

Association between Behçet's disease and apical periodontitis: A cross-sectional study

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Abstract

Background. The correlation between Behçet's disease (BD) and apical periodontitis (AP) has not been investigated.

Objectives. The aim of the study was to evaluate the association between BD and AP using different variables.

Material and methods. A total of 98 individuals (49 with BD and 49 controls) were recruited for the study. The presence of AP was confirmed through radiographic and clinical examination in all patients. The following data was evaluated in both the BD group and the control group: the presence of teeth with AP; the presence of root canal-treated (RCT) teeth; the presence of RCT teeth with AP; the severity of the disease; the types of medication taken; and the duration of the disease. The χ^2 test and the logistic regression analysis were performed to ascertain the association between BD and AP.

Results. A total of 32 patients in the BD group and 12 patients in the control group presented with AP. The prevalence of teeth with AP was significantly higher in the BD group than in the control group (odds ratio = 5.804, $p < 0.05$). The χ^2 analysis demonstrated a statistically significant association between AP and both gender and BD activity ($p < 0.05$). Furthermore, the logistic regression analysis indicated that the severity of the disease was a predictor of BD ($p < 0.05$).

Conclusions. A significantly higher prevalence of AP was observed in patients with BD. However, the success rate of endodontic treatment in patients with BD was comparable to that observed in healthy individuals.

Keywords: Behçet's disease, Behçet's syndrome, apical periodontitis

Cite as

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Introduction

Behçet's disease (BD), also known as Behçet's syndrome, is a form of multisystemic chronic vasculitis first defined by Dr. Hulusi Behçet in 1937. The disease affects the cardiovascular, nervous and gastrointestinal systems and presents with mucocutaneous lesions. The condition is a triple-symptom complex involving the oral, genital and ocular structures.¹ Behçet's disease affects both female and male individuals across a wide geographic area, but it is more prevalent among people along the so-called Silk Road.² The causes of BD include immune system disorder, genetic predisposition and endothelial cell dysfunction.³ Since diagnostic tests cannot be performed for BD, the diagnosis is made based on clinical findings.⁴

Although the pathogenesis of BD is not fully understood, studies have demonstrated that immunological dysregulation plays an important role in its etiology and progression. An important part of the immunopathogenesis of BD is a T cell-mediated immune response.⁵ T cells are divided into 2 groups, known as T helper cells 1 (Th1) and T helper cells 2 (Th2), which have antigen-specific receptors on their cell membranes for the identification of pathogens.⁶ One of the key pathological immune characteristics of BD is the presence of elevated levels of pro-inflammatory Th1 cytokines (interleukin-2 (IL-2), IL-12, IL-18, IL-27 and interferon- γ (IFN- γ)) and Th2 cytokines (IL-2, IL-10, IL13, and tumor necrosis factor- β (TNF- β)), which play crucial roles in the disease.^{7,8} It has been demonstrated that IL-6 is the main cytokine that functions as a promoter in patients with BD.^{9,10} Furthermore, IL-6 and TNF provide both local and systemic responses to pathological stimuli.¹¹

In the event of pulp necrosis, bacteria and their by-products reach the periradicular tissues via the apical foramen and lateral canals, thereby triggering inflammatory and immunologic reactions and causing apical periodontitis (AP).¹² T cells are one of the key factors involved in AP.¹³ They produce cytokines, which may stimulate bone destruction and exert a pro-inflammatory function in AP.¹³ The progression of AP and the subsequent bone resorption have been attributed to a response in Th1.⁸

Arabaci et al. indicated that periodontal status is influenced by the presence and severity of BD.¹⁴ Another study demonstrated a correlation between periodontitis and BD activity.¹⁵ Since AP and BD involve similar destructive and inflammatory reactions, there is a possibility of an association between the two. Thus, this cross-sectional study aimed to evaluate the correlation between BD and AP. The null hypothesis was that no association would be observed.

Material and methods

This study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)

statement. The clinical study was conducted in the Department of Rheumatology, School of Medicine, and the Department of Endodontics, Faculty of Dentistry (Atatürk University, Erzurum, Turkey). The study was approved by the Ethics Committee of the Atatürk University (decision No. 71-09/2022). The sample size was calculated based on the data from a previous study,¹⁶ with an effect size of 0.35, an alpha error of 0.05 and a power of 0.9. According to this analysis, the study should have included 85 patients.

The study population consisted of 49 patients with BD, aged 28–65 years, who were accepted for treatment at the endodontics clinic. The patients did not present with any additional systemic diseases apart from BD. The participants of the study met the criteria set forth by the International Study Group for BD.¹⁷ The control group consisted of 49 sex- and age-matched patients who did not have any systemic diseases.

The BD activity index was used to determine the severity of the disease, with patients classified accordingly.¹⁸ Each symptom was assigned a specific score. The overall disease activity was determined by summing the scores. Oral aphthous ulcers, arthralgia, genital ulcers, erythema nodosum, folliculitis, and papulopustular lesions were classified as mild symptoms and were assigned 1 point each. Moderate symptoms included arthritis, deep vein thrombosis of the legs, anterior uveitis, and gastrointestinal involvement. They were assigned 2 points each. Posterior uveitis/panuveitis, retinal vasculitis, arterial thrombosis, neuro-Behçet's disease, and bowel perforations were classified as severe symptoms and were assigned 3 points each.

Additionally, the duration of the disease and the types of medication administered were documented. The types of medication were scored as follows: a score of 1 was assigned to colchicine; 2 to anti-TNF; 3 to steroids; and 4 to immunosuppressive drugs. If a patient was taking 2 or more medications, the highest score was assigned to the type of medication.

The diagnosis of AP was confirmed by clinical and radiographic examinations. All types of AP, including asymptomatic AP, symptomatic AP, acute apical abscess, and chronic apical abscess were considered. All radiographic images were obtained using the same imaging system (Planmeca Promax; Planmeca, Helsinki, Finland). If the periapical tissue was normal or had minimal changes in bone structure, the related tooth was classified as healthy (PAI 1 and 2), according to the periapical index (PAI).¹⁹ In the event of a lost periodontal ligament or periodontitis with exacerbating features (PAI 3, 4 and 5), the tooth was classified with a periapical pathology.²⁰ The PAI score for multi-rooted teeth was determined based on the highest score observed across all roots.²¹

Digital panoramic radiographs were taken and analyzed by an endodontist and an experienced dentist (Fig. 1,2). Both observers were blinded to the study groups. In cases of disagreement, the analysis was repeated. After the radiographic analysis, pulp sensitivity, percussion and



Fig. 1. Panoramic radiograph of a patient included in the control group



Fig. 2. Panoramic radiograph of a patient included in the experimental group

palpation tests were performed to confirm the clinical diagnosis of AP. Patients with at least 1 tooth exhibiting signs of AP were included in the AP group.

The following data was recorded for all patients: the number of patients with AP; the number of patients with root canal-treated (RCT) teeth; and the number of patients with RCT teeth and AP.

Statistical analysis

The statistical analysis was conducted using the IBM SPSS Statistics for Windows software, v. 20 (IBM Corp., Armonk, USA). The χ^2 test was performed to determine the differences between the BD group and the control group. A univariate analysis of potential predictors of BD and AP, as well as RCT teeth and RCT teeth with AP, was

carried out using the Mann–Whitney *U* test. Furthermore, a model was constructed for the logistic regression analysis to better understand the relationship between cases with BD and AP, RCT teeth, and RCT teeth with AP. A *p*-value <0.05 was considered statistically significant.

Results

A total of 98 individuals with 2,051 teeth (1,026 in the BD group and 1,025 in the control group) were evaluated. While 32 patients were diagnosed with AP in the BD group, only 12 patients were diagnosed with AP in the control group. The prevalence of AP was significantly higher in the BD group (65.3%) compared to the control group (24.4%) (odds ratio = 5.804, $p < 0.001$) (Table 1).

Table 1. Distribution of the analyzed variables in patients with Behçet's disease and the control group

Variable	Experimental group	Control group	<i>p</i> -value	Odds ratio
Patients, <i>n</i>	49	49	–	–
Mean age [years] <i>M</i> ± <i>SD</i>	34.46 ± 9.2	34.46 ± 9.2	1.00	–
Gender, <i>n</i>	female	31	–	–
	male	18	–	–
Patients with AP, <i>n</i> (%)	present	32 (65.3)	<0.001*	5.804
	absent	17 (34.7)		
Patients with RCT teeth, <i>n</i> (%)	present	30 (61.2)	0.837	1.184
	absent	19 (38.8)		
Patients with RCT teeth+AP, <i>n</i> (%)	present	9 (18.3)	0.575	1.613
	absent	40 (81.7)		

M – mean; *SD* – standard deviation; AP – apical periodontitis; RCT – root canal-treated; patients with AP – at least 1 tooth with AP; patients with RCT teeth – at least 1 RCT tooth; patients with RCT teeth+AP – at least 1 RCT tooth and AP; * statistically significant ($p < 0.05$).

At least 1 RCT tooth was found in 30 (61.2%) and 28 (57.2%) patients in the BD and control groups, respectively. The observed difference in the number of RCT teeth between the BD and control groups was not statistically significant ($p > 0.05$). At least 1 RCT tooth with AP was identified in 9 (18.3%) and 6 (12.2%) BD and control patients, respectively. The difference between the groups in terms of the presence of RCT teeth with AP was not statistically significant ($p > 0.05$) (Table 1).

The intragroup analysis revealed a higher prevalence of AP in male BD patients compared to female patients ($p < 0.05$) (Table 2). Additionally, the prevalence of patients with AP was significantly higher in the severe group than in the mild and moderate groups ($p < 0.05$). There was no statistically significant difference between the mild and moderate groups in terms of the AP prevalence ($p > 0.05$). No statistically significant difference was observed in terms of age, the duration of the disease, or the type of medication among patients with BD ($p > 0.05$). To better understand the relative influence of the predictors,

a logistic regression analysis was performed (Table 3). The constructed model demonstrated that BD activity was a predictor of AP ($p < 0.05$).

Table 3. Results of the logistic regression analysis in patients with Behçet's disease

Variable	B*	Standard error	Beta	<i>p</i> -value
Type of medication	score 1	–	–	0.581
	score 2	1.001	1.232	2.721
	score 3	0.041	1.410	1.042
	score 4	–0.808	0.813	0.446
Behçet's disease activity	mild	–	–	0.077
	moderate	–0.391	0.727	0.676
	severe	2.291	1.150	0.046*
Duration of the disease	0.034	0.051	1.034	0.513
Constant	0.757	0.686	2.132	0.270

* statistically significant ($p < 0.05$, χ^2 test).

Table 2. Distribution of the analyzed variables in patients with Behçet's disease

Variable		AP			RCT teeth			RCT teeth+AP		
		present	absent	<i>p</i> -value	present	absent	<i>p</i> -value	present	absent	<i>p</i> -value
Gender, <i>n</i>	female	15	16	0.010*	22	9	0.080	7	24	0.454
	male	15	3		8	10		2	16	
Age [years] <i>M</i> ± <i>SD</i>		33.8 ±8.5	35.5 ±10.5	0.813	34.7 ±9.9	34.1 ±8.4	0.935	33.4 ±8.1	34.7 ±9.6	0.675
Behçet's disease activity, <i>n</i> (%)	mild	11 (52.3) ^a	10 (47.7) ^a	0.040*	13 (61.9)	8 (38.1)	0.200	5 (23.8)	16 (76.2)	0.669
	moderate	8 (50.0) ^a	8 (50.0) ^a		12 (75.0)	4 (25.0)		2 (12.5)	14 (87.5)	
	severe	11 (91.6) ^b	1 (8.4) ^a		5 (41.6)	7 (58.4)		2 (16.6)	10 (83.4)	
Type of medication, <i>n</i> (%)	score 1	19 (63.3)	11 (36.7)	0.789	19 (63.3)	11 (36.7)	0.705	7 (23.3)	23 (76.7)	0.088
	score 2	3 (75.0)	1 (25.0)		3 (75.0)	1 (25.0)		2 (50.0)	2 (50.0)	
	score 3	2 (66.7)	1 (33.0)		1 (33.3)	2 (66.7)		–	3 (100.0)	
	score 4	6 (50.0)	6 (50.0)		7 (58.3)	5 (41.7)		–	12 (100.0)	
Duration of the disease [months] <i>M</i> ± <i>SD</i>		8.2 ±6.3	7.1 ±7.3	0.231	7.8 ±7.2	7.7 ±6.0	0.951	6.6 ±4.4	8.0 ±7.1	0.970

* statistically significant ($p < 0.05$, χ^2 test). Different superscript letters show statistical differences between the groups.

Discussion

Systemic disorders can be regarded as modulating factors affecting the progression of an oral infection, rather than etiologic factors.^{22,23} The success of root canal treatment is adversely affected in individuals with diabetes and hypertension.²⁴ Costa et al. revealed that individuals with cardiovascular diseases are more prone to endodontic pathologies.²⁵ Moreover, patients who had undergone kidney transplantation exhibited a higher prevalence of endodontic pathology compared to healthy individuals.²⁶ However, this is the first study investigating the relationship between AP and BD based on a range of variables.

Apical periodontitis is associated with an elevated level of cytokines and inflammatory mediators secreted by T cells, including IL-1, IL-2, IL-6, and TNF- α .²⁷ In addition, the presence of CD57-positive cells in all cases of chronic AP suggests that activated natural killer (NK) cells contribute to the progression of periapical pathologies.²⁸ Natural killer cells can release cytokines, including IFN- γ and TNF.²⁹ The bone destruction process in periradicular pathology is regulated by pro-inflammatory cytokines, such as IL-1 β , IL-6, IFN- γ , and TNF- α .³⁰ Th1 cells are mainly effective in the pathogenesis of BD. It has been shown that Th1 cells and cytokines are significantly elevated in individuals with active BD.³¹ Interleukin-1, IL-6 and TNF- α are the main cytokines observed in BD patients.³² Hasan et al. have confirmed the association between NK cells and BD and identified a reduction in NK cells in the peripheral blood of active BD patients.³³ The depletion of NK cells in the peripheral blood of BD patients may reflect an increased homing of these cytotoxic cells to inflammatory sites.⁵ Additionally, increased levels of IFN- γ , which are secreted by NK cells, have been reported in individuals with active BD.³¹ Therefore, the association between the 2 diseases can be attributed to increased cytokine similarity and the impact of these cytokines on disease progression in both AP and BD.

The present study indicates that the prevalence of AP was higher in male individuals in the BD group. While BD has an impact on both genders, it is more severe among young males.^{34–36} The relevant clinical difference between men and women is unclear, but it may be related to hormonal factors, such as testosterone and prolactin.^{37,38}

Despite the lack of consensus on a treatment program, colchicine, corticosteroids, anti-TNF agents, and cyclosporine have been demonstrated to effectively control BD symptoms.³⁹ Drug therapy provides symptom control, reduces inflammation, supports the immune system, provides remission, and increases the patient's quality of life.⁴⁰ However, our study did not identify an association between AP and the type of medication used to treat BD. Since no other study has investigated the possible associations between the type of medication and AP, a direct comparison cannot be made.

The study results indicated that there was no statistically significant difference between the groups with regard to the prevalence of RCT teeth and those with RCT teeth and AP. In other words, BD did not affect the maintenance of endodontic treatment. Bone destruction in AP has been related to the Th1 response, which leads to the activation of osteoclasts.⁴¹ The administration of intra-canal medication during endodontic treatment can result in successful outcomes, as evidenced by a previous study which indicated that intracanal medication can reduce the levels of cytokines involved in AP.⁴²

A limitation of this study is the absence of data regarding the patient's oral hygiene. Oral hygiene may influence the prevalence of AP. Previous research has shown that the incidence of AP is higher among patients with periodontal disease (PD) compared to those without PD.⁴³ Another study has reported that dental caries and PD were the most prevalent oral health concerns in individuals with rheumatic diseases (73.1%).⁴⁴ These dental problems could be attributed to the side effects of medications.⁴⁵ Another limitation of the present study is that it was based on an observational cross-sectional design, which only captured data at a single point in time. However, the results of the present study provide baseline information for prospective studies with larger sample sizes. Finally, further controlled clinical trials are required to elucidate the role of AP in BD.

Conclusions

Behçet's disease was shown to be significantly associated with an increased prevalence of AP. It can be concluded that, among all variables, BD activity was the most effective predictor of AP. Individuals with severe BD may be more prone to developing AP in comparison to those with mild and moderate BD activity. No statistically significant difference was observed regarding the prevalence of RCT teeth with AP between the BD and control groups. Thus, it can be concluded that BD did not affect the success rate of root canal treatment. Further prospective studies are required to confirm the relationship between BD and AP.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Atatürk University (decision No. 71-09/2022).

Data availability

All data generated and/or analyzed during this study is included in this published article.

Consent for publication

Not applicable.

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References

- Verity DH, Wallace GR, Vaughan RW, Stanford MR. Behçet's disease: From Hippocrates to the third millennium. *Br J Ophthalmol*. 2003;87(9):1175–1183. doi:10.1136/bjo.87.9.1175
- Akman A, Kacaroglu H, Donmez L, Bacanli A, Alpsoy E. Relationship between periodontal findings and Behçet's disease: A controlled study. *J Clin Periodontol*. 2007;34(6):485–491. doi:10.1111/j.1600-051X.2007.01085.x
- Gül A. Behçet's disease: An update on the pathogenesis. *Clin Exp Rheumatol*. 2001;19(5 Suppl 24):S6–S12. PMID:11760403.
- Chajek T, Fainaru M. Behçet's disease. Report of 41 cases and a review of the literature. *Medicine (Baltimore)*. 1975;54(3):179–196. doi:10.1097/00005792-197505000-00001
- Tong B, Liu X, Xiao J, Su G. Immunopathogenesis of Behçet's disease. *Front Immunol*. 2019;10:665. doi:10.3389/fimmu.2019.00665
- Ihan Hren N, Ihan A. T lymphocyte activation and cytokine expression in periapical granulomas and radicular cysts. *Arch Oral Biol*. 2009;54(2):156–161. doi:10.1016/j.archoralbio.2008.09.014
- Alipour S, Nouri M, Khabbazi A, et al. Hypermethylation of *IL-10* gene is responsible for its low mRNA expression in Behçet's disease. *J Cell Biochem*. 2018;119(8):6614–6622. doi:10.1002/jcb.26809
- Zhou ZY, Chen SL, Shen N, Lu Y. Cytokines and Behçet's disease. *Autoimmun Rev*. 2012;11(10):699–704. doi:10.1016/j.autrev.2011.12.005
- Alipour S, Sakhinia E, Khabbazi A, et al. Methylation status of interleukin-6 gene promoter in patients with Behçet's disease. *Rheumatol Clin (Engl Ed)*. 2020;16(3):229–234. doi:10.1016/j.reuma.2018.06.006
- Senusi AA, Liu J, Bevec D, et al. Why are Behçet's disease patients always exhausted? *Clin Exp Rheumatol*. 2018;36(6 Suppl 115):53–62. PMID:30299243.
- Rohleder N, Aringer M, Boentert M. Role of interleukin-6 in stress, sleep, and fatigue. *Ann N Y Acad Sci*. 2012;1261:88–96. doi:10.1111/j.1749-6632.2012.06634.x
- Galler KM, Weber M, Korkmaz Y, Widbiller M, Feuerer M. Inflammatory response mechanisms of the dentine–pulp complex and the periapical tissues. *Int J Mol Sci*. 2021;22(3):1480. doi:10.3390/ijms22031480
- Márton IJ, Kiss C. Overlapping protective and destructive regulatory pathways in apical periodontitis. *J Endod*. 2014;40(2):155–163. doi:10.1016/j.joen.2013.10.036
- Arabaci T, Kara C, Çiçek Y. Relationship between periodontal parameters and Behçet's disease and evaluation of different treatments for oral recurrent aphthous stomatitis. *J Periodontol Res*. 2009;44(6):718–725. doi:10.1111/j.1600-0765.2008.01183.x
- Habibagahi Z, Khorshidi H, Hekmati S. Periodontal health status among patients with Behçet's disease. *Scientifica (Cairo)*. 2016;2016:7506041. doi:10.1155/2016/7506041
- Karataş E, Kul A, Tepecik E. Association between rheumatoid arthritis and apical periodontitis: A cross-sectional study. *Eur Endod J*. 2020;5(2):155–158. doi:10.14744/eej.2019.52824
- Davatchi F. Diagnosis/Classification Criteria for Behçet's Disease. *Patholog Res Int*. 2012;2012:607921. doi:10.1155/2012/607921
- Krause I, Mader R, Sulkes J, et al. Behçet's disease in Israel: The influence of ethnic origin on disease expression and severity. *J Rheumatol*. 2001;28(5):1033–1036. PMID:11361184.
- Ridao-Sacie C, Segura-Egea JJ, Fernández-Palacín A, Bullón-Fernández P, Ríos-Santos JV. Radiological assessment of periapical status using the periapical index: Comparison of periapical radiography and digital panoramic radiography. *Int Endod J*. 2007;40(6):433–440. doi:10.1111/j.1365-2591.2007.01233.x
- Ørstavik D, Kerekes K, Eriksen HM. The periapical index: A scoring system for radiographic assessment of apical periodontitis. *Endod Dent Traumatol*. 1986;2(1):20–34. doi:10.1111/j.1600-9657.1986.tb00119.x
- López-López J, Jané-Salas E, Estrugo-Devesa A, Velasco-Ortega E, Martín-González J, Segura-Egea JJ. Periapical and endodontic status of type 2 diabetic patients in Catalonia, Spain: A cross-sectional study. *J Endod*. 2011;37(5):598–601. doi:10.1016/j.joen.2011.01.002
- Fouad AF. Diabetes mellitus as a modulating factor of endodontic infections. *J Dent Educ*. 2003;67(4):459–467. PMID:12749575.
- Joshi KJ, Pitiphat W, Hung HC, Willett WC, Colditz GA, Douglass CW. Pulpal inflammation and incidence of coronary heart disease. *J Endod*. 2006;32(2):99–103. doi:10.1016/j.joen.2005.10.039
- Mindiola MJ, Mickel AK, Sami C, Jones JJ, Lalumandier JA, Nelson SS. Endodontic treatment in an American Indian population: A 10-year retrospective study. *J Endod*. 2006;32(9):828–832. doi:10.1016/j.joen.2006.03.007
- Costa THR, de Figueiredo Neto JA, Figueiredo de Oliveira AE, de Figueiredo Lopes e Maia M, de Almeida AL. Association between chronic apical periodontitis and coronary artery disease. *J Endod*. 2014;40(2):164–167. doi:10.1016/j.joen.2013.10.026
- Castellanos-Cosano L, Machuca-Portillo G, Segura-Sampedro JJ, et al. Prevalence of apical periodontitis and frequency of root canal treatments in liver transplant candidates. *Med Oral Patol Oral Cir Bucal*. 2013;18(5):e773–e779. doi:10.4317/medoral.19148
- Gomes MS, Blattner TC, Sant'Ana Filho M, et al. Can apical periodontitis modify systemic levels of inflammatory markers? A systematic review and meta-analysis. *J Endod*. 2013;39(10):1205–1217. doi:10.1016/j.joen.2013.06.014
- Saboa-Dantas CJ, Coutin de Toledo LF, Siqueira JF, Sampaio-Filho HR, Carvalho JJ, Pereira MJS. Natural killer cells and alterations in collagen density: Signs of periradicular herpesvirus infection? *Clin Oral Investig*. 2008;12(2):129–135. doi:10.1007/s00784-007-0165-5
- Biron CA, Nguyen KB, Pien GC, Cousens LP, Salazar-Mather TP. Natural killer cells in antiviral defense: Function and regulation by innate cytokines. *Annu Rev Immunol*. 1999;17:189–220. doi:10.1146/annurev.immunol.17.1.189
- Colić M, Gazivoda D, Vučević D, Vasiljčić S, Rudolf R, Lukić A. Proinflammatory and immunoregulatory mechanisms in periapical lesions. *Mol Immunol*. 2009;47(1):101–113. doi:10.1016/j.molimm.2009.01.011
- Aridogan BC, Yildirim M, Baysal V, Inaloz HS, Baz K, Kaya S. Serum levels of IL-4, IL-10, IL-12, and IFN-gamma in Behçet's disease. *J Dermatol*. 2003;30(8):602–607. doi:10.1111/j.1346-8138.2003.tb00442.x
- Wakefield D, Lloyd A. The role of cytokines in the pathogenesis of inflammatory eye disease. *Cytokine*. 1992;4(1):1–5. doi:10.1016/1043-4666(92)90028-p
- Hasan MS, Ryan PL, Bergmeier LA, Fortune F. Circulating NK cells and their subsets in Behçet's disease. *Clin Exp Immunol*. 2017;188(2):311–322. doi:10.1111/cei.12939
- Jo YG, Ortiz-Fernández L, Coit P, et al. Sex-specific analysis in Behçet's disease reveals higher genetic risk in male patients. *J Autoimmun*. 2022;132:102882. doi:10.1016/j.jaut.2022.102882
- Tursen U, Gurler A, Boyvat A. Evaluation of clinical findings according to sex in 2313 Turkish patients with Behçet's disease. *Int J Dermatol*. 2003;42(5):346–351. doi:10.1046/J.1365-4362.2003.01741.X
- Bang DS, Oh SH, Lee KH, Lee ES, Lee SN. Influence of sex on patients with Behçet's disease in Korea. *J Korean Med Sci*. 2003;18(2):231–235. doi:10.3346/jkms.2003.18.2.231
- Atasoy M, Karatay S, Yildirim K, Kadi M, Erdem T, Senel K. The relationship between serum prolactin levels and disease activity in patients with Behçet's disease. *Cell Biochem Funct*. 2006;24(4):353–356. doi:10.1002/cbf.1227
- Yavuz S, Ozilhan G, Elbir Y, Tolunay A, Eksioğlu-Demiralp E, Direskeneli H. Activation of neutrophils by testosterone in Behçet's disease. *Clin Exp Rheumatol*. 2007;25(4 Suppl 45):S46–S51. PMID:17949551.
- Saleh Z, Arayssi T. Update on the therapy of Behçet disease. *Ther Adv Chronic Dis*. 2014;5(3):112–134. doi:10.1177/2040622314523062
- Asutay F, Atalay Y, Acar AH, Asutay H, Eroğlu S, Burdurlu MÇ. Mandibular bone mineral density in patients with Behçet's disease. *Ther Clin Risk Manag*. 2015;11:1587–1591. doi:10.2147/TCRM.S93286
- Fukada SY, Silva TA, Garlet GP, Rosa AL, Da Silva JS, Cunha FQ. Factors involved in the T helper type 1 and type 2 cell commitment and osteoclast regulation in inflammatory apical diseases. *Oral Microbiol Immunol*. 2009;24(1):25–31. doi:10.1111/j.1399-302X.2008.00469.x

42. Martinho FC, Nascimento GG, Leite Fabio RM, Gomes Ana PM, Freitas LF, Camões Izabel CG. Clinical influence of different intracanal medications on Th1-type and Th2-type cytokine responses in apical periodontitis. *J Endod.* 2015;41(2):169–175. doi:10.1016/j.joen.2014.09.028
43. Ruiz XF, Duran-Sindreu F, Shemesh H, et al. Development of periapical lesions in endodontically treated teeth with and without periodontal involvement: A retrospective cohort study. *J Endod.* 2017;43(8):1246–1249. doi:10.1016/j.joen.2017.03.037
44. Aloyouny AY, Almufarji F, Almutairi GG, Alkait S, Al-Mohaya MA, Alserwi R. Impact of rheumatic diseases on oral health-related quality of life. *Cureus.* 2022;14(12):e32268. doi:10.7759/cureus.32268
45. Valerio JAE, Alberto Garza Elizondo M, Rodríguez Amado J, de la Garza-Ramos MA. Dental conditions in rheumatic diseases. *Rev Mex Estomatol.* 2016;3(2):75–92. <https://www.remexesto.com/index.php/remexesto/article/view/77/129>. Accessed April 7, 2023.