

# The assessment of contributing factors to oral ulcer presence in Behçet's disease: Dietary and non-dietary factors

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## Abstract

**Objective:** The aim of this study was to assess the contributing factors for oral ulcer activity in Behçet's disease (BD).

**Methods:** Ninety-two patients with BD (F/M: 42/50, mean age: 38.7±10.02 years) participated in this cross-sectional study. Data regarding disease-related factors, smoking patterns, and self-reported dietary/non-dietary triggering factors for oral ulcer activity were collected by a questionnaire. Treatment protocol was categorized as mild and intensive groups associated with organ involvements.

**Results:** A mild treatment protocol was more common in females (52.4% vs 20%) than in males (p=0.002). During the last three months, the number of oral ulcers in female patients was higher in the mild treatment group (6.4±6.5) than in the intensive treatment group (3.3±4.9) (p=0.045). In patients with active oral ulcers (n=63), rate of being a non-smoker was also higher in females (86.7% vs 63.6%) than in males. Daily frequency of tooth brushing was 1.2±0.8 in patients with BD, and was higher in females (1.5±0.9 vs 0.9±0.6) (p=0.001). Stress and fatigue (78.3%) were reported as the most frequent triggering factors for oral ulcer presence in patients with BD. A total of 148 different dietary factors associated with oral ulcer presence were reported in the study.

**Conclusion:** A mild treatment protocol and being a non-smoker were found to be the contributing factors associated with oral ulcer activity in patients with BD. Being motivated for oral hygiene and being non-smokers were positive health behaviors observed in females. Irrespective of gender, stress and fatigue were defined as the most common self-reported triggering factors for oral ulcer presence in BD. In addition, the roles of some dietary factors were also reported.

**Keywords:** Behçet's disease, oral ulcer, smoking and diet



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## Introduction

Behçet's disease (BD), first described by Turkish dermatologist Dr. Hulusi Behçet in 1937, is a multi-systemic, chronic inflammatory disorder characterized by mucocutaneous, ocular, vascular, musculoskeletal, and neurological involvement (1, 2). Several auto-inflammatory features such as recurrent self-limited symptoms, notable host predisposition, and an abnormal inflammatory process have been described for BD course (1, 3, 4). A close relationship between the oral environment and disease course is present, and oral microbial infectious foci have been implicated in the etiopathogenesis of BD (5-9). Nowadays a diverse microbial pattern has also been observed in some microbiome studies (8, 10, 11).

Oral ulcer (OU), a keystone for the diagnosis of the disease, is usually the initial symptom in most patients, and is a critical component for the evaluation of the disease activity and treatment response in clinical practice (12). Since oral ulcers negatively affect the daily life of patients, poor oral health related quality of life commonly observed (13-15). Even though several treatment choices are present, the prognosis and the outcomes are still not satisfactory for mucocutaneous involvement in BD (16, 17).

Some environmental factors such as mechanical factors, smoking patterns, and fatigue may affect the presence of oral ulcers (18). Some foods with acidic, salty, spicy, and hard nutrients might also easily irritate oral mucosa to form oral ulcers (19-21). However, the studies investigating these factors are still limited, and the aim of this study was to assess the contributing factors for oral ulcer presence in BD.

## Methods

In this cross-sectional study, 92 patients with BD (F/M:42/50, mean age: 37.8±10.02 years), diagnosed according to the International Study Group criteria (22) and followed in the Behçet's disease Clinic of Marmara University Hospital in Istanbul, were included. Face-to-face interview method based on a structured questionnaire was used to collect data. Two researchers (MI and EO) who were not involved in the clinical assessment of the patients collected data in BD outpatient clinics.

Disease-related factors and self-reported dietary/non-dietary triggering factors for oral ulcer activity were included in the questionnaire. The questions regarding dietary and non-dietary factors were based on a similar previous study (18). In addition, oral-health-related questions regarding the oral hygiene application and the last dental visit pattern were also added into the questionnaire. If patients could not answer questions regarding oral-ulcer-related factors, they were excluded from the study.

The study was performed according to the principles of the Declaration of Helsinki and was approved by the Ethical Committee of Marmara University School of Medicine (09.2016.474). Informed consent was taken from all patients.

## Statistical analysis

Data were analyzed by using Statistical Package for Social Sciences (SPSS) version 16.0 (SPSS Inc.; Chicago, IL, USA). Mann-Whitney U test was used as the data were not normally distributed. However, categorical variables were compared with Chi-square test. A p value less than 0.05 was considered significant.

## Results

Clinical manifestations of patients with BD were oral ulcers (n=92, 100%), genital ulcers (n=76, 82.6%), and cutaneous (n=58, 63.04%), musculoskeletal (n=30, 32.6%), ocular (n=33, 35.9%), vascular (n=36, 39.1%), neurological (n=9, 9.8%), and gastrointestinal (n=3, 3.3%) involvement. The mean duration of disease was 7.8±4.5 years. In the study group, majority of patients had low income (≤440\$, n=71, 77.2%) and poor educational levels (7.8±4.5 years).

The patients with BD were treated with either mild treatment protocols such as colchicine (1-1.5 mg/day), non-steroidal anti-inflammatory drugs and salazopyrine (n=32), or more intensive protocols such as immunosuppressive (IS) medications, interferon-α and anti-TNF-α antibodies (n=60). Male patients received more intensive treatment (n=40, 80%) than

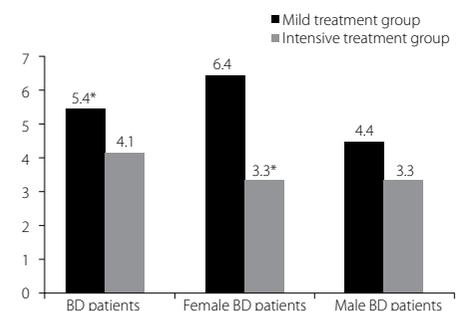
what females received (n=20, 47.6%) (p=0.002) (Table 1).

Age of oral ulcer onset was observed to be 23.2±6.19 years in patients with BD. Majority of the group (n=63, 68.5%) had active oral ulcers during the last three months. The mean number of oral ulcers was 6.6±7.7 in patients with active oral ulcers. The number of oral ulcers during the last three months were lower in the intensive treatment group (4.1±7.6) than in the mild one (5.4±5.8) (p=0.048). This difference was significant only in females (mild protocol: 6.4±6.5 vs intensive protocol: 3.3±4.9, p=0.045), whereas no significant difference was observed in males (mild: 4.4±8.6 vs intensive: 3.3±4.01, p=0.93) (Figure 1). Females reported that their oral health was more influenced by oral ulcers compared to males (64.3% vs 40%, p=0.033). In addition, majority of patients (n=73, 79.3%) defined oral ulcers as "discomforting" in both genders (females: n=36, 85.7% and males: n=37, 74%).

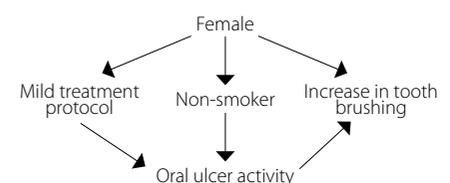
Smoking habits of the group were categorized as current smokers (n=29, 31.5%) and non-smokers such as past smokers/never smokers (n=63, 68.5%). In patients with active oral ulcers, the current smoker rate was lower in females (13.3%) as compared to in males (36.4%) (Table 1). Daily frequency of tooth brushing was 1.2±0.8 in patients with BD. It was higher in females (1.5±0.9) than in males (0.9±0.6) regardless of whether oral ulcer was present (female: 1.4±0.7, male: 0.9±0.6) or not (female: 1.6±1.3, male: 0.7±0.5) (p=0.001; p=0.019 p=0.02 respectively) (Table 1).

**Table 1.** Oral ulcer activity related factors according to gender

	Male	Female	
	n (%)	n (%)	p
<b>Treatment modalities</b>			
Colchicine, NSAID, Salazopyrine, Dapsone	10 (20)	22 (52.4)	0.002
Immunosuppressives, Interferon, Anti-TNF-α antibodies	40 (80)	20 (47.6)	
Total	50 (100)	42 (100)	
<b>Smoking pattern in patients with active oral ulcers</b>			
Current smokers	12 (36.4)	4 (13.3)	
Non-smokers (past smokers/never smokers)	21 (63.6)	26 (86.7)	
Total	33 (100)	30 (100)	
	Mean±SD	Mean±SD	
Duration to last dental visit (years)	1.4±1.4	1.5±1.6	0.80
Age of oral ulcer onset	23.1±6.1	23.7±7.6	0.21
Frequency of tooth brushing	0.9±0.6	1.5±0.9	0.001
Tooth brushing frequency per day in patients without oral ulcers during last three months	0.7±0.5	1.6±1.3	0.02
Tooth brushing frequency per day in patients with oral ulcer during last three months	0.9±0.6	1.4±0.7	0.019
Tooth brushing frequency per day in current smoker patients	0.9±0.7	1.4±0.8	0.056
Tooth brushing frequency per day in non-smoker patients	0.9±0.6	1.5±0.9	0.007



**Figure 1.** Number of oral ulcers in patients with Behçet's disease during the last three months \*p=0.048; \*\*p=0.045



**Figure 2.** The contributing factors for oral ulcer activity in female patients

**Table 2.** Self-reported triggering events and foods for oral ulcer activity in patients with Behçet's disease

Triggering events	Yes (sure/probably)	No	Not known/No response
	n (%)	n (%)	n (%)
Stress and fatigue or distress	72 (78.3)	9 (9.8)	11 (11.9)
Dental treatment	16 (17.4)	52 (56.5)	24 (26.1)
Tooth brushing	13 (14.1)	66 (71.8)	13 (14.1)
Infection	29 (31.5)	43 (46.8)	20 (21.7)
Menstrual period	10 (10.9)	14 (15.2)	68 (73.9)
<b>Triggering Foods</b>			
Salty foods	10 (10.9)	59 (64.1)	23 (25)
Sweet foods	6 (6.5)	70 (76.1)	16 (17.4)
Bitter foods	12 (13.1)	57 (61.9)	23 (25)
Sour foods	11 (11.9)	64 (69.6)	17 (18.5)
Spicy foods	11 (11.9)	60 (65.2)	21 (22.8)
Astringent foods	5 (5.4)	66 (71.7)	21 (22.8)
Hard foods	10 (10.8)	66 (71.7)	16 (17.4)
Hot foods	7 (7.6)	75 (81.5)	10 (10.9)
Cold foods	1 (1.1)	72 (78.3)	19 (20.6)
Eating quickly	7 (7.6)	61 (66.3)	24 (26.1)

**Table 3.** Food items associated with oral ulcer relapses

Foods	n (%)
Eggplant	13 (8.8)
Walnut	8 (5.4)
Sodas	7 (4.7)
Tomato	7 (4.7)
Hot pepper	5 (3.4)
Spices	5 (3.4)
Sunflower seeds	5 (3.4)
Peanut	4 (2.7)
Almond	3 (2)
Chocolate	3 (2)
Mandarin	3 (2)
Zucchini	3 (2)

Duration to last dental visit was found to be  $1.4 \pm 1.5$  years ago in the whole group. Dental routine check-up (n=10, 10.9%) was observed to be very limited. Among dental treatments, tooth extraction was the most common treatment option in the group (n=28, 30.4%). In females, having a mild treatment protocol and being non-smokers were contributing factors for oral ulcer presence. However, in the presence of oral ulcer, they were more motivated for oral hygiene application (Figure 2).

#### Triggering and dietary factors in patients with BD

Major self-reported triggering events were stress/fatigue or distress (n=72 (F/M: 36/36); 78.3%), dental treatments (n=16, 17.4%), tooth brushing (n=13, 14.1%), infection (n=29 (F/M: 15/14); 31.5%), and menstrual periods (n=10, 10.9%) in the group (Table 2).

When dietary habits were examined, consumption of home-cooked meals (n=81, 88%) was observed to be common. Self-reported triggering foods were observed to be very diverse in the patient group. These were bitter (n=12, 13.1%), sour and spicy (n=11, 11.9%), and salty and hard foods (n=10, 10.9%) (Table 2). The relationships between food items and oral ulcer occurrence were reported by 44.6% of the group (n=41). A total of 148 different dietary factors related to oral ulcer presence were observed (Supplement 1). Among them, eggplant (8.8%), walnut (5.4%), sodas (4.7%), tomato (4.7%), hot pepper (3.4%), spices (3.4%), sunflowers (3.4%), peanut (2.7%), almond (2%), chocolate (2%), mandarin (2%), and zucchini (2%) were most frequently associated by patients with oral ulcer presence (Table 3).

#### Discussion

In this study, major contributing factors to oral ulcer presence were investigated in BD. In clinical practice, oral ulcers are the major component of disease activity in patients with BD, with up

to 60% reporting OUs in the last month during regular follow-up (12). In our study, the number of OU during the last three months was higher in patients who received mild therapies compared to in those who were treated with more intensive treatment choices. A less severe treatment protocol was especially associated with oral ulcer activity in female gender, explained by a milder disease course in them (17, 23). Interestingly, the frequency of tooth brushing was also observed to be higher in females. This suggests that females are better motivated for tooth brushing to improve oral health although oral ulcers limit oral hygiene applications (24, 25). Since microbial plaque accumulation due to irregular oral hygiene habits is a risk factor for severe disease course (24), regular oral hygiene is necessary to improve oral health to suppress oral microbial factors in disease pathogenesis (24-27).

Topical treatments such as mouth rinses, pastes, gels and sprays reduce oral-ulcer-related pain and functional limitation, and improve healing process of oral ulcers (15, 21, 28-30) and almost one third of patients received topical medications. This topical approach is given to over the half of the patients in a similar study from France (18). In our patients, colchicine is the first option for the mild mucocutaneous involvement. However, it has limited effects on the elimination of oral ulcers, whereas intensive treatment protocols, used in major organ disease such as ocular or vascular involvement, suppress OUs much better (31).

Several studies have noted the protective effect of smoking on oral ulcer presence in BD and recurrent aphthous stomatitis (32, 33). In this study, being a non-smoker was associated with oral ulcer presence mostly in females. Smoking has possible beneficial effects on recurrent oral ulcers (34), which is attributed to enhanced epithelial proliferation of oral mucosa and systemic inhibitory effects of nicotine on immune system (34, 35).

Among dietary habits, home-cooked meals were commonly reported by the study group, which is possibly related to the low socio-economic conditions and cultural factors. Among environmental factors, some foods with acidic, salty, spicy, and hard nutrients could easily irritate oral mucosa to form oral ulcers in patients with BD (19-21). Therefore, having soft diet and avoidance of irritating foods are critical points during the oral ulcer activity (21, 26).

Stress and fatigue were the most reported factors for oral ulcer presence in patients with BD. Stress is considered as a triggering event in 40% of the patients in the similar study from France. In addition, fatigue (35%) and foods (35%) were other triggering factors in French patients (18).

Similarly, stress is reported to be associated with oral ulcer activity in patients with recurrent aphthous stomatitis (30). Food items such as eggplant, walnut, sodas, tomato, hot pepper, spices, sunflowers, peanut, almond, and zucchini were associated with oral ulcer relapses by our patients. However, different food groups such as nuts, pineapple, citrus fruits, cheeses, strawberries, tomato, spices, banana, dried fruits, and kiwi are reported in French patients with BD (18). Only tomato and spices were similar food items in both the patient groups. Diversities in cultural factors and socio-economic properties may explain the differences in dietary habits between the two countries. Trauma due to mechanical irritation may explain some dietary factors, however, some common elements such as "histamine", may also explain the role of some of the triggering factors in OU etiopathogenesis (18).

The study had some limitations because self-reported triggering factors could be affected by socio-economic conditions, cultural factors, and gender. Since patients with BD from a single institution participated, results cannot be generalized to reflect factors affecting oral ulcer activity. Moreover, self-reported nature of data was the other limitation factor. Therefore, the results must be evaluated within the limits of the study. As a conclusion, a mild treatment protocol and being a non-smoker were contributing factors associated with oral ulcer activity, whereas being non-smoker and motivated for oral hygiene were positive health behaviors in females. Stress/fatigue or distress were defined as the most common self-reported triggering factors for oral ulcer occurrence in patients with BD without a gender difference. There is a wide variety of different food items reported by patients with BD as triggering factors for oral ulcer presence, and it need to be better explored.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Ethical Committee of Marmara University School of Medicine (09.2016.474).

**Informed Consent:** Written informed consent was obtained from the patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - T.E., H.D., G.M.; Design - T.E., H.D., G.M.; Supervision - G.M.; Materials - A.A.; Data Collection and/or Processing - M.I., E.Ö., A.A., F.A.Ö., N.I.; Analysis and/or Interpretation - F.A.Ö., N.I., T.E., H.D., G.M.; Writing Manuscript - N.I., T.E., H.D., G.M.; Critical Review - T.E., H.D., G.M.

**Conflict of Interest:** The authors have no conflict of interest to declare.

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**Supplement 1.** Distributions of Food Items Associated with Oral Ulcer Relapses

	n (%)
Eggplant	13 (8.8%)
Walnut	8 (5.4%)
Soda	7 (4.7%)
Tomato	7 (4.7%)
Hot pepper	5 (3.4%)
Spicy foods	5 (3.4%)
Sunflower seeds	5 (3.4%)
Peanut	4 (2.7%)
Almond	3 (2.0%)
Zucchini	3 (2.0%)
Chocolate	3 (2.0%)
Tangerine	3 (2.0%)
Egg	2 (1.4%)
Tea	2 (1.4%)
Coffee	2 (1.4%)
Orange	2 (1.4%)
Strawberry	2 (1.4%)
Chewing gum	2 (1.4%)
Fried foods	2 (1.4%)
Nuts	2 (1.4%)
Pickles	2 (1.4%)
Apple	2 (1.4%)
Melon	2 (1.4%)
Tomato paste	2 (1.4%)
Desserts	2 (1.4%)
Milk	1 (0.7%)
Alcohol	1 (0.7%)
Spinach	1 (0.7%)
Leek	1 (0.7%)
Lemon	1 (0.7%)
Fig	1 (0.7%)
Pepper	1 (0.7%)
Dried beans	1 (0.7%)
Chips	1 (0.7%)
Hard foods	1 (0.7%)
Cherry	1 (0.7%)
Nut	1 (0.7%)
No specific food	44 (29.7%)
Total	148 (100%)