

Serum advanced glycation end products and glyoxalase-1 levels in Behçet's disease: a cross-sectional study

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Abstract

Objective

Behçet's disease (BD) is a chronic, systemic inflammatory disorder. Despite the presence of chronic inflammation in BD, a clear increase in atherosclerotic cardiovascular mortality has not been documented. However, chronic inflammation may contribute to atherogenesis through various pathways, including accelerated generation of advanced glycation end products (AGEs). The objective of this study was to assess serum AGEs, Nε-carboxymethyllysine (CML), and glyoxalase-1 (GLO1) levels in a cohort of individuals with BD.

Methods

This cross-sectional study comprised 81 patients with BD (mean age: 43±11 years; 51 men/30 women) and 56 control subjects (mean age: 52±11 years; 45 women/11 men). Serum concentrations of AGEs, CML, and GLO1 were assessed using enzyme-linked immunosorbent assay (ELISA).

Results

AGE levels in patients with BD were significantly higher than those in the control group (BD: median 555 [453–864] ng/L vs. controls: median 512 [430–557] ng/L; $p=0.008$). CML levels in patients with BD were also higher than those in controls (median 532 [443–694] ng/mL vs. median 360 [308–442] ng/mL; $p<0.001$). Moreover, GLO1 levels in patients with BD were significantly lower than those in controls (median 15 [13–22] ng/mL vs. median 21 [18–27] ng/mL; $p<0.001$). No significant differences were observed in AGEs, CML, or GLO1 levels in individuals with BD according to smoking status, BMI, colchicine, glucocorticoids, immunosuppressive therapies, or major organ involvement.

Conclusion

Elevated levels of advanced glycation end products and decreased glyoxalase-1 levels were observed in BD. This pattern suggests that the inflammatory process in BD may be associated with AGE accumulation and attenuation of protective antioxidant/dicarbonyl-detoxification pathways. Elevated AGEs may contribute to the pathogenesis of atherosclerosis in individuals with BD.

Key words

Behçet's disease, advanced glycation end products, Nε-carboxymethyllysine, glyoxalase-1

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Introduction

Behçet's disease (BD) is a chronic inflammatory multi-systemic disorder (1). Vascular involvement, the primary contributor to morbidity and mortality in BD, occurs with a frequency of 15–50% and is more prevalent among young male patients (2). BD can affect vessels of varying sizes, with superficial thrombophlebitis of the extremities and deep vein thrombosis being the most prevalent forms of vascular involvement (3). Arterial vascular involvement is marked by the formation of aneurysms in peripheral, visceral, and pulmonary arteries, occurring with a prevalence of 3–5% (4). Thrombosis can also occur in atypical locations, including the inferior and superior vena cava, portal and hepatic veins, cerebral sinus vein, and right heart in BD. Cerebrovascular events and coronary artery disease, however, are extremely uncommon involvements (5).

While persistent inflammation is present in BD, enhanced atherosclerotic cardiovascular mortality associated with other multi-systemic rheumatological disorders is not observed (6). However, a recent meta-analysis reported subclinical atherosclerosis in BD. Impaired flow-mediated dilatation, increased intima media thickness and plaque formation are reported in BD patients (7).

The association between inflammation and accelerated atherosclerosis is well established. Inflammation accelerates the formation of advanced glycation end products (AGEs), contributing to the progression of atherosclerosis in chronic diseases such as diabetes, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) (8, 9). Increased inflammation associated with atherosclerosis leads to increased cardiovascular mortality in diseases such as SLE and RA (10).

Advanced glycation end-products (AGEs) are generated through the oxidative glycation of proteins, lipids, and nucleic acids by saccharides such as glucose, fructose, and pentose, mediated by the Maillard reaction. AGE molecules can be catabolised and eliminated by glyoxalase I and II in renal proximal tubular cells (11). The accumulation of

AGE precursors increases as a result of decreased GLO1 activity in renal failure (12). Monocytes, neutrophils, T cells, innate immune system and endothelial cells, express AGE receptors (RAGE). AGEs induce inflammation by binding to RAGE and increasing endothelial vascular adhesion molecules, proinflammatory cytokines, and reactive oxygen species (ROS) (11).

It has been reported that AGE levels are increased in autoimmune and inflammatory rheumatic diseases (13). Although there are some clinical studies examining the relationship between inflammation and AGEs levels in rheumatic diseases there are only few studies in patients with BD. In this study we analysed serum AGEs levels in patients with BD to explore this association.

Methods

Patient selection

This cross-sectional, case-control included 81 BD patients followed up at Marmara University, Medical Faculty, Behçet's Multi-Disciplinary Clinic in Istanbul, Turkey, and 56 control subjects. Patients with BD met the classification criteria of the International Behçet's study group (ISG) (14). Behçet's patients with DM were excluded. The control group consisted of fifty-six volunteers. Demographic data such as age, gender, disease duration, body mass index (BMI), habits and comorbidities were recorded during routine outpatient clinic visits. Clinical manifestations of BD and medical treatments were reviewed and recorded from the patient files. Blood samples were taken from the patients and C-reactive protein (CRP), creatinine, glucose, HbA1c, cholesterol, AGEs, carboxymethyl lysine (CML) and glyoxalase 1 (GLO 1) laboratory parameters were analysed. Blood samples collected after 8 hours of fasting serum samples were stored -20 C until studied. The Human AGEs kit (Sunred) and the ELISA technique were used to measure the serum AGEs level. The kit had a detection range of 10–4000 ng/L and a sensitivity of 5.23 ng/L. The kits have an intra-assay value of less than 8% and an inter-assay value of less than 10%.

The level of serum carboxymethyl ly-

Competing interests: none declared.

sine was measured using the Human Carboxymethyl lysine (CML) kit (Sunred, China) with the ELISA (Enzyme-linked immunosorbent assay) method. The sensitivity of the kit was 8.013 ng/mL, and the detection range was 10–3000 ng/mL. The intra-assay value of the kits: <12%, the inter-assay value is 10%. The level of serum GLO 1 level was measured using the Human glyoxalase 1 ELISA kit. The sensitivity of the kit was 0.21 ng/mL, and the detection range was 0.5–150 ng/mL. The intra-assay value of the kits less than 8% and the inter-assay value is less than 10%.

Statistical analysis

Continuous variables were summarised using descriptive statistics presented as medians and interquartile range (IQR). Categorical variables were summarised using counts and percentages. The Kolmogorov-Smirnov test assessed the normality of data distribution. The non-parametric analysis of variance test was used to compare the two groups, and Spearman's rank test was used for the correlation analysis. The results were evaluated at a 95% confidence interval, and a *p*-value less than 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS program. This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Marmara University ethics committee (protocol no: 09.2025.25-0129).

Results

The median age of Behçet's patients was lower than the control group (BD: 44 (31–50) years vs. C: 53 (45–58) years, *p*<0.001). Behçet's patients had a higher male sex ratio than the control group (BD:M/F 51(%37) /30(%22), C:M/F 11(%8) /45(%33), *p*<0.001). The median BMI of BD patients was lower than control group (*p*<0.001). Demographic and clinical characteristics of patients and the control group is shown in Table I.

All BD patients had mucocutaneous involvement. Forty-two percent of patients with BD were under 40 years of age. Additionally, more than half ex-

Table I. Demographic and clinical characteristics of patients.

	BD	Control	<i>p</i> -value
n	81	56	
Age, years, median (IQR)	44 (31-50)	53 (45-58)	<0.001
Gender, n, (%)			
Female	30 (%22)	Female 45 (%33)	
Male	51 (%37)	Male 11 (%8)	<0.001
Disease duration, years, median (IQR)	12 (7-17)	–	
BMI, kg/ m ² , median (IQR)	26 (24-28)	32 (27-37)	<0.001
Smoking, n, %	26 (%19)	9 (%7)	0.034
Comorbidities, n, %			
Diabetes mellitus	0	26 (%19)	–
Arterial hypertension	2 (%2)	19 (%14)	<0.001
Hyperlipidaemia	4 (%3)	11 (%8)	0.011
Coronary arterial disease	1 (%1)	3 (%2)	0.304
Laboratory parameters, median (IQR)			
CRP, mg/L	2.8 (1-7)	1.8 (1.4- 2.8)	0.202
Glucose, mg/dl	88 (82-94)	133 (103-194)	<0.001
Creatinine, mg/dl	0.7 (0.6-0.9)	0.8 (0.6-1)	0.018
HbA1c (%)	5.4 (5.2-5.7)	7.1 (6.1-8.2)	0.001
LDL, mg/dl	93 (77-112)	104 (89-142)	0.141
Triglyceride, mg/dl	104 (74-167)	165 (115-231)	0.001

BD: Behçet's disease; CRP: C-reactive protein; LDL: low density lipoprotein.

Table II. Clinical characteristics of Behçet's patients (n=81).

	n (%)
Oral ulcers (recurrent)	81 (100)
Genital ulcers	76 (93.8)
Skin involvement	
Folliculitis	54 (66.7)
Erythema nodosum	31 (38.3)
Pathergy test positivity	31 (38.3)
Eye involvement	30 (37)
Vascular involvement	49 (60.5)
Venous involvement	37 (45.7)
Arterial involvement	19 (23.5)
Joint involvement	15 (18.5)
Central nervous system involvement	9 (11)
Gastrointestinal involvement	1 (1.2)
Major organ involvement	66 (81)
Medical treatment	
Colchicine	44 (54.3)
Glucocorticoid	7 (8.6)
Azathioprine	36 (44.4)
Mycophenolate mofetil	4 (4.9)
Cyclosporine	1 (1.2)
Adalimumab	13 (16)
Infliximab	10 (12.3)

Table III. Serum levels of AGEs, CML and GLO1.

	BD	Control	<i>p</i> -value
AGEs, ng/L, median (IQR)	555 (453-864)	512 (430-557)	0.008
CML, ng/ml, median (IQR)	532 (443-694)	360 (308-442)	<0.001
GLO1, ng/ml, median (IQR)	15 (13-22)	21 (18-27)	<0.001

BD: Behçet's disease; AGEs: advanced glycation end-products; CML: Nε-carboxymethyllysine; GLO1: glyoxalase 1.

hibited vascular involvement (n=49, 60.5%). Seven BD patients were receiving low dose glucocorticoids (GC). Forty-four BD patients were receiving colchicine, more than half of the pa-

tients had major organ involvement, and 55 patients were receiving immunosuppressive therapy. Clinical characteristics of BD patients are shown in Table II.

The median AGEs levels of Behçet's patients were higher than control group (BD: 555 (453-864) ng/L vs. HC: 512 (430-557) ng/L $p=0.008$). Similarly, the median CML levels were higher in BD patients than the control group (BD: 532 (443-694) ng/ml vs. HC: 360 (308-442) ng/ml, ($p<0.001$), whereas median GLO 1 levels of BD patients were lower than the control group (BD: 15 (13-22) ng/ml vs. HC: 21 (18-27) ng/ml, ($p<0.001$). Serum levels of AGEs, CML and GLO1 are shown in Table III and Figure 1.

There was no relationship between smoking, colchicine, GC and immuno-suppressive treatment with AGEs, CML and GLO 1 levels. In addition, there was no significant association between major organ involvement such as vascular and eye involvement with AGEs, CML and GLO 1 levels. Relationship between AGEs, CML and GLO 1 levels smoking, medical treatment and clinical involvement is shown in Table IV.

The relationship between C-reactive protein and AGEs, CML, and GLO 1 was analysed; however, no significant correlations were observed ($p=0.756$, $p=0.657$ and $p=0.174$, respectively). There were negative correlations between age and GLO1 (GLO 1 $p=0.019$, Pearson's $r=-0.322$) in BD group. There was also no correlation between body mass index and AGEs, CML and GLO1 levels (AGEs $p=0.757$, CML $p=0.440$, GLO1 $p=0.657$).

Discussion

To the best of our knowledge, our study is the first one to examine the serum levels of AGEs, CML and GLO 1 in patients with BD. In our study, AGEs and CML levels were increased in patients with BD. In addition, the levels of GLO1, which catabolises AGEs, were decreased in BD.

The association of AGEs with autoimmune and inflammatory rheumatic diseases has been investigated since it has been understood that the interaction of AGEs with sRAGE on the surface of monocytes increases proinflammatory cytokines. Studies have shown that AGEs levels are increased in autoimmune and inflammatory rheumatic diseases (11). In our study, similar to

Table IV. Relationship between AGEs levels smoking, medical treatment and clinical involvement.

	Smoking		<i>p</i> -value
	Yes	No	
AGEs, ng/L, median (IQR)	615 (506-866)	542 (449-665)	0.223
CML, ng/ml, median (IQR)	536 (474-625)	529 (438-622)	0.317
GLO1, ng/ml, median (IQR)	16 (13-29)	14 (13-20)	0.269
Colchicine			
AGEs, ng/L, median (IQR)	544 (452-638)	569 (466-1063)	0.380
CML, ng/ml, median (IQR)	518 (439-605)	536 (465-989)	0.129
GLO1, ng/ml, median (IQR)	14 (12-16)	16 (13-17)	0.108
Glucocorticoid			
AGEs, ng/L, median (IQR)	542 (432-679)	555 (459-866)	0.444
CML, ng/ml, median (IQR)	429 (373-732)	531 (459-691)	0.334
GLO1, ng/ml, median (IQR)	14 (12-20)	15 (12-24)	0.899
Synthetic DMARDs			
AGEs, ng/L, median (IQR)	557 (466-1013)	544 (451-747)	0.487
CML, ng/ml, median (IQR)	530 (442-734)	531 (452-649)	0.962
GLO1, ng/ml, median (IQR)	15 (12-24)	14 (12-19)	0.966
Biologic DMARDs			
AGEs, ng/L, median (IQR)	557 (443-1081)	555 (457-775)	0.718
CML, ng/ml, median (IQR)	533 (464-837)	531 (452-649)	0.460
GLO1, ng/ml, median (IQR)	14 (12-31)	14 (12-19)	0.733
Vascular involvement			
AGEs, ng/L, median (IQR)	567 (473-1009)	526 (450-693)	0.235
CML, ng/ml, median (IQR)	531 (454-747)	529 (441-625)	0.617
GLO1, ng/ml, median (IQR)	15 (13-22)	14 (12-19)	0.312
Eye involvement			
AGEs, ng/L, median (IQR)	512 (488-633)	512 (438-622)	0.754
CML, ng/ml, median (IQR)	512 (332-509)	387 (324-549)	0.765
GLO1, ng/ml, median (IQR)	20.5 (20-27)	21 (16.5-25)	1.0
Major organ involvement			
AGEs, ng/L, median (IQR)	557 (451-850)	555 (461-722)	0.711
CML, ng/ml, median (IQR)	532 (457-723)	512 (407-655)	0.543
GLO1, ng/ml, median (IQR)	15 (13-22)	14 (13-19)	0.299

AGEs: advanced glycation end-products; CML: N- ϵ -carboxymethyllysine; GLO1: glyoxalase-1; DMARDs: disease-modifying anti-rheumatic drugs.

other rheumatic diseases such as RA, SLE and adult Still's disease, AGEs levels were found to be higher than the healthy controls (15, 16). AGEs accumulation in SLE may contribute to the development of accelerated atherosclerosis (17). Similarly to SLE, a study of 52 psoriasis patients found that skin AGE levels were correlated with CIMT, supporting the role of AGEs in early atherosclerosis (18). In BD, the vascular endothelium is affected due to inflammation in the active period, whereas in inactive patients, endothelial impairment is thought to develop

chronically with the contribution of atherosclerosis (19). The accumulation of AGEs causes endothelial damage as a result of the production of inflammatory cytokines and free oxygen radicals, which may lead to the development of atherosclerosis in the inactive period in patients with BD (7).

AGEs increase with age, hyperglycaemia and obesity and increased AGEs are associated with atherosclerosis, diabetic microvascular complications and neurodegenerative diseases (20, 21). In our study, although the mean age and body mass index of BD patients were

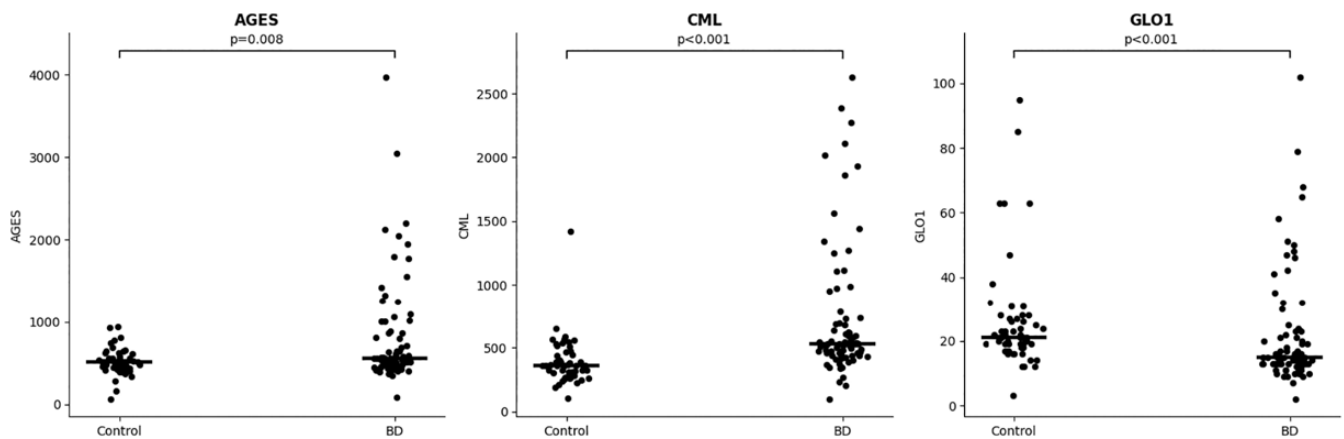


Fig. 1. Comparison of serum AGEs, CML and GLO1 levels between groups.

AGEs: advanced glycation end-products; CML: N ϵ -carboxymethyllysine; GLO1: glyoxalase-1; BD: Behçet's disease.

lower than the control group, AGEs levels were detected to be higher. The majority of Behçet's patients included in our study were in the inactive state. Therefore, mean CRP levels were lower, and no correlation was observed between AGEs and CRP in our study. Similarly, in a study evaluating sRAGE levels among 60 patients with inflammatory rheumatic diseases, including Behçet's disease, no significant correlation was observed between sRAGE concentrations and either disease activity or CRP levels (22).

CML is one of the most important non-fluorescent AGEs molecules. Similar to other AGEs, its accumulation in tissues is thought to be associated with inflammation and endothelial damage (22). In a study examining AGEs in relation to disease activity in 80 patients with RA, results indicated that AGE levels were elevated in RA, and CML was associated with disease activity (8). In addition, in a study involving 91 systemic sclerosis (SSc) patients in which AGEs expression in skin tissue and calcific lesions were examined, CML levels were found to be increased in skin and localised calcific lesions (23).

CML levels have not been analysed in patients with BD previously. Similar to rheumatic diseases such as RA and SSc, in our study, we observed increased levels of CML in patients with BD.

In our study, GLO 1 levels were observed to be lower in patients with BD than in the control group. GLO 1 a member of the glyoxalase enzymatic system, limits the accumulation of

AGEs in tissues by metabolising glyoxal and methylglyoxal, which are precursors of AGEs (12). With aging, GLO 1 decreases in cells such as brain and erythrocytes, but increases in tissues such as skin (12).

Activation of the AGEs cell surface receptor RAGE and tumour necrosis factor- α cytokine release is proposed to decrease expression and activity of GLO 1 by inducing nuclear factor NF- κ B pathway (24-26). In a study involving 30 patients with osteoarthritis that examined AGEs and GLO 1 regulation in human chondrocytes, it was found that GLO 1 expression in chondrocytes decreased due to the inflammation mediated by interleukin-1B (27). GLO 1 levels may be suggested to decrease as a result of excessive activation of proinflammatory cytokine pathways causing cellular inflammation in BD.

AGEs levels have been reported to increase in smokers (28). However, in our study, there were no significant differences in AGEs and CML levels in smokers with BD. A study involving cultured human osteoarthritic cartilage cells demonstrated that colchicine effectively inhibits the elevation of AGEs following its administration (29). However, there was also no significant difference in AGEs and CML levels with colchicine use in our study.

In our study, no significant difference was found in the AGEs and CML levels of BD patients receiving glucocorticoid treatment. Analysis of AGEs accumulation in patients with Graves' orbitopathy showed that AGEs levels decreased

with methylprednisolone treatment (30). RAGE expression decreased after GC treatment in an experimental study in which AGEs activity was investigated by examining RAGE receptor expression (31). However, high dose GC treatment was applied in these studies, unlike our study. Most of the patients with BD in our study were in the inactive period and just seven patients were receiving low dose GC treatment. Therefore, the effect of GC treatment on AGEs levels may not have been demonstrated in our study.

In our study, AGEs and CML levels were not significantly different in patients with BD receiving conventional or biological immunosuppressive therapies. The data on the effects of IS therapies regarding AGEs levels and activity come from studies of anti-tumour necrosis factor alpha (TNF- α) treatment in RA patients and they are conflicting. When the effect of anti TNF- α treatment on oxidative stress markers was evaluated, AGEs levels were found to decrease after 30 weeks of infliximab treatment (32). However, in a different study that examined the effect of anti TNF- α treatment on oxidative stress markers in RA patients, no difference was found in AGEs levels after 6 months of anti TNF- α treatment (33). Likewise, in a clinical study examining AGEs activity through RAGE expression, there was no impact of anti TNF- α treatment on RAGE activity (34).

AGEs levels were not significantly different in patients with BD associated with vascular, ocular and total of major

organ involvements. In the only study in the literature that examined the relationship between clinical involvement and AGEs in BD, increased glycer-AGEs levels were found in 14 BD patients with uveitis (35). The majority of Behçet's patients in our study were male and had major organ involvement. Although higher systemic inflammation was observed in patients with major organ involvement compared to those with isolated mucocutaneous involvement, there was no difference in AGEs levels.

Cross-sectional analysis is one of the limitations of our study. Limited number of active patients and mucocutaneous-limited disease may also affect the applicability of our results to the general BD population. Additionally, waist circumference and waist to height ratio were not measured, which may have limited the assessment of the relationship between anthropometric measures and inflammation. Finally, the absence of disease control groups (e.g. SLE, RA, or adult-onset Still's disease) restricts comparisons across different inflammatory conditions.

In conclusion, the results of our study showed an increase in AGEs and CML levels in patients with BD similar to other inflammatory/rheumatic diseases such as RA and SLE. The increase in AGEs may contribute to the development of atherosclerosis in patients with BD as it does in SLE. In addition, low GLO1 in BD patients may be one of the possible reasons for the increase in AGEs. Additional studies are needed to confirm the results of our study and to understand the relationship between AGEs and atherosclerosis in BD patients.

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