in Behçet's disease

Yasmin Adel[1*], Yousra Sadeq[2] and Shereen A. Machaly[3]

Abstract

Background Although several cytokines and markers have been recognized to assess disease activity in Behçet's disease (BD), they are not routinely utilized in daily practice. This study aimed at assessing the usefulness of calprotectin and ischemia-modified albumin (IMA) serum concentrations to measure disease activity in BD.

Results The active BD cases had significantly greater IMA serum levels than inactive BD cases ($p=0.013$) and controls ($p<0.001$). In addition, the inactive BD group had significantly higher IMA serum levels than controls ($p<0.001$). The serum calprotectin levels in active and inactive BD groups were significantly greater compared to those measured in controls ($p<0.001$). On the other hand, the difference in serum calprotectin concentration was insignificant between the active and inactive BD patients. Binary logistic regression analysis revealed that hs-CRP and IMA serum levels are the strongest predictors for the activity of the active BD ($p=0.011$ and 0.005, respectively). ROC curve analysis for the ability of IMA serum level to discriminate between active and inactive BD groups revealed an AUC = 0.738.

Conclusion Serum calprotectin and IMA concentrations were significantly elevated in BD. IMA was significantly greater among active BD cases in comparison to inactive BD cases indicating its potential importance as a new marker of activity in BD.

Trial registration Trial registration on ClinicalTrials.gov: NCT05868538.

Keywords Calprotectin, Ischemia-modified albumin, Behçet's disease activity

Background

Behçet's disease is a chronic, relapsing, systemic vasculitis, characterized by a diverse spectrum of *clinical presentation*, *variable severity*, and can potentially involve any organ [1]. Thus, it is crucial to explore specific biomarkers useful for the proper assessment of disease activity and therapeutic response [2]. Several biomarkers used for monitoring BDs have been explored, yet the results were conflicting and inconclusive [3]. Therefore, identifying reliable biomarkers for the assessment of BD is still ongoing.

*Correspondence:
Yasmin Adel
Yasmin_adel@mans.edu.eg
[1] Rheumatology, Rehabilitation and Physical Medicine, Faculty of Medicine, Mansoura University Hospital, Gehan Street, PO box 35516, Mansoura, Egypt
[2] Clinical Pathology Department, Faculty of Medicine, Mansoura University, Gehan Street, PO box 35516, Mansoura, Egypt
[3] Rheumatology and Rehabilitation Department, Faculty of Medicine, Mansoura University, Dakahlia, Egypt

Pathologically, BD is an immune-mediated *vasculitis.* It affects almost all organ systems since it can involve arteries and veins of any size, causing serious organ-threatening morbidity and mortalities [4]. Though the exact mechanism involved in BD pathogenesis remains unclear, hyperactivation of innate and adaptive immune systems have a pivotal role [5], resulting in a cascade of autoimmune process characterized by endothelial dysfunction, activation of coagulation, and induction of T lymphocytes [6, 7], with consequent cytokines' synthesis resulting in vasculitis and tissue destruction [8]. However, the production of inflammatory and immune cells during the disease exacerbations, but BD is not characterized by the production of autoantibodies [9]. Though several cytokines and markers have been recognized to assess BD disease activity, they are not routinely utilized in clinical practice [5, 10].

Calprotectin, also known as MRP-8/MRP-14, is a non-covalently associated hetero-complex of 2 S100 Ca^{+2} binding proteins: myeloid-related protein 8 (MRP-8) and MRP-14 [11]. In particular situations, calprotectin is expressed and released by endothelial cells, osteoclasts, and chondrocytes, as well as fibroblast-like synoviocytes [12]. Calprotectin has pro-inflammatory activities mainly through binding the Toll-like receptor 4 (TLR4) and receptor of advanced glycation end products (RAGE) [13]. Calprotectin showed significant association with disease activity in many rheumatological disorders including rheumatoid arthritis [14], ankylosing spondylitis [15], psoriatic arthritis [16], primary Sjögren's syndrome [17], and SLE [18]. Increased circulatory calprotectin concentrations were also reported in BD. However, no association was shown with C-reactive protein (CRP) values, erythrocyte sedimentation rate (ESR), and disease activity scores [19].

Ischemia-modified albumin is a biomarker of ischemia and oxidative damage. The latter has a key role in endothelial dysfunction and vasculitis [20]. Growing evidence suggested that oxidative damage increases in BD due to ROS overproduction and reduced antioxidants [21]. Structural alterations that influence the N-terminal peptides of albumin were observed under conditions of ischemia, increased oxidative stress, and endothelial dysfunction. Therefore, albumin loses its capacity to bind heavy metals like cobalt and nickel [22]. This altered albumin molecule is known as IMA [23]. It has been reported that IMA is elevated in different rheumatic diseases [24, 25]. Higher serum IMA concentrations were reported in active BD cases than in inactive cases and control subjects [26–28].

This study aimed at assessing the usefulness of calprotectin and IMA serum values to evaluate disease activity in BD.

Methods

Study population

This study was a cross-sectional study conducted on sixty BD cases diagnosed by the International Study Group classification criteria for BD [29]. BD cases were recruited from the outpatient clinic of the Rheumatology and Rehabilitation Department Patients aged ≥ 18 years and patients with malignancy or liver diseases were excluded. The study also included 60 age- and gender-matched normal subjects served as controls. Exclusion criteria were concomitant autoimmune or auto-inflammatory disorder, acute or chronic infections, cancer, diabetes, heart failure, and gestation or up to 6 months after birth. The study protocol obtained its approval from the Local Ethics Committee. Written consent was taken from all participants after the declaration of the study's aims and procedures. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Sample size calculations

Sample size calculation was based on the difference in IMA and or calprotectin between patients with BD and the healthy control group retrieved from previous research [10]. Using G power program version 3.1.9.4 to calculate sample size based on the effect size of 0.521, using 2-tailed test, αn error = 0.05, and power = 80.0%, the total calculated sample size will be 59 at least.

Clinical assessment

A comprehensive personal and medical history was obtained from every participant through interviews. The medical records of BD cases were reviewed. The BD clinical features such as duration of BD, current treatment used, and current organ involvement were recorded for all patients.

Assessment of BD activity

BD (Behçet's disease) activity was assessed with BDCAF (Behçet's disease current activity form) which assesses clinical characteristics present during the previous 1 month before evaluation. BDCAF includes the following components: headaches (not at all or present up to 4 weeks), mouth ulcers (not at all or present up to 4 weeks), erythema (not at all or present up to 4 weeks), genital ulcers (not at all or present up to 4 weeks), arthritis (not at all or present up to 4 weeks), arthralgia (not at all or present up to 4 weeks), nausea/emesis/pain in the abdomen (not at all or present up to 4 weeks), rectal bleeding (not at all or present up to 4 weeks), diarrhea (not at all or

present up to 4 weeks), and new ocular (red eye or painful eye or reduced or blurred vision), vascular (chest pain or breathlessness or coughed up blood or pain/swelling/discoloration of the face/arm/leg), and nervous symptoms (blackouts, difficulty with speech, difficulty with hearing, blurring of/double vision, weakness/loss of feeling of face/arm/leg, memory loss, or loss of balance). Each component takes a score of (0) if absent or (1) if present. The total BDCAF score was calculated by adding up the positive components (maximum score = 12). A BDCAF patient index score ≥ 2 was considered as active BD, while a score less than 2 was considered as inactive BD [30].

Laboratory tests

Blood samples were withdrawn from all participants 12 h after fasting. Samples underwent centrifugation at 4000 rpm for 10 min. The sera were collected and kept at −80°C till analysis.

Serum calprotectin concentrations were quantified utilizing a commercial calprotectin ELISA kit (Hycult Biotech Inc., USA) based on the manufacturer's instructions. Levels of CRP and high-sensitivity CRP (hsCRP) and albumin were detected using the immunoturbidimetric technique. The limit of detection for hsCRP was 0.02 mg/l while for calprotectin, it was 1.6 ng/ml. IMA was quantified based on albumin cobalt binding colorimetric assay according to Bar-Or and colleagues [31], and the levels were expressed in absorbance units (ABSU). To obtain corrected IMA values, the equation (individual albumin level/median albumin level of population) × IMA ABSU value was applied [32].

Statistical analysis

Data were analyzed by SPSS for Windows v 20.0 (SPSS, Chicago, IL). Variables with continuous data were examined for normality of distribution using the Shapiro test. Variables with continuous data showing normal distribution were presented in means ± standard deviations (SDs) and compared utilizing the independent sample Student's *t* test. Variables with continuous data showing abnormal distribution were represented as medians and interquartile ranges and were compared by Mann–Whitney *U* test. Categorical data were represented in numbers and percentages. Linear regression analysis was carried out to determine the laboratory tests strongly predict the active BD. A significance of a result was judged at $p \leq 0.05$.

Results

General characteristics of BD cases and control subjects

The study included 60 patients with BD, 32 (53.3%) had active BD while 28 (46.7%) had inactive BD (Table 1). The active BD group included 25 males and 7 females while the inactive BD group included 23 males and 5 females.

Table 1 Clinical manifestations of studied patients

	n = 60[a]	%
Headache	21	35
Mouth ulcer	15	25.0
Erythema	18	30.0
Genital ulcer	19	31.7
Arthritis	34	56.7
Arthralgia	31	51.7
Nausea	29	48.3
Diarrhea	28	46.7
New ocular	27	45.0
Vascular	26	43.3
Skin pustules	10	16.7
Nervous symptoms	22	36.7

A BDCAF patient index score ≥ 2 was considered as active BD, while a score less than 2 was considered as inactive BD

Active BD in 32 patients (53.3%) while 28 (46.7%) had inactive BD

[a] Categories are not mutually exclusive

The study also enrolled 60 normal volunteers, 49 men and 11 women, in the control group. The mean ± SD of the age of patients in the active BD group was 43.3 ± 9.9 years, in the inactive BD group was 41.9 ± 9.7 years and in controls was 41.5 ± 9.4 years. The age and sex distribution did not differ significantly among the groups of active BD, inactive BD, and controls. In addition, the current therapy used, and duration of BD did not demonstrate a significant difference between active and inactive BD patients (Table 2).

Comparison of the laboratory findings among the groups

Active BD cases had significantly greater ESR, CRP, and hs-CRP than patients in inactive BD cases (p value = 0.013, p value = 0.035, and p value = 0.031, respectively). In addition, active and inactive BD cases had significantly greater ESR, CRP, and hs-CRP than controls (p value < 0.001) (Table 3).

The IMA serum level demonstrated significant differences among the groups, being highest in active BD cases and lowest in controls. The median [IQR] of the IMA serum level in active and inactive BD groups was 0.52 [0.26] and 0.45 [0.22] ABSU, respectively (p value = 0.013). In addition, the median [IQR] of the IMA serum level in the control group was 0.36 [0.28] ABSU which is significantly lower than active BD cases (p value < 0.001) and inactive cases (p value < 0.001) (Table 3, Fig. 1).

On the other hand, the median [IQR] of the serum calprotectin level did not demonstrate a significant difference between both BD groups 5.0 [1.1] and 4.8 [0.7] μg/ml, respectively (p = 0.108). However, the median [IQR]

Table 2 Comparison of the demographic among the groups and comparison of duration of BD and current medical therapy between active and inactive BD groups

	Active BD group (32 patients)	Inactive BD group (28 patients)	Control group (60 individuals)	P1	P2	P3
Age (mean ± SD) (years)	43.3 ± 9.9	41.9 ± 9.7	41.5 ± 9.4	0.583	0.393	0.854
Male sex (*n*, %)	25, 78.1%	23, 82.1%	49, 81.6%	0.698	0.684	0.956
Disease duration (years) (median [IQR])	9.0 [7.0]	9.0 [9.0]		0.960		
Current medical therapy, *n* (%)						
Colchicine	21, 65.6%	17, 60.7%		0.694		
Azathioprine	10, 31.3%	7, 25.0%		0.592		
Cyclophosphamide	3, 9.4%	1, 3.6%		0.369		
Corticosteroids	11, 34.4%	6, 21.4%		0.267		
Biological	3, 9.4%	1, 3.6%		0.369		

P1 comparison between the active BD group and inactive BD group, *P2* comparison between the active BD group and control group, *P3* comparison between the inactive BD group and control group. Significance considered with $P \leq 0.05$

IQR interquartile range, *Statistical test* one-way ANOVA

Table 3 Comparison of the laboratory findings among the groups

	Active BD group (32 patients)	Inactive BD group (28 patients)	Control group (60 individuals)	P1	P2	P3
ESR (mm) (median [IQR])	45.0 [21.0]	40.0 [29.0]	21.0 [16.0]	0.013	< 0.001	< 0.001
CRP (mg/dl) (median [IQR])	34.1 [29.1]	24.9 [15.4]	3.4 [3.7]	0.035	< 0.001	< 0.001
hs-CRP (mg/dl) (median [IQR])	9.3 [7.7]	7.9 [9.8]	1.8 [1.6]	0.031	< 0.001	< 0.001
IMA (ABSU) (median [IQR])	0.52 [0.26]	0.45 [0.22]	0.36 [0.28]	0.013	< 0.001	0.002
Calprotectin (µg/ml) (median [IQR])	5.0 [1.1]	4.8 [0.7]	3.4 [0.4]	0.108	< 0.001	< 0.001

P1, comparison between the active BD group and inactive BD group; *P2*, comparison between the active BD group and control group; *P3* comparison between the inactive BD group and control group

ABSU absorbance units, *hs-CRP*, high sensitive CRP; *IMA* ischemia-modified albumin, *IQR* interquartile range

Statistical test, one-way ANOVA

Significance considered with $P \leq 0.05$

of serum calprotectin concentration in active and inactive BD groups was significantly higher than in control subjects (p value < 0.001) (Table 3, Fig. 2).

Factors predicting BD activity

Binary logistic regression analysis was carried out to explore factors which can predict BD activity. As shown in Table 4, hs-CRP and IMA serum levels are the strongest predictors for the activity of the active BD (p value = 0.011 and 0.005, respectively).

ROC curve analysis

ROC curve analysis for the ability of the IMA serum level to discriminate between active and inactive BD groups revealed an AUC = 0.738. At a cutoff point of 0.415 IMA has a sensitivity of 71.2% and specificity of 52% for discriminating patients with active BD with 58.3% positive predictive value and 55.2% negative predictive value (Fig. 3).

Discussion

The major findings of our study were as follows: (a) serum IMA and calprotectin concentrations were significantly greater in active and inactive BD cases compared with the control group, (b) active BD cases had significantly greater IMA serum levels than inactive BD cases, and (c) in contrast, calprotectin serum level showed no significant difference between both BD groups.

IMA is a biomarker of ischemia, oxidative damage, and endothelial dysfunction [33]. Therefore, we assumed IMA can have a role in BD pathogenesis. The findings of our study had shown that serum IMA level was significantly higher among active and inactive BD cases than among controls. Moreover, patients with active BD had significantly greater IMA serum concentration compared with those with inactive BD. In the present study, binary logistic regression analysis revealed that hs-CRP and IMA serum levels are the strongest predictors for the activity of the active BD. ROC curve analysis revealed an

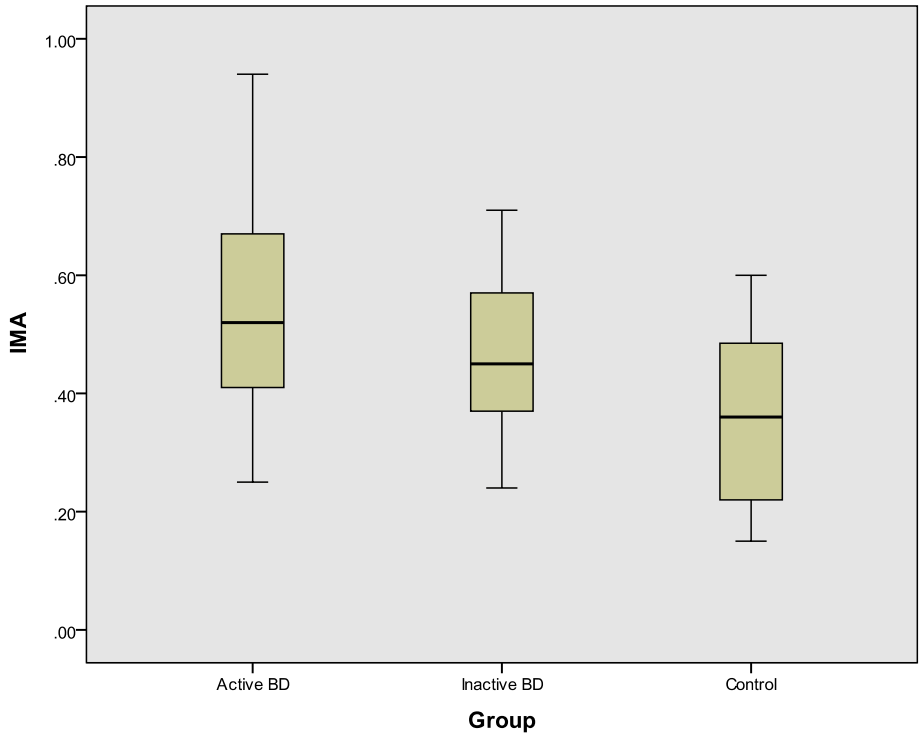

Fig. 1 Comparison of the serum IMA level among active BD group, inactive BD group, and control group

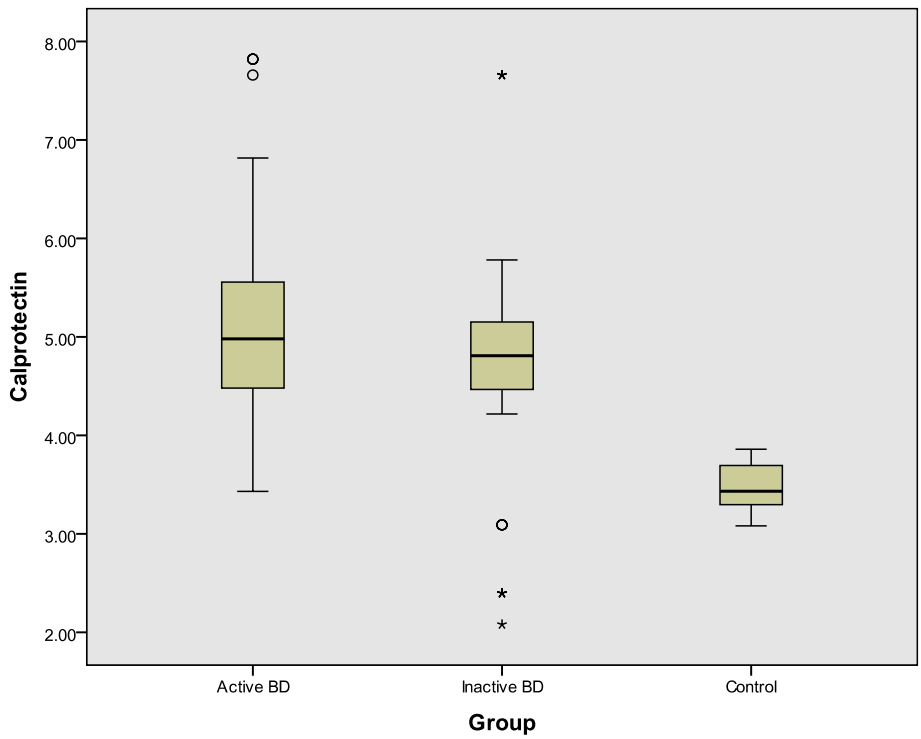

Fig. 2 Comparison of the serum calprotectin level among the active BD group, inactive BD group, and control group

Table 4 Binary logistic regression analysis for factors that can predict BD activity

	Unstandardized coefficients		Standardized coefficients	Sig	Exp(B)
	B	Std. error	Wald		
ESR	0.024	0.013	3.231	0.072	0.977
CRP	0.072	0.045	2.597	0.107	0.931
hs-CRP	0.047	0.017	7.854	0.011	0.954
IMA	4.164	1.639	6.451	0.005	0.016
Calprotectin	0.483	0.298	2.625	0.105	0.617
Constant	7.284	2.039	12.759	< 0.001	1457.276

IMA ischemia-modified albumin, *hs-CRP*, high sensitive CRP, *Statistical test* logistic regression analysis

Significance considered with $P \leq 0.05$

AUC of 0.738 of the IMA serum level for discrimination between active and inactive BD groups.

In accordance with the results of this study, Fouad and co-workers compared the serum IMA level between 48 BD cases and 38 matched control subjects and showed that the serum IMA concentration was significantly greater among BD cases than control subjects. They also found a statistically significant higher IMA level between active BD patients than inactive BD cases as measured by BDCAF [34].

Kılıç et al. evaluated the serum IMA in 26 BD cases (8 cases had active BD) and 28 matched controls and demonstrated that serum IMA concentration was significantly greater among BD cases compared to control subjects. Furthermore, significantly higher IMA concentrations were reported in the active BD group than in the inactive group or controls [28]. Ozyazgan et al. revealed that serum IMA level was significantly greater in active BD cases than in controls and also significantly higher than IMA serum level during the remission periods of BD patients [26]. Such findings are consistent with our study results.

The study of Omma et al. [10] showed that serum IMA concentrations as well as calprotectin and hs-CRP were significantly higher among BD cases in comparison to the control group. This was consistent with our results. However, the study reported that though active BD cases had greater mean concentrations of calprotectin, IMA, and hs-CRP as compared with inactive BD cases, only the difference in hs-CRP concentration was significant. Moreover, there were no correlations between calprotectin concentration and IMA, hsCRP, ESR, CRP, or disease activity score.

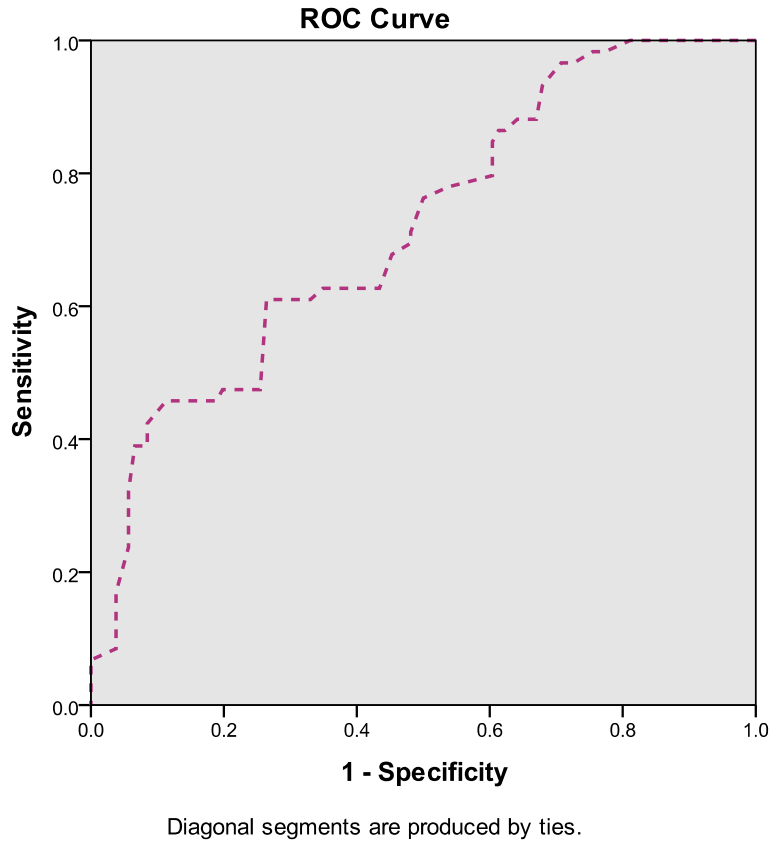

Fig. 3 ROC curve analysis for the ability of the IMA serum level to discriminate between patients with active and inactive BD (AUC = 0.738)

Similar results were obtained by the study of Oktayoglu et al. [19] that enrolled 48 BD cases (25 men and 23 women) to assess serum calprotectin concentrations and its relationship with disease activity. The study revealed that serum calprotectin concentrations were significantly greater among BD cases than among control subjects; however, the study found that serum calprotectin concentrations were not correlated with CRP, ESR, or BDCAF scores. And this difference could be due to different ethnicity and small sample size in both studies due to the low prevalence of BD which make the need for multicenter studies.

Another study observed greater serum IMA concentrations among BD cases than those in controls. In addition, BD cases that had vascular involvement had significantly greater IMA concentrations compared with cases with no vascular involvement [27]. This finding emphasizes the concept of the relationship between the serum IMA value and the activity of BD based on the elevated oxidative stress and endothelial dysfunction.

This study indicated that serum calprotectin and IMA concentrations were significantly high in BD. IMA was significantly greater among active BD cases compared with inactive BD cases indicating its potential importance as a novel marker of activity in BD. Oxidative damage is an important factor in vasculitis. IMA is a biomarker of oxidative damage, and increased concentrations in BD cases were reported in many studies [27, 28]. Oxidative damage might develop in the active phase of BD as a result of inflammation [9]. Calprotectin has a key role as a biomarker of the inflammatory process in rheumatic disorders [11]. Calprotectin is expressed in involved vessels and deposited on the endothelial cells. With the treatment of vasculitis, calprotectin values are decreased; hence, it is believed to have a key role in vasculitis [35]. In our study, serum calprotectin concentrations were significantly greater among BD cases as compared with controls.

The main limitations of our study was the cross-sectional design. A longitudinal study to evaluate the alterations of serum IMA and calprotectin levels with changes in the BD activity score may be more efficient in the determination of the utility of the two biomarkers in the detection of BD activity. Data were obtained from only one center; thus, bias in patient's selection was not fully avoided. A multicenter study with a larger population is warranted. At the time of patient selection, the entire BD cases were on steroids and immunosuppressants, which might have an effect on calprotectin concentrations.

Conclusion

Serum calprotectin and IMA concentrations were significantly increased in BD. IMA was significantly greater in active BD than inactive BD indicating its potential importance as a new marker of activity in BD.

Abbreviations

BD	Behçet's disease
BDCAF	Behçet's disease current activity form
IMA	Ischemia-modified albumin
RAGE	Receptor of advanced glycation end products

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The authors acknowledge RA cases that gave consent and agreed to participate.

Authors' contributions

YA: conceptualization, methodology, and software. YS: project administration, resources, and writing—original draft preparation. MS: supervision, software, validation, and interpretation of the data. The authors have read and approved the manuscript.

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Availability of data and materials

All data availability for this work are available upon request to the corresponding author.

Declarations

Ethics approval and consent to participate

All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Our institutional IRB Proposal Code: R.22.10.1905 - 2022/10/17

Consent from participants

Written informed consent has been obtained from all participants.

Consent for publication

Consent for publishing patient details was obtained.

Competing interests

The authors declare no competing interests.

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