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Oral health is impaired in Behçet's disease and is associated with disease severity

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***Objectives*. This study aimed to investigate the oral health of Turkish patients with Behçet's disease (BD) and whether it is associated with the disease course.**
***Methods*. One hundred and twenty patients with BD, 35 patients with recurrent aphthous stomatitis (RAS) and 65 healthy Turkish controls (HC) were included in the study. Oral health was investigated by indices applied in a BD out-patient clinic.**
***Results*. The mean scores of plaque, sulcus bleeding and gingival indices, probing depth and the number of extracted teeth were observed to be higher in patients with BD and RAS compared to HC ($P < 0.05$). In the linear regression analysis, plaque index score was associated with the presence of oral ulcers and male gender. An elevated plaque index score was observed to be a significant risk factor for increased severity score in patients with BD in the logistic regression analysis ($P = 0.034$).**
***Conclusions*. Oral health is impaired in BD and associated with disease severity. Improvement of the oral health of BD patients may affect their disease course, leading to a better prognosis.**

KEY WORDS: Oral ulceration, Oral health, Behçet's disease, Severity score.

Behçet's disease (BD) is a multisystemic disorder characterized by oral and genital ulcers and cutaneous (erythema nodosum, pustular vasculitis), ocular (anterior or posterior uveitis), arthritic, vascular (both arterial and venous vasculitis), central nervous system (meningoencephalitis) and gastrointestinal involvement [1–4]. BD is commonly seen around the Mediterranean Sea and along the ancient 'Silk Road' in places such as Turkey, Iran, Korea and Japan. The prevalence of the disease is reported to be 1:250 to 1:1000 in Turkey and 0.1:100 000 to 0.6:100 000 in the USA and northern Europe [2].

Both genetic and microbial (viral and streptococcal) factors are implicated in the aetiopathogenesis of BD [2, 5–7]. HLA-B51, although not completely responsible for the genetic load, is still the main possible genetic factor in BD [3, 5]. Various clinical and basic data also strongly point to an infectious triggering agent, such as *Streptococcus sanguis* in the pathogenesis of BD [6–9]. As BD starts mostly from the oral mucosal surfaces (oral aphthae being the first manifestation in 70% of patients), oral microbial flora have long been implicated in the pathogenesis [10]. The relationship between streptococcal infections and BD can also explain the clinical observations such as increased oral manifestations after dental treatments, hypersensitivity to streptococcal skin tests, elevated pro-inflammatory cytokine responses to streptococcal antigens [7–13] and recent reports of beneficial antibacterial therapy [14, 15]. Severe organ involvement and an impaired prognosis is described mainly in young male patients, suggesting that gender also as a risk factor [16, 17].

Recurrent painful oral ulceration in the mouth is a major restriction upon regular oral hygiene habits [18]. In patients with BD, poor oral health, poor prognosis for the natural dentition, increased number of extracted teeth due to multiple carious lesions and changes in oral pH have been previously reported [18–21]. However, the relationship between oral health and the clinical course of BD is insufficiently explored. With this background, this study aimed to investigate the oral health of patients with BD and its relationship to the clinical manifestations, severity of disease and gender.

Materials and methods

Patients and controls

In this study, 120 BD patients [female:male (F:M) 55:65, mean age 33.2 ± 10.5 yr] diagnosed according to the International Study Group for Behçet's Disease (ISG) criteria [22] and followed in the Behçet's disease clinics of the Marmara and Cerrahpasa Medical Schools in Istanbul were investigated. Thirty-five age-matched patients with recurrent aphthous stomatitis (RAS) (F:M 16:19, mean age 34.3 ± 10.6 yr) and 65 healthy Turkish controls (HC) (F:M 33:32, mean age 33.4 ± 8.7 yr) were also included.

The control group was selected randomly from healthy people who accompanied BD and RAS patients attending Behçet's disease out-patient clinics. Having no symptoms of any disorder and being no member or close relative of patient's family were the inclusion criteria for the control group. Healthy controls were matched with regard to age and socio-economic status, but not gender. Matching of the controls with regard to gender was not done due to the limited number of eligible controls. However, the confounding effect of gender was analysed later by multivariate analysis to minimize selection bias.

Active clinical manifestations of BD patients were as follows: oral ulcers (76.6%), genital ulcers (72.5%) and cutaneous (70.8%), arthritic (53.3%), ocular (25%), vascular (21.6%), neurological (2.5%) and gastrointestinal involvement (0.8%). A positive pathergy reaction was observed in 70% of patients.

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Seventy-one of the patients, mainly with active mucocutaneous involvement, were treated by colchicine (1–2 mg/day) whereas 39 patients used an immunosuppressive agent such as cyclosporin A, azathioprine and corticosteroids for extracutaneous manifestations of arthritic ($n=20$), vascular ($n=16$), ocular ($n=22$), neurological ($n=3$) and gastrointestinal ($n=1$) involvement. Ten newly diagnosed patients were not under any treatment. Topical steroids and antimicrobial agents were chosen for oral ulcers in patients with RAS.

In BD patients, the total clinical severity score was determined as previously described [23]. This score was calculated as the sum of 1 point each for mild symptoms (oral aphthosis, genital ulcers, arthralgia and typical skin lesions such as erythema nodosum, papulopustular lesions and folliculitis), 2 points each for moderate symptoms (arthritis, deep vein thrombosis of the legs, anterior uveitis and gastrointestinal involvement) and 3 points each for severe disease manifestations (posterior/panuveitis, retinal vasculitis, arterial thrombosis, neuro-Behçet's and bowel perforation). The mean severity score in the whole group was 5.2 ± 2.2. Patients were categorized according to the disease severity score as follows: severe group, ≥7 points ($n=34$); moderate group, a score between 4 and 6 points ($n=42$); mild group, <4 points ($n=44$). Patients were also grouped according to the presence of active oral ulcerations ($n=92$).

Patients recorded the follow chart that included the number and the healing time of oral and genital ulcerations and erythema nodosum per month between 3-monthly clinical examinations. The study was performed according to the principles of the Declaration of Helsinki and was approved by the Ethical Committee of Marmara University Medical School. Informed consent was obtained from the patients.

Oral health

The same dentist (GM) examined the dental and periodontal status of the patients and controls in BD out-patient clinics. Both clinical manifestations and the oral health of patients with BD were evaluated at each visit. The plaque index assesses the thickness of plaque at the gingival area [24, 25], the gingival index evaluates the severity of gingivitis [25, 26], the sulcus bleeding index records the presence of initial inflammatory gingival disease [27], probing depth assesses the state of periodontal health and the decayed/missing/filled/teeth (DMFT) score determines the total dental caries experience. The number of extracted teeth and carious teeth were also recorded. Recordings included all the teeth except third molars [28].

Statistical analysis

Analysis of variance (ANOVA), the Tukey *post hoc* test, the unpaired *t*-test, Kruskal–Wallis, the Mann–Whitney U-test, multiple regression analysis and logistic regression analysis were used. A *P*-value of less than 0.05 is accepted to be significant. In logistic regression analysis being male, having moderate and severe BD symptoms (severity score ≥4), treatment with immunosuppressive drugs and having active oral ulceration were coded as 1, whereas being female, having mild BD symptoms (severity score <4), treatment with colchicine, having no active oral ulceration and having no medication regularly were coded as 0.

Results

Oral health in the study groups

The mean scores of plaque, sulcus bleeding, gingival indices and probing depth were found to be significantly higher in patients with BD and RAS compared with HC ($P<0.05$, Table 1). However, no statistically significant difference was observed between BD and RAS in any of the indices. Similarly, the number of extracted teeth was significantly higher in BD (3.6 ± 5.2) and RAS (3.7 ± 4.5) compared with HC (0.8 ± 1.5) ($P<0.003$ and $P=0.021$ respectively), also without a significant difference between BD and RAS (Table 1).

The DMFT score was observed to be similar in the three study groups [BD, 7.2 ± 5.9; RAS, 6.6 ± 4.5; HC, 6.6 ± 4.9: $P=$ not significant (NS)]. No significant difference was found in the number of carious teeth among the three groups. The number of oral ulcers per month, healing time of ulcers and disease duration were also not significantly different between BD (6.5 ± 6.9, 8.9 ± 3.7 days and 8.8 ± 7.5 yr respectively) and RAS patients (5.3 ± 4.9, 9.7 ± 4.1 days and 9.3 ± 6.9 yr respectively) ($P=$NS). The daily frequency of tooth brushing was similar in patients with BD and RAS (1.1 ± 0.8 and 1.1 ± 0.7 respectively, $P=$NS) but was higher in HC (1.5 ± 0.7) compared with BD ($P=0.007$ and $P=0.01$ respectively) (Table 1). None of the patients and controls used dental floss regularly. The mean number of cigarettes consumed was higher in HC ($n=16$, 15.2 ± 12.2/day) than in BD ($n=29$, 3.3 ± 6.5/day) and RAS ($n=7$, 0.5 ± 1.3/day) ($P<0.0001$).

Oral health and gender

The mean severity score in the whole group was 5.2 ± 2.2. Patients were categorized according to the disease severity score as follows: severe group, ≥7 points ($n=34$, F:M 9:25); moderate group, a score between 4 and 6 points ($n=42$, F:M 24:18); mild group, <4 points ($n=44$, F:M 22:22). The mean severity score was 3.04 ± 0.2 in the mild group, 5.02 ± 0.4 in the moderate group and 8.4 ± 1.2 in the severe group.

Total clinical severity scores were higher in males (5.6 ± 2.5) than females (4.7 ± 1.9) ($P=0.018$). All scores of periodontal

Table 1. Oral health of patients with Behçet's disease, recurrent aphthous stomatitis and healthy controls

	Behçet's disease ($n=120$) Mean ± SD	Recurrent aphthous stomatitis ($n=35$) Mean ± SD	Healthy controls ($n=65$) Mean ± SD	*P*
Plaque index	1.9 ± 1.02	1.9 ± 1.2	1.2 ± 1.1	0.000*
Gingival index	2.1 ± 1.1	2.1 ± 1.2	1.3 ± 1.2	0.014*
Sulcus bleeding index	1.9 ± 1.03	2.0 ± 1.2	1.3 ± 1.3	0.002*
Probing depth (mm)	2.7 ± 1.03	2.8 ± 1.1	2.1 ± 1.2	0.046*
DMFT	7.2 ± 5.9	6.6 ± 4.5	6.6 ± 4.9	0.773
Number of extracted teeth	3.6 ± 5.2	3.7 ± 4.5	0.8 ± 1.5	0.000*
Number of carious teeth	2.6 ± 2.4	1.9 ± 2.1	2.8 ± 2.5	0.626
Tooth brushing (number/day)	1.1 ± 0.8	1.1 ± 0.7	1.5 ± 0.7	0.004*
Cigarette consumption (number/day)	3.3 ± 6.5	0.5 ± 1.3	15.2 ± 12.2	0.000*

*Statistically significant.

TABLE 2. Oral health and related factors in patients and controls according to gender

	Behçet's disease			Recurrent aphthous stomatitis			Healthy controls		
	Male ($n=65$) Mean ± SD	Female ($n=55$) Mean ± SD	*P*	Male ($n=16$) Mean ± SD	Female ($n=19$) Mean ± SD	*P*	Male ($n=32$) Mean ± SD	Female ($n=33$) Mean ± SD	*P*
Plaque index	2.2 ± 0.9	1.7 ± 1.01	0.007*	2.1 ± 1.2	1.3 ± 0.8	0.031*	1.2 ± 1.2	1.0 ± 1.02	0.36
Gingival index	2.3 ± 0.8	1.9 ± 1.2	0.045*	2.5 ± 0.8	1.6 ± 1.3	0.025*	1.8 ± 1.3	1.2 ± 1.1	0.09
Sulcus bleeding index	2.2 ± 0.8	1.8 ± 1.1	0.045*	2.5 ± 0.9	1.5 ± 1.2	0.0093*	1.5 ± 1.4	1.0 ± 1.2	0.13
Probing depth (mm)	3.1 ± 0.8	2.5 ± 0.9	0.005*	3.4 ± 0.6	2.3 ± 1.1	0.003*	2.6 ± 0.9	2.1 ± 1.1	0.09
DMFT	7.01 ± 5.1	7.1 ± 6.1	0.949	8.1 ± 7.5	7.7 ± 4.5	0.683	5.6 ± 5.4	6.4 ± 3.7	0.51
Extracted teeth	3.6 ± 4.3	3.6 ± 5.6	0.347	5.3 ± 7.3	4.7 ± 4.8	0.806	1.6 ± 2.3	1.0 ± 1.6	0.20
Carious teeth	2.5 ± 2.2	2.3 ± 2.4	0.613	0.9 ± 1.3	3.1 ± 2.2	0.002*	1.8 ± 2.1	2.9 ± 2.8	0.14
Oral ulcers (number/month)	5.7 ± 6.1	7.4 ± 7.6	0.198	6.01 ± 5.9	4.7 ± 3.8	0.473	–	–	–
Healing time (days)	8.9 ± 3.9	9.04 ± 3.5	0.852	9.7 ± 4.4	9.9 ± 4.02	0.886	–	–	–
Disease duration (yr)	6.1 ± 4.6	12.01 ± 8.9	0.000*	11.3 ± 8.7	7.5 ± 4.3	0.201	–	–	–
Tooth brushing (number/day)	1.1 ± 0.9	1.1 ± 0.8	0.875	0.6 ± 0.7	1.4 ± 0.8	0.003*	1.4 ± 0.7	1.7 ± 0.5	0.025*
Cigarette consumption (number/day)	6.2 ± 8.2	1.6 ± 3.1	0.021*	0 ± 0	0.4 ± 1.2	–	11.1 ± 12.0	12.5 ± 11.3	0.758

*Statistically significant.

TABLE 3. Oral health and disease-related factors according to the presence (+) or absence (−) of oral ulcerations and the severity of BD symptoms

	Oral ulcer (+) ($n=92$) Mean ± SD	Oral ulcer (−) ($n=28$) Mean ± SD	*P*	Severe ($n=34$) Mean ± SD	Moderate ($n=42$) Mean ± SD	Mild ($n=44$) Mean ± SD	*P*
Plaque index	2.2 ± 0.9	1.2 ± 0.9	0.000*	2.4 ± 0.7	2.1 ± 0.9	1.5 ± 1.03	0.000*
Gingival index	2.4 ± 0.9	1.5 ± 1.01	0.000*	2.6 ± 0.6	2.3 ± 1.1	1.7 ± 1.1	0.001*
Sulcus bleeding index	2.2 ± 0.9	1.4 ± 1.1	0.001*	2.6 ± 0.7	2.1 ± 0.9	1.6 ± 1.04	0.000*
Probing depth (mm)	3.1 ± 0.8	2.1 ± 0.8	0.000*	3.4 ± 0.7	2.9 ± 1.01	2.4 ± 0.9	0.000*
DMFT	6.9 ± 5.02	7.2 ± 7.1	0.566	6.5 ± 4.1	7.6 ± 6.03	6.9 ± 6.04	0.536
Number of extracted teeth	3.7 ± 4.9	3.2 ± 4.9	0.246	4.1 ± 4.4	4.1 ± 5.7	2.9 ± 4.6	0.423
Number of carious teeth	2.6 ± 2.3	1.9 ± 2.1	0.176	2.03 ± 2.1	2.5 ± 2.5	2.6 ± 2.1	0.540
Oral ulcers (number/month)	6.3 ± 6.7	–	–	3.7 ± 5.1	9.4 ± 8.1	6.1 ± 6.1	0.004
Healing time of oral ulcers (days)	8.7 ± 3.5	–	–	8.6 ± 3.1	9.3 ± 4.1	8.8 ± 3.8	0.637
Disease duration (yr)	9.1 ± 7.3	8.1 ± 8.1	0.591	6.9 ± 5.4	10.5 ± 8.6	9.02 ± 7.9	0.171
Tooth brushing/day	1.1 ± 0.9	1.1 ± 0.7	0.877	0.8 ± 0.8	1.2 ± 1.01	1.2 ± 0.7	0.186
Cigarette consumption/day	5.1 ± 7.6	1.6 ± 4.7	0.033*	7.3 ± 8.5	2.1 ± 4.7	2.7 ± 6.3	0.013*

*Statistically significant.

indices were also higher in male patients ($P<0.05$) (Table 2). However, females had a longer disease duration than males (12.01 ± 8.9 *vs* 6.1 ± 4.6 yr, $P<0.0001$). The healing time of oral ulcerations was similar in both groups (females 9.04 ± 3.5 days *vs* males 8.9 ± 3.9 days, P = NS). No significant difference was found in DMFT scores (7.01 ± 5.1 in males and 7.1 ± 6.1 in females), the numbers of extracted teeth (3.6 ± 4.3 and 3.6 ± 5.6 respectively) or carious teeth (2.5 ± 2.2 and 2.3 ± 2.4 respectively) according to gender. The daily frequency of tooth brushing and the number of oral ulcerations per month were also similar (females 1.1 ± 0.8 and 7.4 ± 7.6 respectively and males 1.1 ± 0.9 and 5.7 ± 6.1 respectively, P = NS). The mean cigarette consumption was 1.6 ± 3.1 in females ($n=9$) and 6.2 ± 8.6 in males ($n=20$) ($P=0.021$) (Table 2).

In patients with recurrent aphthous stomatitis, all periodontal indices were also higher in male patients compared with females ($P<0.05$). The DMFT score and the number of extracted teeth were similar in females (7.7 ± 4.5 and 4.7 ± 4.8 respectively) and males (8.1 ± 7.5 and 5.3 ± 7.3 respectively, $P=0.08$ and $P=0.77$), but the number of carious teeth and the frequency of tooth brushing were higher in females (3.1 ± 2.2 and 1.4 ± 0.8 respectively) than males (0.9 ± 1.3 and 0.6 ± 0.7 respectively) ($P=0.002$ and $P=0.05$ respectively) (Table 2).

In healthy controls, although a trend for increased scores of all periodontal indices was observed in males, no significant difference was observed according to gender. Besides, the frequency of tooth brushing was higher in females (1.7 ± 0.5) compared with males (1.4 ± 0.7) ($P=0.025$) (Table 2).

The analyses were also performed according to gender in BD. Accordingly, number of extracted teeth, scores of plaque, gingival and sulcus bleeding indices and pocket depth were higher in male patients with BD and RAS compared with HC. In female BD patients, the number of extracted teeth and scores of plaque, gingival and sulcus bleeding indices were significantly higher compared with HC ($P<0.05$). Although pocket depth was lower in female HC than BD patients, the difference did not reveal statistical significance ($P=0.06$). The number of extracted teeth was the only parameter that showed a statistically significant difference between female patients with RAS and HC ($P=0.008$). In each gender, scores of dental and periodontal indices were similar in patients with BD and RAS ($P>0.05$).

Oral health and clinical course

Scores of periodontal indices were higher in patients having active oral ulcers than in patients without ulcers (Table 3). Scores of all periodontal indices were significantly higher in patients with severe and moderate BD symptoms compared with milder ones ($P<0.05$). Although the scores tend to increase in patients with severe symptoms than in those with moderate ones, no significant differences were found between these two groups.

TABLE 4. Logistic regression analysis for increased severity score ϕ in BD

	B	S.E.	*P*	OR	95.0% C.I. for OR Lower–upper
Plaque index score	0.838	0.395	0.034*	2.311	1.065–5.012
Probing depth (mm)	0.430	0.383	0.261	1.537	0.726–3.255
Gender (male)	0.912	0.604	0.131	2.489	0.763–8.123
Number of oral ulcers (month)	−0.022	0.036	0.536	0.978	0.912–1.049
Disease duration (yr)	−0.013	0.036	0.726	0.987	0.919–1.060
Constant	−3.054	1.213	0.013	0.047	

ϕ: Increased severity score = 1 (severity score ≥4), severity score < 4 = 0.
B, the partial regression coefficient for each variable in the regression equation.
*Statistically significant.

The number of oral ulcers per month was higher in patients with moderate symptoms (9.4 ± 8.1) than patients with severe symptoms (3.7 ± 5.1) ($P = 0.0003$). Another difference was cigarette consumption, which was higher in patients with severe symptoms ($n = 14$, 7.3 ± 8.5) compared with moderates ($n = 7$, 2.1 ± 4.7) ($P = 0.037$) and milder ones ($n = 8$, 2.7 ± 6.3) ($P = 0.04$) (Table 3).

The results of logistic regression analysis of the factors affecting the severity score of BD patients are presented in Table 4. Dental and periodontal indices, oral ulcers and related factors were included in the logistic regression analysis. An elevated plaque index was found to be a significant risk factor for higher severity scores in BD ($P = 0.034$).

The analysis was also performed according to gender in BD. Scores of periodontal indices were observed to be significantly higher in male patients with active oral ulcers than in ulcer-free patients. These scores were lower in patients with mild symptoms than in patients with severe or moderate symptoms ($P < 0.05$). In the second step, predictive factors were analysed for the increased severity score in each gender. Probing depth in males [odds ratio (OR) = 4.05, $P = 0.04$] and score of plaque index in females (OR = 6.07 $P = 0.04$) were found to be the risk factors for the increased severity score in BD. An increased risk associated with plaque index was also observed (OR = 1.8) in male BD patients, without reaching statistical significance.

Active oral ulcers, male gender and lack of tooth brushing were included in linear regression analysis for factors affecting plaque index scores. Male gender and the presence of active oral ulcers were observed to be significant risk factors for increases in plaque index scores in BD ($R^2 = 0.23$, $P = 0.006$ and $P < 0.0001$ respectively). Lack of tooth brushing was the only significant risk factor in patients with RAS ($R^2 = 0.17$, $P = 0.025$) and HC ($R^2 = 0.24$, $P = 0.001$) (Table 5).

Active oral ulcers and lack of tooth brushing were also significant predictive factors for elevated scores of gingival index ($R^2 = 0.22$, $P = 0.002$ and $P = 0.003$ respectively) in BD. Active oral ulcers, lack of tooth brushing and male gender were risk factors for elevated scores of sulcus bleeding index ($R^2 = 0.17$, $P = 0.005$, $P = 0.046$ and $P = 0.037$ respectively). Male gender and active oral ulcers were predictive factors for elevated scores of probing depth ($R^2 = 0.20$, $P = 0.042$ and $P < 0.0001$ respectively). Increase in the number of oral ulcers per month and immunosuppressive treatment ($R^2 = 0.14$, $P = 0.042$ and $P = 0.045$ respectively) were the risk factors for an elevated number of extracted teeth.

In patients with RAS, male gender was a significant predictive factor associated with scores of gingival index ($R^2 = 0.17$, $P = 0.024$), sulcus bleeding index ($R^2 = 0.23$, $P = 0.01$) and probing depth ($R^2 = 0.22$, $P = 0.006$). Lack of tooth brushing was the only risk factor for increases in number of extracted teeth ($R^2 = 0.35$, $P = 0.008$). In healthy controls, lack of tooth brushing was the significant risk factor for elevated scores of gingival index ($R^2 = 0.13$, $P = 0.05$), sulcus bleeding index ($R^2 = 0.41$, $P < 0.0001$), probing depth ($R^2 = 0.10$, $P = 0.025$) and the number of extracted teeth ($R^2 = 0.25$, $P = 0.001$).

Discussion

Systemic disease resulting from infectious oral agents is generally recognized to be present in patients with immunological deficiencies. When individual host defences are compromised, oral microbes are allowed to gain systemic access, but systemic complications of oral microbes are accepted to be confined to a few specific clinical scenarios (bacterial endocarditis etc.). However, several prospective studies have recently demonstrated a significant association between oral infections and atherosclerosis and coronary heart disease [29]. In this context, oral ulcers are an essential component of BD and various studies have implicated the role of immune responses against oral

TABLE 5. Results of linear regression analysis of predictors of plaque index score in patients with BD, RAS and healthy controls

	Unstandardized coefficients		Standardized coefficients		
	B	S.E.	β	*t*	*P*
Behçet's disease[a]					
Gender (male)	0.524	0.187	0.264	2.808	0.006*
Active oral ulcers	0.899	0.216	0.391	4.155	0.000*
Constant	1.991	0.337		5.906	0.000
Recurrent aphthous stomatitis[b]					
Tooth brushing (frequency/day)	−0.534	0.225	−0.416	−2.376	0.025*
Constant	2.162	0.309		7.005	0.000
Healthy controls[c]					
Tooth brushing (frequency/day)	−0.835	0.225	−0.524	−3.718	0.001*
Gender	0.309	0.324	0.134	0.953	0.346
Constant	1.957	0.511		3.826	0.000

B, the partial regression coefficient for each variable in the regression equation.
β, the standardized partial regression coefficient.
*Statistically significant.
[a]Behçet's disease: $n = 120$, $R = 0.48$, $R^2 = 0.23$, adj. $R^2 = 0.21$.
[b]Recurrent aphthous stomatitis: $n = 35$, $R = 0.41$, $R^2 = 0.17$, adj. $R^2 = 0.14$.
[c]Healthy controls: $n = 65$, $R = 0.49$, $R^2 = 0.24$, adj. $R^2 = 0.21$.

streptococci, implicating oral health as an important factor in BD pathogenesis.

Oral health, determined by plaque accumulation, probing depth, gingival inflammation/bleeding and the number of extracted teeth, was observed to be impaired in patients with BD and RAS compared with HC in our study. Elevations in periodontal indices were also associated with active oral ulcerations and a severe to moderate disease course of BD. These results are in accordance with the study of Çelengil-Nazlıel *et al.* [18] who reported higher scores of plaque index, periodontal index, sulcus bleeding index and probing depth in patients with BD compared with healthy controls. Similarly, Nakae *et al.* [20] also observed that the presence of five or more decayed (OR = 11.8) and extracted teeth (OR = 4.1) were higher in BD compared with the healthy Japanese population. In addition to a poor prognosis for natural teeth, multiple carious lesions were also seen [19].

BD and RAS, two closely related disorders, may have similar aetiopathological mechanisms of 'primary' ulcer formation related to immune disturbances in innate or adaptive cellular mechanisms [2, 3]. However, in contrast to RAS, BD has a systemic nature possibly associated with the contributing role of other external or genetic factors. Plaque accumulation is the primary aetiological factor in dental caries and periodontal diseases which are largely preventable by plaque control. Tooth brushing and dental flossing are effective methods for removing plaque and reducing gingival inflammation and probing depth [28]. Since oral ulcers are painful, they limit effective, regular tooth brushing and may then lead to poor oral health in BD and RAS [18]. Similarities in periodontal status and low tooth brushing numbers in BD and RAS in our study may be associated with these poor oral hygiene conditions caused by active oral ulcers. Oral microbial stimuli which are increased due to this impaired oral hygiene may then trigger further oral ulcer formation in these patients [30]. In this context, we further demonstrated the presence of plaque index as a significant risk factor for disease severity score, showing the association between microbial flora and the systemic nature of BD. Supporting our observation, the role of dental manipulations or oral infections as a stimulus for systemic activation of BD has previously been reported [8, 9, 11].

An impaired prognosis of BD is observed in males who have a higher mortality risk associated with an earlier disease onset and vascular involvement [16, 17]. Elevated scores of disease severity and periodontal indices were also observed in males compared with females in our study. According to the results of regression analysis, male gender was a significant risk factor for the parameters of oral health in patients with BD and RAS. Although not reaching significance in every index analysed, a trend towards impaired oral health in male healthy controls also supports the role of gender as an independent risk factor for oral health. It was found that probing depth in males and plaque accumulation in females were the risk factors for the increased severity score in BD. As these factors are markers of infection foci for systemic diseases [28, 29, 31] and periodontal infection promotes systemic inflammatory and immune responses [32], the association between severe clinical course and poor oral health may play a role in the prognosis of patients with BD.

In the severe BD group mostly treated with immunosuppressives, the number of oral ulcers was lower than in moderate and milder groups, possibly due to more effective treatment. The elimination of oral ulcers is fairly important in the promotion of oral health and immunosuppressive agents are one of the most effective types of drug for this purpose. However, as they alter host defences and affect oral health negatively, alternative treatment approaches to immunosuppression should be pursued [28]. Similarly, patients with RAS were treated only with topical steroids and antimicrobial agents in the present study. As elevated healing time of oral ulcers was another risk factor to oral health, alternative treatment protocols eliminating oral ulcers more effectively should also be investigated for patients with RAS.

As a conclusion, whether due to a direct role in disease pathogenesis or as a secondary effect of insufficient oral hygiene, a close association was observed between oral health and the course of BD in our study. We therefore suggest that maintenance of oral health by effective, regular tooth brushing and dental flossing, regular dental check-ups and dental procedures should also be considered as a part of the therapeutic spectrum of BD. Instructions for tooth brushing and dental flossing, the most effective methods of plaque control, must be given in the clinical evaluations of BD patients. In addition, systematic oral health education programmes must be developed. In this context, further studies are required to confirm the effects of impaired oral hygiene on the prognosis of BD and whether treatments aimed at improving oral health might affect the course of the disease.

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