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Relationship between dietary histamine intake and clinical parameters in Behçet syndrome

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ABSTRACT

Aims: This study investigated histamine intake and its associations with clinical and biochemical findings in patients with Behçet syndrome.

Methods: Patients with Behçet syndrome were prospectively enrolled using a cross-sectional, multicenter, and online survey design. Sociodemographic parameters, including age, gender, smoking and alcohol intake, nutritional counseling history, anthropometric measurements, clinical characteristics, and biochemical results, were obtained using an online questionnaire. Dietary histamine intake was determined using a food frequency questionnaire.

Results: The study included 66 patients (mean age: 37.5±11.3 years, women: 53%. Food consumption was reported to trigger oral aphthae in 81% of the individuals, and the most frequently reported triggers were eggplant (37.5%), tomatoes (37.5%), and citrus fruits (34.3%). There was a significant positive correlation between dietary histamine intake and white blood cell counts (r=0.650; p=0.050). There were no significant differences in the clinical characteristics, including oral aphthae, genital ulcers, uveitis, dermatologic lesions, gastrointestinal system involvement, joint involvement, and vascular involvement between patients with low and high dietary histamine intake. A positive correlation was found between dietary histamine intake and the frequency of attacks (r=0.324; p=0.008).

Conclusions: This study showed that increased dietary histamine intake was associated with an increased frequency of attacks in patients with Behçet syndrome. Oral aphthae are associated with certain foods, such as eggplant, tomatoes, and citrus fruit.

Introduction

Behçet syndrome is a recurrent inflammatory multiorgan syndrome affecting the skin, mucosa, eyes, joints, gastrointestinal tract, and central nervous system, and is characterized by diverse clinical presentations (1). Oral and genital ulcers are common in Behçet syndrome and typically manifest as initial symptoms (2). In severe cases, gastrointestinal and/or central nervous system symptoms, known as neuro-Behçet symptoms, may occur (3). The etiology of Behçet syndrome remains unclear. It is considered an autoinflammatory and autoimmune trait triggered by genetic or infectious factors in genetically predisposed and susceptible individuals (2). Although disease flares in Behçet syndrome cannot be estimated, various potential triggers, including nutrients, stress, mucosal trauma, menstruation, tooth extraction, and infections, have been reported (4). Given the rarity of Behçet syndrome, no established nutritional protocol specific to this condition exists. However, the nutritional status of patients is influenced by the clinical presentation of the syndrome, ongoing inflammation, and medication use, given its classification as a chronic inflammatory disorder. Consequently, these factors often induce alterations in appetite, gastrointestinal function, and metabolic status (5). Hence, regular monitoring of nutritional status is of paramount importance.

Histamine, a bioactive amine, is synthesized from histidine via the action of the enzyme L-histidine decarboxylase, which is a process reliant on pyridoxal phosphate (6). It is notable for its role as a mediator possessing proinflammatory properties, influencing the activity of various immune cells, such as T and B lymphocytes, neutrophils, eosinophils, basophils, macrophages, dendritic cells, and endothelial cells. Histamine is naturally present in certain foods. Histamine is linked to exacerbations of symptoms in Behçet syndrome (7). Several foods have been reported to contribute to increased recurrence rates of oral aphthae, many of which are either histamine-rich, such as ripened cheeses, or histamine-releasing, including nuts, pineapple, citrus fruits, strawberries, tomatoes, peanuts, alcohol, spices, eggplant, and vinegar (4,8). Oral aphthae in Behçet syndrome may be attributed to a mucosal pathergy reaction induced by histamine-rich foods or the degranulation or activation of mast cells triggered by various dietary or non-dietary factors. The prevalence of commonly cited trigger foods rich in histamine or capable of eliciting histamine release suggests a mechanism of hyper-reactivity (7).

Histamine, present in foods at different concentrations, tends to escalate during ripening and fermentation processes (9,10). This upsurge in histamine levels stems from the microbial conversion of amino acids, a process influenced by several factors, including precursor amino acids in foods, freshness, salt content, processing techniques, storage conditions, environmental factors conducive to microbial growth (e.g., temperature and pH), and the activity of bacterial decarboxylases (10). The European Food Safety Authority (EFSA) issued a scientific report in 2011 to outline the average histamine levels in various foods. Food categories with the highest histamine concentrations include dried anchovies (348 mg/kg), fish sauce (196-197 mg/kg), fermented vegetables (39.4-42.6 mg/kg), cheese (20.9-62 mg/kg), other fish and fish products (26.8-31.2 mg/kg), and fermented sausages (23.0-23.6 mg/kg) (11). Beyond histamine-rich foods, certain items, including citrus fruits, nuts, tomatoes, spinach, chocolate, spices, egg whites, various beverages, additives, and medications, are considered to either stimulate histamine release from tissue mast cells (as histamine liberators) or impede the enzyme essential for its degradation (8).

This study aimed to determine the dietary histamine intake of patients with Behçet syndrome and its association with clinical and biochemical markers.

Methods

Study design and participants

This study adopted a descriptive cross-sectional design to present observational data on Behçet syndrome. Participants were enrolled between March 2022 and December 2022 using an online questionnaire hosted on Google Forms. Recruitment efforts were facilitated through social media announcements. Participants hailed from all across the regions in Türkiye and received treatment at different healthcare facilities. The online questionnaire was formulated by drawing upon the methodology of a previous study with a similar design (12). An online questionnaire link was sent to individuals willing to participate. The inclusion criteria were age between 18 and 65 years and a diagnosis of Behçet syndrome by a rheumatologist. The exclusion criteria were histamine intolerance, pregnancy, breastfeeding, and cancer. A power analysis was conducted to determine the required sample size, determining that a minimum of 139 participants was necessary for an effect size of 0.5 at a 95% confidence level and 80% power. However, the study was able to recruit only 66 participants. The study was conducted following the guidelines laid down in the Declaration of Helsinki, and the procedures involving human subjects/patients were approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (Code: 2022/06-09 on 19.10.2021).

Data collection

Sociodemographic variables included were age, sex, nutritional counseling history, anthropometric variables, clinical characteristics, biochemical variables, past flares, and dietary histamine intake.

Anthropometric measurements

The weight and height of the participants were self-reported. Participants were informed to measure their weight in the morning on an empty stomach, wearing minimal and light clothing, without shoes, using a 100-g sensitive scale; their height was measured with their feet together and in an upright position, with their head in the Frankfort plane. Body mass index (BMI) was calculated according to the classification provided by the World Health Organization (13,14).

Clinical and biochemical findings

Clinical findings, including oral aphthosis, genital aphthosis, dermatologic lesions, ocular lesions, joint involvement, vascular manifestations, gastrointestinal involvement, and the frequency of flares (i.e., exacerbations of clinical symptoms/findings), were assessed (15). These clinical manifestations were presented in the questionnaire, prompting patients to indicate both specific findings and frequency annually. The clinical findings reported by the participants as flares were recorded based on self-reports.

Because patients were from different regions of Türkiye, the hospital protocols varied. Therefore, patients were requested to manually enter the results of their biochemical findings from their medical records into the questionnaire. The variables were C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), hemoglobin level, white blood cell (WBC) count, platelet count, mean corpuscular volume (MCV), red cell distribution width

(RDW), blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), iron-binding capacity, and ferritin levels obtained within the preceding six months.

Histamine intake

We assessed dietary histamine intake using a food frequency questionnaire that captured 30 days of food consumption. It was specifically tailored to evaluate histamine intake. A structured food consumption frequency form consisting of 24 items was used to quantify histamine consumption. This study was based on the EFSA publication titled "Panel on Biological Hazards (BIOHAZ). Scientific Opinion on risk-based control of biogenic amine formation in fermented foods" (11). The collected data were processed via the Nutrition Information System to calculate the participants' dietary histamine intake. Given the absence of established cutoff values for low or high histamine intake, we used the median dietary histamine intake as the threshold.

Study endpoints

The primary outcome was the relationship between dietary histamine intake and the frequency of flares. Differences in clinical and biochemical findings between the low and high histamine groups were secondary outcomes.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences statistics for Windows, version 27.0 (IBM Corp., Armonk, NY: USA, 2020). Continuous variables are presented as mean±standard deviation. Qualitative variables are presented as numbers and percentages. The normality of data distribution was determined using the Shapiro-Wilk test. The Mann-Whitney U or Kruskal-Wallis analysis was used to test between-group differences. Chi-square analysis was used to compare categorical data. Correlation analyses were performed using the Spearman test. In all analyses, $p<0.05$ was considered statistically significant.

Results

Descriptive statistics

The study included 66 patients (mean age: 37.5±11.3 years, women: 53%). The mean BMI was 25.3±5.3 kg/m^2, and 6.1% were underweight, 51.5% were normal, 25.8% were overweight, and 16.7% were obese.

The median dietary histamine intake was 886.3 (28.0-6065.9) mg in total, 883.5 (303.6-5321.9) mg in women, and 1092.6 (28.0-6065.9) mg in men. There was no significant difference in dietary histamine intake between men and women (p=0.944). Of the participants, 54.5% believed that food consumption reduced syndrome symptoms. Only 28.8% of the participants received nutritional counseling.

Of the participants, 48.5% experienced symptoms of Behçet syndrome after consuming certain foods. The foods associated with increased symptoms were eggplant (37.5%), tomatoes (37.5%), citrus fruits (34.3%), nuts (31.2%), chocolate (15.6%), dessert (15.6%), dairy products (9.3%), acidic foods and drinks (9.3%), spicy foods (9.3%), sauces (6.2%), strawberries (6.2%), fish (3.1%), bacon (3.1%), fried foods (3.1%), bananas (3.1%), apples (3.1%), and cherries (3.1%). Concerning the symptoms upon consumption of these foods, 81% of the individuals reported oral aphthae, 31.2% experienced a burning sensation in the oral mucosa, 21.9% observed occurrence of new ulcers, 21.9% reported joint involvement, 6.2% indicated experiencing fatigue, 6.2% reported abdominal pain, and 3.1% reported fever.

The frequency of flares increased with BMI, but the relationship was not statistically significant.

Table 1 presents the comparisons of biochemical results according to dietary histamine intake. Notably, WBC counts exhibited a statistically significant increase among patients with higher dietary histamine intake.

Table 2 presents the comparison of clinical diagnoses according to dietary histamine intake. The prevalence rates of oral aphthae, genital ulcers, uveitis, dermatologic lesions, gastrointestinal, joint, and vascular involvement were 86.4%, 47.0%, 37.9%, 45.4%, 15.2%, 60.6%, and 27.3%, respectively. There was no significant difference in the incidence of oral aphthae, genital ulcers, uveitis, dermatologic lesions, gastrointestinal involvement, joint involvement, or vascular involvement between the groups with low and high dietary histamine intake (p>0.05).

Table 3 presents the correlation analysis between the frequency of flares, BMI, and dietary histamine intake. Notably, no significant relationship was observed between BMI and the frequency of flares (r=-0.020; p=0.872). However, a statistically significant and positive correlation was found between dietary histamine intake and the frequency of flares (r=0.324; p=0.008).

Concerning the relationship between dietary histamine intake and biochemical findings, a significant positive correlation was found only with the WBC (r=0.650; p=0.05) (Table 4).

Discussion

The findings of this study suggest a notable association between increased dietary histamine intake and a high frequency of flares among patients with Behçet syndrome. Moreover, there was a positive correlation between WBC count and dietary histamine intake. Notably, oral aphthae emerged as the predominant symptom of Behçet syndrome following food consumption, predominantly eggplant, tomato, and citrus fruit.

The inflammatory nature of obesity and the status of body composition impact the severity and activity of chronic

Table 1. Biochemical results according to dietary histamine intake

	Dietary histamine intake <886.3 mg		Dietary histamine intake >886.3 mg		p*
	n	Mean±SD	n	Mean±SD	
Biochemical results					
CRP (mg/dY)	18	20.5±46.8	14	3.9±7.3	0.220
ESR (mm/h)	7	11.0±9.4	10	12.6±13.0	0.887
Hemoglobin (g/dL)	13	13.3±1.4	9	15.7±11.0	0.324
WBC (x10^3/uL)	11	6.6±1.4	6	11.0±6.15	**0.037**
Platelet count (x10^3/uL)	10	269.2±39.9	6	266.7±69.6	0.875
MCV (fL)	11	84.7±6.8	5	90.6±9.53	0.320
RDW (%)	10	17.0±7.8	5	25.8±26.8	1.000
BUN (mg/dL)	7	13.9±6.4	4	12.0±7.84	0.527
ALT (IU/L)	13	30.8±28.0	10	24.4±12.8	0.879
AST (IU/L)	13	25.1±13.6	9	20.4±8.3	0.556
Iron binding capacity (ug/dL)	5	328.0±23.7	5	290.0±111.6	0.151
Ferritin (mY/ng)	6	97.1±186.8	5	26.3±13.7	0.792

*Mann-Whitney U test. Significant p values are shown in bold.
SD: Standard deviation, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, WBC: White blood cell, MCV: Mean corpuscular volume, RDW: Red cell distribution width, BUN: Blood urea nitrogen, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

Table 2. Dietary histamine intake and clinical characteristics

	Dietary histamine intake <886.3 mg		Dietary histamine intake >886.3 mg		Total		p*
	n	%	n	%	n	%	
Oral aphthae	28	84.8	29	87.9	57	86.4	0.500
Genital ulcer	13	39.4	18	54.5	31	47	0.162
Uveitis	16	48.5	9	27.2	25	37.9	0.064
Dermatologic lesions	15	45.5	15	45.5	30	45.4	0.597
Gastrointestinal involvement	5	15.2	5	15.2	10	15.2	0.633
Joint involvement	20	60.6	20	60.6	40	60.6	0.599
Vascular involvement	7	21.2	11	33.3	18	27.3	0.204

*Chi-square test

Table 3. Correlations between frequency of flares, BMI, and dietary histamine intake

	BMI (kg/m^2)	
	r*	p*
Frequency of flares	-0.020	0.872
	Dietary histamine intake	
	r*	p*
	0.324	**0.008**

*Spearman's rho correlation analysis. Significant p values are shown in bold.
BMI: Body mass index

inflammatory conditions like Behçet syndrome (16). Although the current study revealed an increase in the frequency of flares with higher BMI, no significant correlation was observed between BMI and the frequency of flares. Koca et al. (17) reported that patients with rheumatism and obesity exhibit greater disease activity than their non-obese counterparts. However, because we did not monitor longitudinal disease activity, other potential correlations may have been missed. Another significant factor contributing to the absence of statistical significance in observed differences could be the prevalence of participants within the ideal BMI range. Patients outside this range were excluded. Nonetheless, it can be inferred that patients with Behçet syndrome would benefit from achieving and maintaining an ideal weight and BMI to mitigate the frequency of flares.

Dietary factors have been implicated in intensifying Behçet syndrome, particularly mucocutaneous lesions (18,19). Some studies have identified specific foods, including vegetables and fruits (such as eggplant, tomatoes, melon, figs, kiwi, and bananas), nuts (walnuts, peanuts, almonds, sunflower seeds), spices (such as pepper), and carbonated beverages, as exacerbating symptoms like oral aphthae, genital ulcers,

Table 4. Correlations between biochemical results and dietary histamine intake

	Dietary histamine intake	
Biochemical results	**r***	**p***
CRP (mg/dL)	-0.336	0.600
ESR (mm/h)	-0.250	0.334
Hemoglobin (g/dL)	-0.276	0.214
WBC (x10^3/uL)	0.650	**0.050**
Platelet count (x10^3/uL)	-0.018	0.948
MCV (fL)	0.097	0.721
RDW (%)	0.168	0.550
BUN (mg/dL)	-0.027	0.937
ALT (IU/L)	-0.111	0.613
AST (IU/L)	-0.180	0.422
Iron binding capacity (ug/dL)	-0.467	0.174
Ferritin (mL/ng)	-0.87	0.800

*Spearman's rho correlation analysis. Significant p values are shown in bold. CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, WBC: White blood cell, MCV: Mean corpuscular volume, RDW: Red cell distribution width, BUN: Blood urea nitrogen, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

mucocutaneous lesions, and ocular inflammation in patients (4,19). Consistent with previous research, our study found that 48.5% of participants reported experiencing worsening symptoms upon consuming certain foods. Our findings align with the existing literature, as citrus fruits, acidic beverages, chocolate, spices, and bananas, particularly eggplant, tomatoes, and nuts, emerged as common triggers for symptom exacerbation. Upon further examination of symptoms triggered by these foods, our findings indicated the simultaneous occurrence of oral and genital ulcers alongside dermatologic lesions, consistent with previously documented results. The histamine content of these foods may explain their association with oral and genital ulcers and dermatologic lesions (20). Nuts may elicit allergic reactions by inducing histamine release (21). Additionally, certain foods with acidic, salty, spicy, and coarse textures can irritate the oral mucosa, potentially leading to oral aphthae (22).

The correlation between dietary histamine intake and clinical diagnosis in patients with Behçet syndrome is unclear. However, two studies have reported that certain foods trigger symptoms, such as oral aphthae, genital ulcers, ocular lesions, and dermatologic lesions, in these patients. It was concluded that many of these products were histamine-rich, including ripened cheeses and fermented alcoholic products (4,7). In the current study, we did not observe a significant difference between groups with low and high dietary histamine intake concerning the prevalence of oral aphthae, genital ulcers, uveitis, dermatologic lesions, gastrointestinal involvement, joint involvement, or vascular involvement. Additionally, there was no significant difference in the frequency of flares between the low and high histamine intake groups. However, we did identify a significant positive correlation between dietary histamine intake and the frequency of flares. Histamine exerts its effects on a diverse array of cells, including smooth muscle cells, neurons, endocrine and exocrine cells, blood cells, and various immune system cells. Given its role in regulating leukocyte maturation and activation, as well as its capacity to induce chronic inflammation, histamine plays a pivotal role in driving the development of inflammatory syndromes (23). Hence, it is reasonable to anticipate an association between histamine intake and the frequency of flares in inflammatory conditions such as Behçet syndrome. Consistent with this notion, managing dietary histamine intake may offer a potential route for syndrome management in Behçet patients. Conversely, factors such as stress, trauma, seasonal variations (e.g., temperature, humidity), menstruation, and other dietary constituents with antioxidant or prooxidant properties also influence the frequency of flares (4).

Biochemical findings of Behçet syndrome may be influenced by histamine intake and release (24,25). However, no studies have compared biochemical findings based on histamine intake levels among patients with Behçet syndrome. In the current study, we observed no significant differences in RDW, hemoglobin, and MCV between groups with low and high histamine intake. However, the WBC count was significantly different between the two groups. Moreover, we identified a positive correlation between dietary histamine intake and WBC. This finding suggests that histamine may be associated with an adverse biochemical profile in Behçet syndrome by augmenting inflammation, as evidenced by the elevated WBC count as an inflammatory marker. Only CRP levels were significantly higher than those of the control group, with higher CRP levels and ESR during the flares (26). Higher CRP levels and ESR are commonly observed in various rheumatic syndromes and may arise because of inflammatory processes leading to heightened oxidative stress (27). However, we did not observe significant differences in CRP and ESR levels between the low and high histamine intake groups. Besides, a previous study reported no significant difference in ferritin, iron-binding capacity, ALT, AST, or BUN levels between patients with Behçet syndrome and the control group (28). We observed no significant differences in ferritin, iron-binding capacity, ALT, AST, and BUN levels between the low and high histamine intake groups. It can be concluded that food consumption may be associated with inflammatory markers. Nevertheless, our findings are not consistent with those of previous studies likely due to the short-term follow-up of the clinical findings.

Study Limitations

There are some limitations in this study. First, the study was conducted online and self-funded due to Coronavirus disease-2019 (COVID-19) pandemic measures, which might have reduced the preciseness of the data. COVID-19 has been related to some changes in chronic diseases (29,30).

Additionally, COVID-19 is associated with laboratory findings that may be mixed with the acute phase response seen in Behçet flares and abnormal conditions reported by patients with COVID-19 (31,32). Second, specific biochemical test results were not available to confirm disease activity. Third, other than the oral aphthae, we did not assess the dermatologic findings using objective methods. Whether a participant was in the active disease period could have been erroneous in some patients.

Conclusions

In summary, our study revealed a correlation between heightened dietary histamine intake and an increased frequency of flares in patients with Behçet syndrome. However, biochemical markers such as CRP and ESR were not associated with histamine intake. Nonetheless, limiting the intake of foods that exacerbate symptoms, particularly eggplant, tomatoes, and acidic foods or beverages, during flares may improve quality of life.

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Ethics

Ethics Committee Approval and Informed Consent: Ethics approval for the study was obtained from the Hacettepe University Non-Interventional Clinical Research Ethics Committee (decision no: 2022/06-09, date: 19.10.2021), and all participants provided written informed consent. Since voluntariness was taken as the basis for participation, all the participants signed a voluntary consent form.

Authorship Contributions

Surgical and Medical Practices: H.E., N.E., Concept: H.E., N.E., Design: H.E., N.E., Data Collection or Processing: H.E., N.E., Analysis or Interpretation: H.E., N.E., Literature Search: H.E., N.E., Writing: N.E.

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