

Relation of ischemia-modified albumin to disease manifestations and activity in Egyptian patients with Behçet's disease

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Aim of work

To determine level of ischemia-modified albumin (IMA) in patients with Behçet's disease (BD) and to assess its role in disease manifestations and activity.

Patients and methods

The study included 48 patients with BD and 38 matched controls. Disease activity was estimated by the BD current activity form. Serum IMA was measured.

Results

Mean age of the patients was 33.8±7.9 years. There were 42 males and six females, and the disease duration was 52.9±48.8 months. The serum IMA level was significantly increased in the patients with BD (50.9±12.9 U/ml) compared with the control (7.76±1.6 U/ml) ($P<0.001$). There was a statistically significant association between IMA level and disease activity, with high mean IMA level among active cases ($P=0.01$). There was no statistically significant association between IMA level and any of other clinical characteristics in patients with BD. Sensitivity and specificity test for IMA level in detection of cases illustrated accuracy of 98.5% with sensitivity 95.8% and specificity 78.9% at cutoff value of 9.4 U/ml.

Conclusion

There is growing evidence indicating the role of oxidative stress in BD. IMA is accepted as an essential marker of oxidative stress in patients with BD. It has a potential diagnostic value for the detection of the disease. Furthermore, it correlates with the disease activity.

Keywords:

Behçet's, disease, ischemia-modified albumin, oxidative stress

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Introduction

Behçet's disease (BD) is a recurring inflammatory multisystem disease; it is characterized by recurrent oral aphthosis, genital ulceration, ocular and variable skin is frequently associated with vascular thrombosis and formation of arterial aneurysms [1]. Male individuals are more frequently affected compared with female individuals, and it is more common in the second to fourth decade of life [2].

The etiology, pathogenesis, and mechanisms that underlie vascular disease occurring in BD are unknown. Alterations of the immunoregulatory system have been suggested to play an important role; many proinflammatory cytokines and B-cell activation have been involved in the pathogenesis of the disease [3,4]. Endothelial dysfunction and disturbed neutrophil functions, such as phagocytosis, chemotaxis, and generation of reactive oxygen species (ROS) have been suggested to be factors in the pathophysiology and etiology of BD. Overproduction of ROS with decreased level of antioxidant defense system was found to occur in BD, leading to increase of oxidative stress [5].

Ischemia-modified albumin (IMA) is recently accepted as a biomarker of ischemia and oxidative stress. It is broadly studied in many types of ischemic diseases [6–8]. In addition, its level is found to be elevated in diseases accompanied by vascular endothelial cell dysfunction [9].

The aim of this study is to determine levels of IMA in patients with BD and to assess its role in disease manifestations and activity.

Patients and methods

A total of 48 patients with BD and 38 age-matched and sex-matched healthy volunteers as controls were recruited in the study. BD diagnosis was made based on The International Criteria for Behçet's Disease [10].

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The study was approved by the Local Research Ethical Committee of Fayoum University and conforms to the 1995 Declaration of Helsinki. After obtaining informed consent from all of the study participants, complete systemic and ophthalmologic examinations were done for all patients to define systemic and ophthalmic involvement. The current activity form of Behçet's disease was assessed [11]. Patients having any systemic disease were excluded from the study.

Serum IMA was measured quantitatively using the Human IMA ELISA Kit (Sun Long Biotech Co. Ltd) according to the manufacturer's protocol. To obtain serum, blood samples were centrifuged at 3000 rpm for 10 min and stored at -80°C . IMA levels were detected by adding 40 μl of sample dilution buffer and 10 μl of sample (dilution factor is 5) in sample wells; empty well was left as blank control. Closure plate membrane was used to cover wells to be incubated at 37°C for 30 min. According to the manufacturer's protocol, dilution of the concentrated buffer with distilled water washing was done. The plate was incubated and washed after adding 50 μl HRP-conjugate reagents to each well excluding the blank control well. Then, 50 μl of chromogen solution A and 50 μl of chromogen solution B were then added to each well for 15 min in the dark. The color reaction was terminated by adding 50 μl of stop solution to each well to terminate the reaction. By comparing the absorbance values at 450 nm using a Microtiter Plate Reader, IMA concentrations were measured.

Statistical analysis

Data were analyzed by statistical package of social science software, version 18, in Windows 7 (Milton, QLD, Australia). Simple descriptive analyses in the form of numbers and percentages were used for qualitative data, and arithmetic means as central tendency measurement and standard deviations as measure of dispersion were used for quantitative parametric data. Quantitative data included in the study was first tested for normality by one-sample Kolmogorov–Smirnov test in each study group, and then inferential statistic tests were selected. For quantitative parametric data, independent Student's *t* test was used for comparing measures of two independent groups of quantitative data. For qualitative data, χ^2 test was used to compare two or more than two qualitative groups. Bivariate Pearson's correlation test was used to test association between variables. Sensitivity and specificity of IMA level in diagnosis of Behçet's disease with receiver operating characteristic (ROC) curve. The *P* value less than or equal to 0.05 was considered as the cut-off value for significance.

Results

The mean age of study group was 33.8 ± 7.9 years, with 87.5% were males and 12.5% were females. The patients' characteristics are presented in Table 1. The serum level of IMA was significantly increased in the group of patients with BD (50.9 ± 12.9 U/ml) compared with the control group (7.76 ± 1.6 U/ml) ($P < 0.001$) (Fig. 1).

There was a statistically significant association between IMA level and disease activity, with high mean IMA level among active cases ($P = 0.01$). There was no statistically significant association between IMA level and any of other clinical characteristics of patients with BD (Table 2). Moreover, there was no statistically significant correlation (*P* value more than 0.05) between IMA level and any of age of the patients or duration of the disease ($r = 0.03$, $P = 0.9$ and $r = -0.40$, $P = 0.06$, respectively), which indicated that there was no effect of these variables on IMA level.

Table 1 Demographic, clinical, laboratory characteristics; received medications; and disease activity in patients with Behçet's disease

Parameters	Behçet's disease patients (<i>N</i> =48)
Age (years)	33.8±7.9
Disease duration (months)	52.9±48.8
Sex	
Male	42 (87.5)
Female	6 (12.5)
Positive family history	10 (20.8)
Clinical manifestations	
Oral ulcers	18 (37.5)
Genital ulcers	4 (8.3)
Ocular	16 (33.3)
Cutaneous	14 (29.2)
Pathergy positivity	22 (45.8)
Arthritis	2 (4.2)
Vascular	8 (16.7)
Laboratory investigations	
Hb (g/dl)	11.4±1.3
WBC ($\times 10^3/\text{mm}^3$)	6.8±1.7
Platelets ($\times 10^3/\text{mm}^3$)	365.4±84.3
ESR (mm/1st h)	37.4±28.8
AST (U/l)	27.9±16.5
ALT (U/l)	24.2±23.4
Albumin (mg/dl)	3.4±0.35
Creatinine (mg/dl)	0.83±0.17
Medications	
Steroids	34 (70.8)
Colchicine	28 (58.3)
Azathioprine	14 (29.2)
BDCAF	2.13±1.3

Data are presented as *n* (%) and mean±SD. ALT, alanine transaminase; AST, aspartate transaminase; BDCAF, Behçet's disease current activity form; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; WBC, white blood cells.

Sensitivity and specificity test for IMA level in detection of cases illustrated accuracy of 98.5% with sensitivity 95.8% and specificity 78.9% at cutoff value of 9.4 U/ml (Fig. 2).

Discussion

BD is a systemic relapsing inflammatory disease; vascular involvement commonly occurs and predisposes to thrombosis [12]. Oxidative stress plays a major role in endothelial dysfunction and vascular injury [13,14].

Table 2 Serum ischemia-modified albumin according to the presence and absence of clinical characteristics in patients with Behçet’s disease

Clinical characteristic	IMA (U/ml) in patients with BD (N=48)		
	Presence	Absence	P
Family history	13.5±2.7	12.6±2.1	0.3
Oral ulcer	12.8±2.5	12.8±2.1	0.9
Genital ulcers	14.2±3.5	12.7±2.2	0.4
Ocular	12.7±2.1	12.8±2.4	0.9
Skin lesions	12.1±2.3	13.1±2.2	0.3
Positive pathergy	12.6±2.1	12.9±2.4	0.7
Arthritis	15.3±0	12.7±2.2	0.3
Vascular	12.2±2.9	12.9±2.1	0.5
Steroid	12.8±2.2	12.7±2.4	0.9
Colchicine	12.7±2.2	12.9±2.3	0.8
Azathioprine	13.03±1.9	12.7±2.4	0.8
BDCAF	15.04±2.6	13.1±2.4	0.01

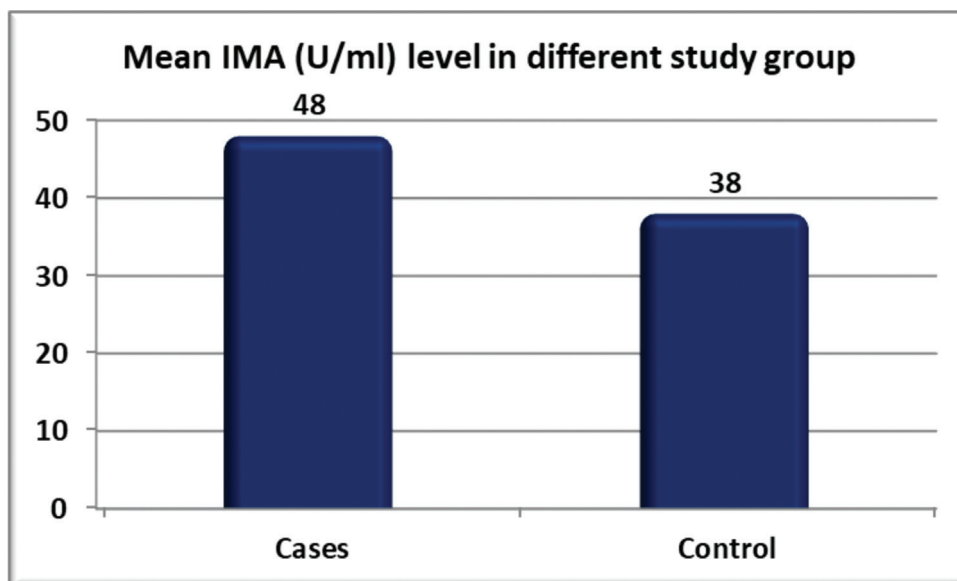
Data are presented as mean±SD. BD, Behçet’s disease; BDCAF, Behçet’s disease current activity form; IMA, ischemia-modified albumin. Bold values are significant at P value less than 0.05.

ROS and lipid peroxides have been involved in the pathogenesis of various immune-mediated diseases [15,16]. IMA has been studied in diseases associated with oxidative stress and endothelial dysfunction [9,17,18]. Moreover, it is considered as a biomarker of ischemia, oxidative stress, and endothelial dysfunction [9,19].

Levels of IMA are increased as a result of oxidative stress induced during inflammation. As a marker of oxidative stress, IMA is assumed to be connected to the pathogenesis of BD [20]. It is a metabolic variant of the protein which is generated during acute ischemic conditions owing to a free radical damage, resulting in decrease in the albumin-binding capacity for transition metals, such as cobalt, copper, and nickel [19,21]. The binding capacity of the albumin to transition metals can also be modified as a result of oxidative stress [22]. In the present study, IMA level was detected, and the association between it and specific clinical features and disease activity of BD was investigated, and it was found that level of serum IMA was significantly increased in the patients with BD compared with the control. In addition, it significantly correlated with Behçet disease current activity form.

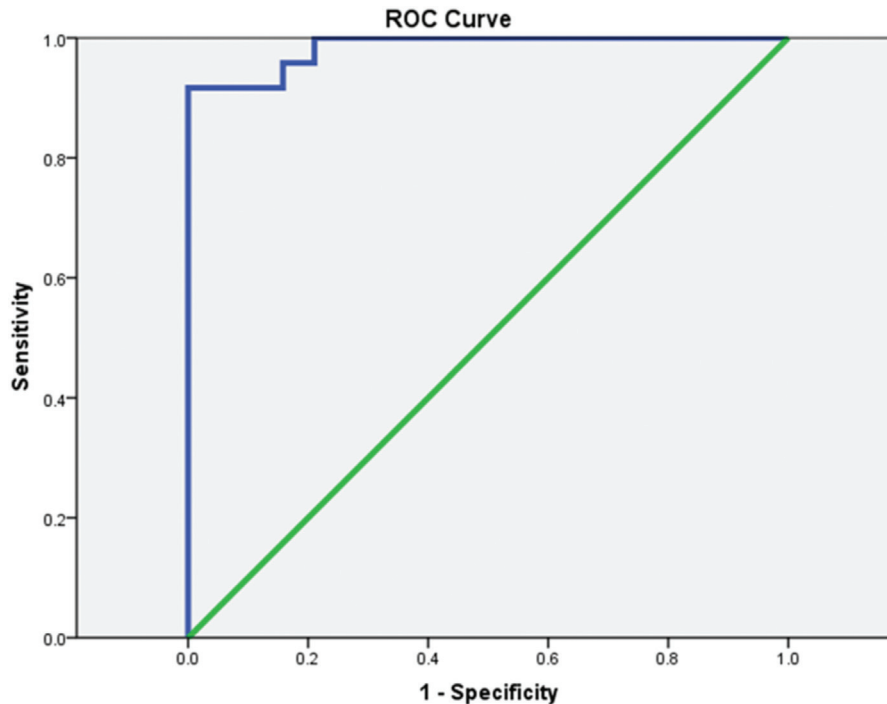
In accordance with the current study, Kılıç *et al.* [23] found that the IMA values of patients with BD during the active phase of the disease were significant as compared with the inactive phase and with the control group. Moreover, a study by Ozyazgan *et al.*

Figure 1



Serum ischemia-modified albumin (IMA) level in patients with Behçet’s disease and controls.

Figure 2



ROC curve for ischemia-modified albumin level in Behçet's disease. ROC, receiver operating characteristic.

[20] showed higher level of IMA in patients with BD during the active state of the disease.

Capkın *et al.* [18] concluded that IMA is a marker for patients with BD with vascular affection. They found that IMA levels were statistically significantly higher in patients with BD with vascular manifestations. However, the present study did not confirm this association.

Conclusion

There is growing evidence indicating the role of oxidative stress in BD. IMA is accepted as an essential marker of oxidative stress in patients with BD. It has a potential diagnostic value for the detection of the disease. Furthermore, it correlates with the disease activity.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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