Relationship between periodontal findings and Behçet’s disease: a controlled study


Abstract

Background: Behcet’s disease (BD) is a chronic, relapsing, systemic vasculitis of unknown aetiology. The involvement of oral mucosal surfaces represents the onset feature of the disease in the majority of patients.

Objective: The aim of this study was to evaluate the periodontal status of BD patients and then compare with recurrent aphthous stomatitis (RAS) patients and healthy controls. We also determined the relationship between the periodontal condition and the clinical severity of the disease in BD patients.

Methods: Eighty-six patients with BD, 63 patients with RAS and 82 healthy subjects were included in the study. The periodontal status of all subjects was evaluated according to the community periodontal index of treatment needs (CPITN). BD patients were also assessed for clinical severity score (CSS) as described previously.

Results: The mean CPITN were observed to be higher in BD patients (1.79 ± 0.96) compared with RAS patients (1.22 ± 0.87) and healthy controls (1.18 ± 0.98) (p < 0.001). There was a positive association between CSS and CPITN (p = 0.017) in BD patients.

Conclusion: Our results showed that periodontal status is worse in BD patients and associated with disease severity. We can speculate that periodontitis may induce a systemic inflammatory process that may contribute to the development and/or progression of BD.

Behçet’s disease (BD) is a chronic, relapsing, systemic vasculitis of unknown aetiology (Sakane et al. 1999, Verity et al. 2003). Although several immunological abnormalities have been demonstrated in patients with BD, the exact mechanism of the inflammatory changes occurring remains to be elucidated (Ovec/kgioglu 2005). The most probable hypothesis is that of an immunologically driven inflammatory response set off by infectious agents such as herpes simplex virus 1 or streptococcus species in genetically predisposed individuals, and its major pathologic process is vasculitis (Sakane et al. 1997, Alpsoy et al. 1998). Current evidence suggests that the activated lymphocytes contribute to neutrophile and endothelial cell activation in these patients. Overexpression of proinflammatory cytokines from various cellular sources seems to be responsible for the enhanced inflammatory reaction in BD, and it may be associated with genetic susceptibility (Sakane et al. 1997, Guld 2001).

Oral microbial flora have long been implicated in the pathogenesis of BD. Dental interventions or tonsillitis have been indicated to result in disease attacks such as oral ulcers as well as activation of other manifestations (Kaneko et al. 1997, Mizushima et al. 1998). Antimicrobial agents including antibiotics and antiseptic agents have been used to control disease activation (Alpsoy 2005, Mumcu et al. 2005). In a recent study, Mumcu et al. (2006) have shown that oral health-related quality-of-life assessments were impaired in patients with BD and associated with disease activity and treatment modalities. Previous studies demonstrated that periodontal scores were higher in patients with BD than healthy subjects (Nakae et al. 1981, Nakae et al. 1982).
Celenligil-Nazliel et al. 1999, Mumcu et al. 2004). BD is particularly prevalent in ‘‘Silk Route’’ populations but has a global distribution. The highest prevalence of BD has been reported in Turkey. The prevalence of the disease in Turkey is found to be in approximately 1 in 250 of the population aged 12 or older (Azizlerli et al. 2003), whereas that in England is less than 1 in a 100,000 (Sakane et al. 1999). This marked geographic variation in BD can be explained by the genetic basis of the disease and/or environmental triggers. Considering the effect of genetic and environmental factors on the occurrence of BD, it could be important to determine periodontal scores of our population. Therefore, we aimed to investigate the periodontal status of BD patients, and compared them with recurrent aphthous stomatitis (RAS) patients and healthy controls. In addition, we extended the study to determine the effects of periodontal condition on the clinical findings and severity of the disease in patients with BD.

Materials and Methods
Eighty-six unrelated patients (43 women, 43 men; mean ± SD age, 34.9 ± 10.1 years) with BD fulfilled the classification criteria of the International Study Group for Behcet’s Disease (1990); 63 patients with RAS (31 women, 32 men; mean ± SD age, 33.7 ± 13.3 years) and 82 healthy controls (50 women, 32 men; mean ± SD age, 33.9 ± 14.1 years) attending Dermatology&Venerology Outpatient Clinic at the University of Akdeniz Hospital were enrolled in the study, in compliance with the principles of the Declaration of Helsinki. The mean ± SD durations of BD and RAS were 7.2 ± 6.1 years (range 1–25 years) and 7.6 ± 6.5 years (range 0.5–23 years), respectively. The RAS patients were evaluated for immunosuppressive or inflammatory disorders and systemic treatments. Only immunocompetent patients exhibiting idiopathic minor RAS were included in the study. The RAS patients and healthy control groups had neither a family history nor any other symptoms of BD. The clinical and laboratory findings till the beginning of the study in patients with BD are summarized in Table 1.

In BD patients, the total clinical severity score (CSS) was determined as described previously (Krause et al. 2001). This score was calculated as the sum of 1 point each for mild symptoms (oral ulcers, genital ulcers, arthralgia and typical skin lesions such as erythema nodosum-like lesions, 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 uveitis, retinal vasculitis, arterial thrombosis, neuro-Behcet’s and bowel perforation). The mean severity score in the whole group was 4.8 ± 1.7. Patients were categorized according to the disease CSS as follows: severe group, ≥7 points (n = 12); moderate group, a score between 4 and 6 points (n = 56); and mild group, <4 points (n = 18). Patients were grouped according to the presence of active oral ulcers (n = 22). The patients were also evaluated for the choice of treatment such as colchicine, immunosuppressive treatment or no treatment at the time of dental examination. In addition, BD patients were recorded for the frequency and the healing time of oral ulcers during the previous 3 months.

Table 1. Clinical and laboratory findings* of patients with Behcet’s disease

<table>
<thead>
<tr>
<th>Patients (n = 86)</th>
<th>(%)</th>
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<tr>
<td>Clinical characterisrics</td>
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<tr>
<td>Oral ulcer</td>
<td>86</td>
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<tr>
<td>Genital ulcer</td>
<td>75</td>
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<tr>
<td>Papulopustular lesions</td>
<td>65</td>
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<tr>
<td>Articular involvement</td>
<td>60</td>
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<tr>
<td>Erythema nodosum</td>
<td>36</td>
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<tr>
<td>Ocular symptoms</td>
<td>25</td>
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<tr>
<td>Thrombophlebitis</td>
<td>8</td>
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<td>Neurologic involvement</td>
<td>4</td>
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<tr>
<td>Gastrointestinal involvement</td>
<td>2</td>
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<tr>
<td>The skin pathergy test</td>
<td>43</td>
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<tr>
<td>HLA B51</td>
<td>25</td>
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* Till the beginning of the study.

Dental examination
The same dentist (H.K.) examined the dental and periodontal status of the patients and controls. To assess the periodontal condition, he used the World Health Organization (WHO) community periodontal index of treatment needs (CPITN) and a specially designed WHO periodontal probe with a sensing force of not > 20 g (Ainamo et al. 1982). Brieﬂy, the mouth of each patient was divided into sextants, each sextant only being examined if there were ≥ 2 teeth present and not indicated for extraction; the teeth examined were 17, 16, 11, 21, 26, 27, 47, 46, 41, 31, 36, 37. For each sextant, we recorded the highest index found according to the following score: 0, periodontal health; 1, gingival bleeding; 2, calculus detected during probing; 3, pocket 4–5 mm depth; and 4, pocket ≥ 6 mm depth. The periodontal condition of every patient was reported as the worst sextant CPITN condition. The number of carious teeth were also recorded. The patients and healthy controls were questioned concerning the daily frequency of tooth brushing and the use of dental floss by the dentist.

Statistical analysis
We used analysis of variance (ANOVA) and X2 analysis to compare the age, gender, CPITN, the number of carious teeth and the daily frequency of tooth brushing, the presence of oral ulcer and prosthesis of the cases and controls. ANOVA, X2 test and Kruskal–Wallis tests were used to compare the age, CSS, CPITN, the number of carious teeth, the daily frequency of tooth brushing, gender; the presence of active oral ulcer, the treatment used at the time of dental examination and the presence of prosthesis in each CSS group in patients with BD. The Mann–Whitney U test was used when the periodontal condition was analysed according to the clinical features of the BD patients. Forward conditional logistic regression analysis was used to determine the factors affecting severe CPITN score (CPITN > 4). Study groups, gender, the presence of prosthesis as categorical variables and age, the number of carious teeth and the daily frequency of tooth brushing as
Results

Oral health in the study groups

The mean CPITN was observed to be higher in patients with BD (1.79 ± 0.96) compared with healthy controls (1.19 ± 0.98) \((p<0.001)\). Although the mean CPITN was higher in patients with RAS (1.22 ± 0.87) compared with healthy controls, the difference was not statistically significant.

No statistically significant difference was observed according to age and gender among the groups. The daily frequency of tooth brushing was lower in BD patients than in other groups but the difference was not statistically significant \((p = 0.19)\). In addition, there was no significant difference among the groups when the patients were examined according to the number of carious teeth and having prosthesis.

None of the patients or controls were using dental floss regularly (Table 2). Twenty-two patients with BD (27.5%) and 11 patients with RAS (23.4%) had active oral ulcers at the time of the periodontal examination. However, no statistically significant difference was observed between the patients with oral ulcers (1.59 ± 1.05) and patients without oral ulcers (1.90 ± 0.93) \((p = 0.210)\) in the mean CPITN.

The results of forward conditional logistic regression analysis of the factors affecting severe CPITN are presented in Table 3. Age \((p = 0.008)\), having BD \((p = 0.005)\) and frequency of tooth brushing \((p = 0.018)\) were found to be significant risk factors for higher periodontal severity scores.

Oral health and clinical course in patients with Behçet’s disease

There was an association between groups of CSS and periodontal disease severity \((p = 0.017)\) in patients with BD. A correlation close to the statistical significance between the number of carious teeth and CSS (3.06 ± 3.02 in the mild group, 4.86 ± 2.88 in the moderate group, 5.25 ± 2.77 in the severe group) was observed \((p = 0.052)\). However, the presence of prosthesis and the daily frequency of tooth brushing were not significantly different among groups of CSS. No statistically significant difference was observed in CSS according to age, gender and the disease duration (Table 4).

However, when the CPITN were analysed according to the clinical features, it was seen that the score was significantly higher in patients with central nervous system (CNS) involvement \((p = 0.015)\). The CPITN was also higher in patients with eye involvement than those of patients without these findings but the difference was not statistically significant \((p = 0.084)\). The number of carious was significantly higher in patients with arthritis \((p = 0.006)\) (Table 5). The number of carious was also higher in patients with thrombophlebitis, but the difference was not statistically significant \((p = 0.089)\).

At the time of dental examination, 12 of the patients with BD, mainly with
Patients without arthritis \((n/C6)^1\), 1.67 according to the choice of treatment (with cant difference was observed in CPITN using colchicine. No statistically significant difference was observed in the presence of prosthesis among patients with BD and RAS compared with Mumcu’s group \((n = 35)\). However, memory factor could also have affected the knowledge about the frequency of brushing. The answer may vary according to persons who have or do not have periodontal disease. Thus, patients with periodontal disease may be more sensitive to recalling the frequency of brushing than healthy persons. Our findings support the notion that tissue-specific autoimmunity could be the probable mechanism in the pathogenesis of RAS (Lewkowicz et al. 2003). However, it seems likely that this immune response is not sufficient for the development of severe periodontitis in RAS patients. On the other hand, BD is a systemic inflammatory disease and not limited to oral mucosa.

Current data implicate that oral health might be an important factor in the pathogenesis of BD. In our study group, there was a relationship between severe periodontitis and BD according to the logistic regression analysis \((p = 0.004, OR = 3.4)\). It can be speculated that BD might develop after the periodontitis. However, because of possible different variables in the development of the two conditions, the cause and effect relationship between periodontitis and BD might also be far from established. In addition, previous studies and our study have an important limitation because of their design. Because probable reason (periodontitis) and BD were evaluated at the same time, it was not possible to determine which one started first. Therefore, we cannot conclude that periodontitis is a significant risk factor for the development of BD as we were only able to examine the periodontal status of impaired oral health in these patients. Indeed, there is still a need for further longitudinally designed studies in a larger series to ascertain the cause of impaired oral health in these patients. It seems that in addition to insufficient tooth brushing, other factors like gene polymorphisms and uncontrolled inflammatory response to various stimuli by the overreacting genes might play a role in

### Discussion

Our results demonstrated that oral health is impaired in BD and associated with disease severity. Nakae et al. (1981) observed that the presence of five or more decayed and extracted teeth were higher in BD compared with the healthy Japanese population. Celenligil-Nazliel et al. (1999) suggested that poor oral hygiene leads to rapid bacterial plaque accumulation. In our study, in addition to having BD, age and frequency of tooth brushing were found to be risk factors for severe periodontitis. Mumcu et al. (2004) have recently determined that oral health was impaired in patients with BD and RAS compared with healthy controls. Oral ulcers being painful, therefore, limiting effective tooth brushing was explained in this data. However, in our study, the difference was not statistically significant between patients with RAS and healthy controls. Oral ulcers being painful, therefore, limiting effective tooth brushing was explained in this data. However, in our study, the difference was not statistically significant between patients with RAS and healthy controls.
higher CPITN in patients with BD compared with other groups. Genetic alterations such as IL-1 and TNF-α polymorphisms in BD (Coskun et al. 2005, Akman et al. 2006) could contribute to genetic susceptibility in the development of periodontitis via an enhanced inflammatory reaction. At least one variant allele in the TNF-α −1031, −831 or −857 single-nucleotide polymorphisms has been reported to be associated with severe periodontitis in the Japanese population (Soga et al. 2003). Aito et al. (2004) suggest that systemic inflammatory response is higher in severe periodontitis patients carrying rare alleles for functional inflammatory gene polymorphisms.

Besides BD, several other inflammatory diseases have been reported to be associated with severe periodontal disease (Fowler et al. 2001, Angeli et al. 2003). Amar & Han (2003) suggested that the infection-related host inflammatory response, which may influence a variety of homeostatic mechanisms, could be an explanation for the periodontal–systemic disease association. Some studies have shown that the levels of IL-1 and TNF-α are sufficiently elevated in gingival crevicular fluid to be detectable systemically by a biological serum assay in advanced periodontitis (Slots & Kamma 2001, Teng et al. 2002). Investigators have hypothesized that periodontitis-induced elevations of inflammatory mediators and acute-phase proteins may play a major role in the development of a variety of systemic diseases and conditions (Iacopino & Cutler 2000, Slots & Kamma 2001). Aito et al. (2004) showed that IL-1, IL-6 and TNF-α gene polymorphisms are associated with higher levels of serum IL-6 and serum CRP. Amar et al. (2003) demonstrated endothelial vasomotor dysfunction in the brachial artery and elevated serum levels of high-sensitivity C-reactive protein in patients with severe periodontal disease. Desvarieux et al. (2003) showed that tooth loss is a marker of past periodontal disease and is related to subclinical atherosclerosis.

BD starts mostly from the oral mucosal surfaces. Interestingly, atypical streptococci species were observed in the oral flora of BD patients. Streptococcus sanguis KTH-1-specific T-cell lines secrete the proinflammatory mediators IL6, IL-8, TNF-α in patients with BD (Direskeneli 2001). Antistreptococcal HSP60 antibodies are raised in the serum of patients with BD. Antibody response to microorganisms in the bacterial plaque ecology and elevated inflammatory mediators in BD may also circulate in the blood stream and interact with endothelial tissue.

Different from the previously published data, we extended our research to analyse the CPITN of patients according to their clinical features. As an interesting finding, patients with CNS and eye involvement were found to have higher periodontal scores. In addition, the number of carious was significantly higher in patients with arthritis. Studies focused upon demographic features, and prognosis, showed that male gender and early age at onset were associated with more severe presentations of the disease (Al-Otaibi et al. 2005). The present data suggest that BD patients with higher CPITN scores, who are under chronic inflammatory status because of advanced periodontal disease, showed more severe organ involvement. Therefore, we can speculate that advanced periodontal disease may represent a risk factor for severe organ involvement. On the other hand, this relationship is not as strong in the male gender, according to the logistic regression analysis.

This result can also be explained by the more frequent use of immunosuppressive treatments in patients with severe organ involvement. As expected, these compounds alter host defences and may affect oral health negatively (Mumcu et al. 2004). However, CPITN was not higher.
in those patients treated with immuno-suppressive agents compared with other BD patients receiving treatments other than immuno-suppressive drugs or not receiving any treatment at all. Nevertheless, more work needs to be carried out to analyse the periodontal effects of the immuno-suppressive drugs.

Our results show that oral health is impaired in BD and associated with disease severity and severe organ involvement. It is possible that chronic infections of periodontal structures in genetically susceptible patients could accelerate BD by promoting a chronic systemic inflammatory status through the release of bacterial products, heat shock proteins, acute-phase reactants and any other inflammatory mediators (Direskeneli 2001, Angeli et al. 2003). Therefore, BD patients should be informed about the risk of periodontitis and long-term periodontal follow-up should be encouraged by dental professionals to prevent (BD and periodontal) disease progression.

Acknowledgements

The study is supported by Akdeniz University Scientific Research Projects Unit.

References


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<table>
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<th>Clinical Relevance</th>
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<td><strong>Scientific rationale for the study:</strong> As the pathophysiologies of inflammatory diseases and periodontitis have similar features, we decided to investigate the relationship between BD and periodontal status. <strong>Principal findings:</strong> A significant relationship was found to suggest that patients with BD exhibited higher community periodontal index of treatment needs (CPITN) scores than RAS patients and healthy control groups. In addition, the high CPITN score was associated with disease severity and severe organ involvement in patients with BD. <strong>Practical implications:</strong> BD patients should be informed about the risk of periodontitis and long-term periodontal follow-up by dental professionals should be encouraged in order to prevent their (BD and periodontal) disease progression.</td>
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