Serum zonulin levels and intestinal permeability in Behçet's syndrome: a cross-sectional study

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Abstract

Objective

Increased intestinal permeability has been implicated in the pathogenesis of autoimmune and inflammatory conditions, including Behçet syndrome (BS). Zonulin, an endogenous regulator of intestinal tight junctions, serves as a biomarker for assessing intestinal barrier integrity. We aimed to evaluate intestinal permeability in patients with BS using serum zonulin levels, a novel and validated biomarker for intestinal barrier dysfunction.

Methods

A total of 173 participants were enrolled: 87 patients with BS, 20 patients with Crohn's disease (CD), and 66 healthy controls. Patients with active gastrointestinal symptoms, risk factors or using medications known to affect intestinal permeability, were excluded. Serum zonulin levels were measured using ELISA. High levels indicate increased intestinal permeability. Behçet Disease Current Activity Form and Crohn's Disease Activity Index were used to assess disease activities.

Results

Median serum zonulin level was significantly lower in BS patients (24 ng/mL, IQR: 18–43) compared to CD patients (112 ng/mL, IQR: 22–204) and healthy controls (109 ng/mL, IQR: 36–226) ($p<0.01$). Multivariate logistic regression analysis identified female sex as the only independent predictor of elevated zonulin levels (OR=13.5, 95% CI: 2.5–72). Immunosuppressives, disease duration, age, and major organ involvement were not significantly associated with serum zonulin levels.

Conclusion

In this cross-sectional study, patients with BS did not exhibit increased intestinal permeability. Longitudinal studies, including treatment-naive patients, are required to better understand the role of intestinal permeability and gut microbiota alterations in the pathogenesis and disease activity of BS.

Key words

Behçet's syndrome, zonulin, intestinal permeability, Crohn's disease, immunosuppressive agents, enzyme-linked immunosorbent assay

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Introduction

The role of gastrointestinal system (GIS) pathologies in the pathogenesis of inflammatory or autoimmune diseases has been postulated for years because the intestinal system is a large reservoir for various exogenous toxins and microorganisms (1, 2). The gut epithelium is the largest barrier surface in the human body between the external environment and the host immune system. The tight junction (TJ) has a crucial role in this barrier function. Damage to these TJs can result in paracellular leakage of the antigens to the submucosal area and potentially trigger an autoimmune or inflammatory disease in genetically susceptible individuals (3). It is also possible that the inflammation and related cytokines can disrupt intestinal permeability (IP) and cause a leaky gut (1, 4). Zonula occludens toxin (Zot) is an enterotoxin of vibrio cholera, causing a reversible opening in the intercellular TJs. Recently, an endogenous homolog of this molecule, known as pre-haptoglobin 2 or zonulin, was identified (5). Serum zonulin measurement via ELISA using anti-zonulin antibodies has emerged as a simple and sensitive method for defining intestinal barrier dysfunction. Exposure to antigens and microorganisms stimulates zonulin overexpression in the gut epithelium, thereby increasing serum zonulin levels and reflecting damage to the epithelial TJs in the small intestine (6).

Behçet syndrome (BS) is a vasculitis of unknown aetiology (7). Previous studies have suggested that altered gut flora could be important in the pathogenesis (8-11). Moreover, studies have evaluated gastroduodenal and small intestinal mucosal permeability in BS using methods such as the sugar absorption test and radioactive tracers. With this study, we aimed to evaluate intestinal permeability in patients with BS by serum zonulin measurements, which is a more current and validated method (12, 13).

Material and methods

Consecutive patients with BS who attended the outpatient clinic of the Behçet's Disease Research Centre of Istanbul University - Cerrahpaşa between January 2019 and April 2021 were screened for eligibility. Patients between the ages of 18 and 65 years and meeting the International Study Group Behçet's disease criteria (14) were included. Patients with symptoms or signs that could be attributed to gastrointestinal (GI) involvement or clinical conditions that may affect intestinal permeability were excluded. Patients with other major organ involvement such as uveitis, vascular (deep vein thrombosis or arterial involvement), or neurologic involvement (NBS) (parenchymal or dural sinus thrombosis) could be included. Patients who received immunosuppressives were allowed in the study. However, patients over 65 years of age and those with conditions or exposures known to influence intestinal permeability such as recent use (within the last four weeks) of non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, mycophenolate, antibiotics, chemotherapy, curcumin supplements, or alcohol consumption were excluded. In addition, individuals with clinical conditions that may directly affect intestinal permeability, such as gluten hypersensitivity, lactose intolerance, cancer, diabetes, cystic fibrosis, inflammatory bowel disease, or prolonged fasting, as well as those with conditions that have been associated with impaired intestinal permeability, including asthma and chronic dermatitis, or with symptoms attributable to GI disease such as persistent diarrhoea or unexplained abdominal pain, were also not included (15-21).

Demographic, clinical, and laboratory data were collected using a standardised data collection form. The disease activity was assessed using Behçet's Disease Current Activity Form (BDCAF). Patients with a diagnosis of Crohn's disease (CD) who were followed in the gastroenterology outpatient clinic and healthy individuals without any of the exclusion criteria were included as controls. The disease activity of patients with CD was assessed using the Crohn's Disease Activity Index (CDAI).

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Istanbul University-Cerrahpaşa, Cerrahpaşa Medical School (approval no. 171699-10/5/2018). Written in-

formed consent for publication was obtained from all participants at the time of enrolment.

Zonulin measurements

Venous blood samples were allowed to clot for 1 hour at room temperature before centrifugation for 20 minutes at 1000 x g at 2–8°C. The collected supernatants were stored at -80°C until ELISA assessment, between 2 to 20 months.

All reagents and samples were melted at room temperature (18~25°C) before the ELISA and preheated for 15 min before optical density measurement. We used specific ELISA Kits (Elabscience, Houston, Texas, USA), which recognise Human Zonulin with the Sandwich-ELISA principle. The micro-ELISA plate in this kit has been pre-coated with an antibody specific to Human Zonulin. We added samples to the micro-ELISA plate wells and combined them with the specific antibody. Then, a biotinylated detection antibody specific for Human Zonulin and Avidin-Horseradish Peroxidase (HRP) conjugate was added successively to each microplate well and incubated. Free components were washed away after incubation. The substrate solution was added to each well. Only those wells that contain Human Zonulin, biotinylated detection antibody, and Avidin-HRP conjugate would appear blue. The enzyme-substrate reaction was terminated by adding a stop solution, and the colour turned yellow. The optical density (OD) was measured spectrophotometrically at a wavelength of 450 nm ± 2 nm. We calculated the concentration of Human Zonulin in the samples by comparing the OD of the samples to the standard curve.

Serum C-reactive protein (CRP) was assessed through the method of the particle-enhanced immunonephelometric system using BN-II, Systems (Siemens Healthcare Diagnostics, Marburg Germany). Results were given as mg/L.

Statistical analysis

Considering the magnitude of group differences reported in previous zonulin studies and aiming to ensure adequate representation of the major Behçet subgroups (mucocutaneous, ocular, and vascular) a conservative standardised effect size of Cohen's d=1.0 was assumed for sample size planning, and approximately 20-25 participants per group were targeted (22).

Statistical analyses were conducted using IBM SPSS Statistics (version 25) for primary analyses and Python's SciPy and Statsmodels libraries for advanced statistical modelling. Continuous variables were reported as median (interquartile range, IQR), while categorical variables were expressed as frequencies and percentages. The normality of data distribution was assessed using the Kolmogorov-Smirnov test, which indicated that zonulin levels were not normally distributed ($p<0.05$). Therefore, differences in zonulin levels among the three groups (BS, CD, and healthy controls) were analysed using the Kruskal-Wallis test.

Post-hoc pairwise comparisons were conducted using Dunn's test with Bonferroni correction, performed in Python. Categorical variables were compared among the three groups using the Chi-square or Fisher's exact test, depending on expected cell counts.

To assess factors associated with elevated zonulin levels, participants were categorised into two groups: those with zonulin levels above the median value and those below or equal to the median. The association between potential predictor variables and this classification was examined using Chi-square tests to identify statistically significant factors. Logistic regression analysis was performed using variables that were either statistically significant in univariate analyses or deemed clinically relevant. Logistic regression was performed within the BS subgroup only. Variance Inflation Factor (VIF) analysis was conducted to evaluate multicollinearity, and variables with high collinearity were excluded to improve model stability. Statistical significance was set at $p<0.05$.

Table I. Demographic and clinical characteristics of patients with Behçet's syndrome.

Number of men/women	60/27
Age at onset of BS (years), median (IQR)	25 (18-30)
Disease duration, years (IQR)	19 (13-27)
BS manifestations (ever), n (%)	
Oral ulcers	85 (98)
Genital ulcers	48 (55)
Erythema nodosum like lesions	45 (52)
Papulopustular lesions	58 (67)
Uveitis	39 (45)
CNS involvement	3 (3)
Deep vein thrombosis	29 (33)
Joint involvement	13 (15)
Active BS manifestations (at blood collection), n (%)	47 (54)
Oral ulcers	30 (34)
Genital ulcers	3 (3)
Erythema nodosum like lesions	4 (5)
Papulopustular lesions	25 (29)
Uveitis	4 (5)
CNS involvement	0
Deep vein thrombosis	2 (2)
Joint involvement	13 (15)
Treatment modalities at the time of blood collection, n (%)	48 (64)
Glucocorticoids	14 (16)
Azathioprine	33 (38)
Mycophenolate mofetil	0
Cyclosporine-A	9 (10)
Interferon-α2b	9 (10)
TNF inhibitors	13 (15)
Adalimumab	3
Infliximab	10

BS: Behçet's syndrome; CNS: central nervous system; TNF: tumour necrosis factor.

Results

A total of 173 participants, comprising 76 females (44%) and 97 males (56%), with a median age of 39 years (IQR: 31-

Table II. Characteristics of study participants in each group.

	Behçet's syndrome (n=87)	Crohn's disease (n=20)	Healthy controls (n=66)	*p*-value
Age (years), median (IQR)	40 (35-52)	41 (29-47)	32 (22-42)	0.01
Sex, F/M ratio	0.44	1.2	1.36	<0.01
Number of patients with active disease*(%)	29 (33)	0	NA	NA
CRP (mg/L), median (IQR)	2.1 (1.2-5.5)	3.5 (1.4-7.5)	1.5 (0.4-3.3)	<0.01
Serum zonulin level (ng/mL), median (IQR)	24 (18-43)	112 (22-204)	109 (36-226)	<0.01

*BDCAF score ≥2 for patients with BS, CDAI score for patients with CD.
BDCAF: Behçet's Disease Current Activity Form; CRP: C-reactive protein; IQR: interquartile range.

46), were enrolled based on eligibility criteria. The cohort included 87 patients with BS (50%), 20 patients with CD (12%), and 66 healthy controls (38%). Among BS patients, 33% had a BDCAF score of ≥2, while all the CD patients were in remission (CDAI<150). The median disease duration among BS patients was 19 years (IQR: 13–27). A total of 58 BS patients (67%) had at least one major organ involvement, with uveitis in 48 patients (55%), vascular involvement in 34 patients (39%), and central nervous system involvement in 3 patients (3%). Sixty-four percent of BS patients were receiving immunosuppressive therapy, and 24% were on biological agents such as infliximab, adalimumab, or interferon alpha-2b. A detailed summary of the demographic and clinical characteristics of BS patients is given in Table I.

The median serum zonulin level for the overall study population was 36 ng/mL (IQR: 20-158). Across all groups, females had significantly higher zonulin levels than males (149 ng/mL [IQR: 42-226] *vs*. 24 ng/mL [IQR: 16-42], $p<0.01$). Compared to healthy controls and Crohn's disease patients, Behçet syndrome patients had significantly lower serum zonulin levels ($p<0.01$), as detailed in Table II.

In the univariate logistic regression analysis, female gender was found to be significantly associated with elevated zonulin levels, with an odds ratio (OR) of 11.27 (95% CI: 3.31–38.36, $p<0.001$). None of the other clinical variables showed a statistically significant association with elevated zonulin levels in univariate analysis.

In multivariate logistic regression analysis, female gender remained an independent predictor of elevated zonulin levels (OR=13.5, 95% CI: 2.5–72, $p<0.001$). Other factors, including the presence of immunosuppressive treatment (OR=1.0, 95% CI: 0.2–4.8), BDCAF score ≥2 (OR=0.6, 95% CI: 0.1–2.4), vascular involvement (OR=1.7, 95% CI: 0.1–26), ocular involvement (OR=1.1, 95% CI: 0.1–36), and other types of organ involvement (OR=0.9, 95% CI: 0.02–29), were not associated with elevated zonulin levels (Table III).

Table III. Univariate and multivariate logistic regression analyses of factors associated with elevated zonulin levels.

Variable	Univariate OR (95% CI)	Univariate *p*-value	Multivariate OR (95% CI)	Multivariate *p*-value
Gender (female)	11.27 (3.31-38.36)	*<0.001*	13.5 (2.5-72)	*<0.001*
Immunosuppressive	0.96 (0.32-2.84)	0.9	1 (0.2-4.8)	0.9
BDCAF score ≥2	1.11 (0.38-3.21)	0.8	0.6 (0.1-2.4)	0.5
Vascular involvement	0.83 (0.27-2.53)	0.7	1.7 (0.1-26)	0.7
Ocular involvement	0.41 (0.14-1.25)	0.1	1.1 (0.1-36)	0.4
Other subgroups	2.78 (0.9-8.57)	0.08	0.9 (0.02-29)	0.9

BDCAF: Behçet's Disease Current Activity Form; OR: odds ratio.

Discussion

Increased IP and dysbiosis have been an object for many sceptics to delineate the role of the gastrointestinal system in the pathogenesis of inflammatory diseases, including rheumatic diseases (1, 22-26). Traditionally, urinary measurement of unabsorbable sugars has been the most used method for assessing IP (27). However, serum zonulin measurement provides a more convenient alternative, showing a strong correlation with sugar permeability tests and serving as a reliable biomarker for increased IP in multiple clinical conditions (28, 29).

Despite numerous studies reporting altered IP in various inflammatory diseases, only three studies have specifically examined IP in patients with BS (12, 13, 30). The first study, conducted by our group, had demonstrated increased IP in BS patients compared to healthy hospital staff but not when compared to patients with ankylosing spondylitis or systemic lupus erythematosus, using a chromium-51 ethylenediaminetetraacetic acid (Cr-EDTA) tracer test (12). The second study investigating the upper GI permeability by sucrose absorption test revealed increased IP in patients with BS compared to healthy controls. Furthermore, patients with active disease and those receiving colchicine had higher permeability than patients with inactive disease who were not on colchicine (13). Finally, a recent study reported that zonulin levels were elevated in patients with active Behçet uveitis and Fuchs uveitis syndrome without treatment compared to healthy controls, indicating a potential disruption of the gut barrier in these conditions (30).

Our study did not reveal increased IP in patients with BS compared to healthy controls or CD patients. There are certain key differences between this study and the previous studies that may be responsible for the different results. First, in the current study, we excluded patients with additional risk factors that could potentially increase IP, such as colchicine or NSAID use (5, 6, 18, 19,

28, 31-36). Additionally, a substantial proportion of BS patients (64%) were using at least one immunosuppressive, including glucocorticoids, TNF inhibitors, azathioprine, and cyclosporine A. Given that glucocorticoids, TNF inhibitors, and other immunosuppressives have been shown to stabilise tight junctions and reduce IP, it is plausible that the lack of zonulin elevation in our BS cohort may be attributed to the impact of immunosuppressives on gut barrier dysfunction, together with the meticulous exclusion of BS patients with additional risk factors for IP (37-39). Although patients with inflammatory bowel diseases typically exhibit increased IP due to epithelial barrier damage (40), in our study, CD patients, who were all in remission, had similar IP to healthy controls.

Furthermore, microbial dysbiosis has been associated with altered zonulin levels in uveitis patients. In particular, *Fusicatenibacter* abundance was inversely correlated with zonulin levels, while Moraxella, Clostridia_UCG-014_unclassified, and Alloprevotella showed a positive correlation (30). This suggests that specific microbial compositions might modulate zonulin secretion, influence IP and potentially contributing to systemic inflammation. The majority of BS patients in our study were receiving immunosuppressive therapy, which may have mitigated such microbiota-mediated effects.

Given these findings, our results should be interpreted cautiously regarding the relationship between zonulin levels, IP, and BS pathogenesis. Future studies should aim to compare zonulin levels in treatment-naïve BS patients and those on immunosuppressive therapy, as well as integrate microbiome analyses to better understand how gut microbial alterations contribute to disease pathogenesis and zonulin regulation in BS. Longitudinal studies comparing zonulin levels at the time of diagnosis and later in the disease course and comparing levels during active disease and remission in the same patient would also help our understanding of the relevance of IP for BS.

Interestingly, female sex was the only independent predictor of increased zonulin levels in multivariate analysis. The gut microbiome exhibits sex-based variations (41), yet studies assessing whether sex influences IP have yielded conflicting results (42-44). Although female sex appeared as an independent predictor of higher zonulin levels, this should be interpreted cautiously due to age and sex imbalances between groups, especially the younger and predominantly male BS cohort. It remains unclear whether these differences in IP contribute to variations in immune response, autoimmune disease prevalence, or disease severity. In contrast, age, BS symptoms (current or past), disease activity, and ongoing treatments were not associated with zonulin levels. Several recent reports have questioned the analytical specificity of commercially available zonulin ELISA kits, suggesting that these assays may detect proteins other than true pre-HP2. This limitation may have contributed to the low zonulin levels observed in our BS and CD groups. Although the same kit was uniformly used across all participants which supports internal validity, these methodological issues should be kept in mind when interpreting our findings and when concluding that intestinal permeability is not increased in BS (45-47). Adding a sucrose permeability test in at least some participants as an internal validation method for our zonulin test assay performance would have added to the reliability of the results. Such methodological constraints may have influenced our findings and should be considered when interpreting the lack of increased intestinal permeability in BS.

The cross-sectional design precludes causal inference regarding the relationship between intestinal permeability and disease activity. Also, the absence of a treatment-naïve group and the lack of pre- and post-treatment assessments limit the ability to disentangle the effects of disease-related mechanisms from those of ongoing immunosuppressive therapy. Given that a substantial proportion of patients were receiving treatment, the findings may reflect treatment-related modulation of intestinal permeability rather than intrinsic disease characteristics. These factors should be considered when interpreting the generalisability of our results.

In conclusion, in this cross-sectional study, patients with BS did not exhibit increased IP. Future longitudinal studies assessing patients before and after treatment or during disease exacerbations would be helpful to better elucidate the relationship between IP, disease activity, and immunosuppressive therapy. The absence of elevated zonulin levels in our cohort should be interpreted with caution, as it may reflect a combination of biological factors, treatment effects, and limitations of the biomarker used. We reason such studies will also help clarify whether IP alterations contribute to BS pathogenesis or are merely a consequence of inflammation and treatment.

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