Review

Evaluation the Relationship Between Periodontal Disease and Inflammatory Bowel Diseases by Emphasizing the Role of Cytokines

Periodontal Hastalık ve İnflamatuar Bağırsak Hastalıkları Arasındaki İlişkinin, Sitokinlerin Rolünü Vurgulayarak Değerlendirilmesi

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ABSTRACT

Periodontal disease is a local, chronic and inflammatory process that results from complex interactions between biofilm and inflammatory immune response. Biofilm infections generally cause simultaneous activation of both natural and adaptive immune responses. Inflammatory bowel diseases are characterized by chronic inflammation in the intestines with exacerbations and remissions. Although the etiopathogenesis is not fully known, it is suggested that the disease is caused by chronic immune-mediated intestinal damage as a result of the complex interaction of genetic susceptibility and endogenous and exogenous triggers. Cytokines take place in many events including proliferation, growth, differentiation, hemostasis, regeneration, repair and inflammation. We aim in this review to evaluate the studies dealing with periodontal disease, inflammatory bowel diseases and their relation by emphasizing the role of cytokines.

Keywords: Cytokines; Inflammatory bowel diseases; Periodontal disease

ÖZET

Periodontal hastalık, biyofilm ve inflamatuar immün yanıt arasındaki komplike etkileşimlerden kaynaklanan lokal, kronik ve inflamatuar yanıttır. Biyofilm enfeksiyonları genellikle hem doğal hem de kazanılmış immün yanıtlarında aktivasyonuna neden olur. İnflamatuar bağırsak hastalıkları, aktivasyon ve remisyonla birlikte bağırsaklarda kronik inflamasyon ile karakterizedir. Etiyopatogenezi tam olarak bilinmemekle birlikte, hastalığa genetik yatkınlık ile endojen ve ekzojen tetikleyicilerin komplike etkileşiminin bir sonucu olarak kronik immün aracılı bağırsak hasarından kaynaklandığı ileri sürülmektedir. Sitokinler, proliferasyon, büyüme, farklılaşma, hemostaz, rejenerasyon, onarım ve inflamasyon gibi birçok olayda yer alır. Bu derlemede, sitokinlerin rolünü vurgulayarak periodontal hastalık, inflamatuar bağırsak hastalıkları ve bunların ilişkisini ele alan çalışmaları değerlendirmeyi amaçlamaktayız.

Anahtar Kelimeler: Sitokinler; İnflamatuar bağırsak hastalıkları; Periodontal hastalık

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Periodontal Disease

Periodontal disease (PD) is a local, chronic, and inflammatory process seen in periodontal tissues in response to dental biofilm.[1] Gingivitis and periodontitis are the most common forms of periodontal diseases.[2] In Federation World Workshop Classification (2017); the main headings of PD are noted in Table 1[3].

Periodontal destruction results from complex interactions between biofilm and inflammatory immune response. Biofilm infections generally cause simultaneous activation of both natural and adaptive immune responses. Frequently, these responses fail to eliminate biofilm pathogens and often result in collateral tissue damage.[4]

Although the way that gingivitis transforms into periodontitis has not been fully elucidated[5], periodontal disease occurs as a result of interactions between microbial dental plaque and host response. Page and Schroeder[6] examined periodontal lesions histopathologically and divided them into four stages. Initial lesions begin within 2-4 days to a beginning of microbial plaque accumulation. At this stage, inflammatory mediators such as interleukin (IL) -1ß, tumor necrosis factor (TNF)-α, IL-8, matrix metalloproteinase (MMP), prostaglandin E2 (PGE2) are released. Vascular permeability increases, infiltration of polymorphonuclear leukocytes and loss of perivascular collagen are observed. Early lesions develop within 4-7 days. Capillary proliferation and retepeg formation in the epithelium have occurred. Bleeding on probing and erythema which are the clinical manifestations of gingivitis can be seen. The dominant cells are T lymphocytes. After 2-3 weeks, the early lesion turns into an established lesion. Established lesions continue with collagen destruction in connective tissue, with the predominant cells being B lymphocytes and plasma cells.[6] While some established lesions may remain stable for many years, some transform into progressive and destructive lesions.[7] Advanced lesions are the final stage that manifests by periodontal tissue destruction. Initial, early and established gingival lesions indicate gingivitis, and advanced gingival lesions indicate periodontitis.[5]

While microorganisms cause direct tissue destruction with their enzyme and metabolic products, they indirectly activate the host response through virulence mechanisms and cause inflammation in the gingiva through the release of cytokines and natural defense mechanisms.[8]

Tissue destruction in PD occurs as interaction between MMP of lipopolysaccahides (LPS), toxins or enzymes with cells such as polymorphonuclear leukocytes (PMNL), macrophages, lymphocytes, fibroblasts and osteoblasts in periodontal tissues, thus ILs have been formed through the release of mediators such as TNF-α and PGE2.[9]

LPS has been shown to induce novo synthesis and secretion of IL-1β, TNF-α, IL-6, Interferon gamma (IFN)-γ and IL-10 from mast cells, thus contributing to the initiation of the inflammatory response.[10]

Inflammatory Bowel Diseases

Inflammatory Bowel Disease (IBD) is a term used for Ulcerative Colitis (UC) and Crohn's disease (CD), characterized by chronic inflammation in the intestines with exacerbations and remissions. Its etiology has not been fully elucidated.[11]

CD is a chronic inflammatory disease that can involve any part of the gastrointestinal tract from the mouth to the anus transmurally. The involvement is segmental where healthy tissues are seen among the inflamed areas. Obstructions, fistulas, fissures

Table 1. The main headings of periodontal disease[3].

Periodontal Health, Gingival Diseases and Conditions				
Periodontal health and gingival health	Plaque related gingivitis	Not plaque related gingival diseases		
Periodontitis				
Necrotizing periodontal diseases	Periodontitis	Periodontitis as a symptom of systemic diseases		
Other Conditions Affecting Periodontium				
Systemic diseases or conditions affecting the periodontal supporting tissues	Periodontal abscesses and endodontic-periodontal lesions	Mucogingival deformities and conditions	Traumatic occlusal forces	Dental and prosthesis related factor

and granulomas due to thickening of the intestinal wall and lumen narrowing, bloody and mucous diarrhea are common symptoms. In children, the involvement is mostly seen in the terminal ileum and colon.[12,13]

In UC, the area of inflammation is limited in the mucosal part of colon. The disease starts from the rectum and progresses towards the proximals without interruption. Unlike CD, the involvement is continuous and usually mucosal. Common symptoms in the course of the disease are bloody diarrhea, tenesmus, as well as systemic symptoms such as fever and weight loss.[14,15]

Although the etiopathogenesis of IBD is not fully known, it is suggested that the disease is caused by chronic immune-mediated intestinal damage as a result of the complex interaction of genetic susceptibility with endogenous and exogenous triggers.[16]

IBD is more common in the northern countries. This situation has been associated with lifestyle and environmental factors. While the incidence of IBD in the United States is similar in black and white races, its incidence in black people living in Africa is low.[11] Over time, the incidence of IBD has changed. In the first few decades of the 20th century, while UC was more common than CD in northern Europe and America, it was observed that the incidence of UC remained stable from the 1950s to the 1980s with an increase in the incidence of CD.[17]

The actual incidence of IBD in our country is not fully known. There are a limited number of studies on this subject. As a result of a study conducted in our country, the incidence of UC was 4.4 / 100.000; while the incidence of CD was determined as 2.2 / 100.000.[18]

The receptors of intestinal epithelial cells, phagocytes (macrophages and neutrophils) and natural killer cells (NK), are managed by the innate immune system that with their activation, proinflammatory cytokines (TNF, IL-1, IL-6, IL-8), chemokines and transcription genes of adhesive molecules are stimulated. They form a nonspecific line of defense that develops within hours. Disorders in these pathways cause an abnormal response to bacteria and trigger the development of IBD.[19,20]

It has been known that T helper (Th) 2 response in UC and the Th1 response in CD are more pronounced. Th17 is a group of T cells whose importance in inflammation has recently been demonstrated and has been shown to produce various cytokines, mainly IL-6 and IL-17.[19]

Cytokines

Cytokines are small polypeptide soluble proteins that affect the characteristics of the target cells locally or systemically. Although they are produced by a large cell group involved in many physiological events, their main sources are macrophages and T lymphocytes.[21]

Cytokines produced by macrophages, T lymphocytes, B lymphocytes, mast cells, endothelial cells, fibroblasts, and various stromal cells, it is known that they play an important role in the resolution of inflammation, wound healing, repair and regeneration.[22]

Cytokines are divided in two groups as pro-inflammatory and anti-inflammatory.

-Pro-inflammatory cytokines:
TNF-α, IL-1α, IL-1β, IL-6, IL-7 IL-8, IL-12, IL-17, IL-18, IL-19, IL-21, IL-23, IL- 24, IL-33, IL-36, IFN-γ, IFN-α, TGF-β, Leukemia inhibitory factor (LIF), IL-1F8, IL-1F6, IL-1F9

-Anti-inflammatory cytokines:
IL-1Ra, IL-4, IL-10, IL-6, IL-11, IL-13, IL-1F1, IL-1F5, IL-1F7, Il-1F10, IFN-α, TGF-β, LIF

-Pro-inflammatory and anti-inflammatory cytokines:
IL-6, IFN-α, TGF-β, LIF

Certain cytokines such as IL-1β, TNF-α, IL-6 and IL-8 play a role in the initiation of acute inflammation thus the excessive release of cytokines causes many different situations to develop.[23] In healthy periodontal tissues there is a balance between production and destruction mechanism. ILs such as IL-4, IL-10, and IL-13, called anti-inflammatory cytokines, suppress inflammation and prevent bone resorption.[24,25] Bone destruction and collagen loss in periodontal tissues have been seen as consequences of this balance disturbance.[26]

The relationship between Periodontal disease and Inflammatory Bowel Diseases

IBD and PD have recently become a global diseases that are frequently observed.[27,28]

By resulting in temporary bacteremia, increase of circulatory inflammatory mediators or autoimmune reactions, periodontitis have a role in chronic systemic diseases. There is a biological model that accepts this situation as a risk factor for systemic diseases.[29] It was reported in a study conducted on mice that CD is associated with periodontal diseases.[30]

It has been concluded that the prevalence and severity of PD were found to be higher in individuals with IBD.[31] The presence of periodontitis in patients diagnosed with IBD indicates that both inflammatory conditions may have similar pathogenic mechanisms.[32]

In an investigation regarding the evaluation of cytokines expression in intestinal mucosa and gingival tissue of patients having both periodontitis and IBD; expression of IL-17A, IL-17F, IL-22, IL-25, IL-33, IL-10 and INF-γ was significantly seen to be higher in gingival tissue than intestinal mucosa of IBD patients diagnosed with periodontitis.[33]

In a study by Koutsochristou *et al*., it has been found that patients with CD who need periodontal treatment, symptoms of gingival inflammation, and the frequency of caries were higher than healthy patients, though they had the same oral hygiene level.[34]

In a pilot study by Figueredo *et al*., chronic periodontitis patients were divided into three groups as CD, UC and systemically healthy control individuals. Blood, periodontal clinical indexes from 6 sites of all teeth excluding 3rd molars and gingival crevicular fluid (CGF) from 4 shallow sites and 4 deep sites were collected from each group. IL-1ß, IL-4, IL-6, IL-10, IL12p40, IL12p70, INF-y and TNF-α were examined in gingival fluid, and IL-18 in serum. As a result, IL-4 was found to be high in CGF while IL-8 was found to low in serum of the control group with no difference founded between all groups regarding clinical indexes.[35]

Forty five patients diagnosed with periodontitis (15 CD, 15 UC and 15 systemically healthy) were recalled for microbiological evaluation of subgingival plaque samples. While there was no difference between all groups in terms of pocket depth, clinical attachment level and bleeding in probing, in microbiological evaluation, *Bacteroides ureolyticus*, *Campylobacter gracilis*, *Prevotella melaninogenica*, *Staphylococcus aureus*, *Streptococcus (S) mitis*, *S.anginosus*, *S.intermedius*, were found to be higher in the CD group than the UC group. All micro-organisms except *S.mitis* were found to be systemically higher in the CD group than in the healthy group.[36]

The impact of TNF-α polymorphisms on periodontal parameters and inflammatory lesions of oral mucosa as a characteristic of CD was investigated. A total of 142 patients with CD were included in the study. Blood collection beside oral soft tissue alterations and periodontal parameters were assessed. It was reported that TNF-α is a significant risk indicator in oral soft tissue changes in patients with CD.[37]

Intraoral soft tissue changes were observed in 54 patients out of 147 patients who were diagnosed with CD. Gingival edema 27.2%, hyperplastic lesions in the buccal mucosa 20.4%, lichen planus 2.7%, candidiasis 3.4% and aphthous ulcer 4.1% were observed.[38]

The Th1/Th2 paradigm provided a framework for understanding the pathogenesis of several conditions such as IBD, and periodontitis. According to the Th1/Th2 paradigm, it was initially hypothesized that IL-12, hence, Th1 cells were playing the central role in the inflammatory diseases; however, it was demonstrated that functional Th1 pathways downregulate the onset and progression of IL-12-deficient mice.[39,40]

The relationship between CD and periodontal health was aimed to determine in a study. The higher plaque and bleeding at probing, and deeper periodontal pockets in the CD group than the healthy control group were found.[41]

The evaluation of the effect of 8-week drug therapy on subgingival microbiota in pediatric patients with CD was performed and it was observed that subgingival microbiota differed from healthy individuals. Antibiotic use affected the bacterial population in CD patients.[42] It has been reported a delay in recovery of CD patients receiving systemic medication after mucogingival surgeries.[43]

Habashneh *et al*., determined the relationship (prevalence, severity and extent) between IBD and periodontitis. The prevalence, severity and extent of periodontitis in IBD group were found to be higher than systemically healthy group[44]. Periodontitis has

an effect on systemic autoimmunity or inflammatory diseases. It was reported that IBD diseases, especially peri-anal disease, is associated with periodontitis.[45]

The cytokine expression in gingival and intestinal tissues from periodontitis patients with IBD was measured and it was evaluated whether IBD activity incorporate with the amount of gingival cytokines. Cytokine expression (IL-1β, IL-4, IL-6, IL-10, IL-21, IL-22, IL-23, IL-25, IL-31, IL-33, IL-17A, IL-17F, IFN-γ, sCD40L, and TNF-α) was evaluated using bead-based multiplex technology from paired gingival and intestinal tissues that collected from 21 patients. It was reported that cytokine expression in gingival tissue influenced by the activity of inflammatory bowel disease.[46]

A review study provided an overview of the current knowledge about the differentiation of Th17 cells and the role of the IL-17 / IL-23 axis in the pathogenesis of immune-mediated inflammatory diseases. It was also aimed to review the association of these diseases with periodontitis. It has been concluded that IL-17 played an important role in inflammatory events that lead to the manifestation of IBD and many clinical randomized controlled trials proved the efficacy of cytokine inhibitors that manipulate IL-17 and related pathways in the management.[47]

In an investigation of the relationship between PD and IBD in a meta-analysis study conducted by She *et al*., it was demonstrated that periodontitis was significantly associated with IBD.[48]

Healing after nonsurgical primary/secondary endodontic treatment of apical periodontitis (AP) in patients with IBD treated with anti TNF-α biologic medications (BMs) was evaluated. Nineteen patients with 22 teeth affected by AP from the gastroenterology unit of the hospital with IBD under treatment with BMs formed the study group (the IBD group). Fourteen patients with 22 teeth with AP, matched by age and sex, without systemic diseases and not taking medications formed the control group. It was observed that the treatment of AP in patients taking BMs had no complications; furthermore, it was associated with faster healing than the controls. These results support the possible therapeutic aid of BMs in treating AP.[49]

The expression of the cytokines IFN-γ, IL-1β, IL-4, IL-6, IL-10, IL-21, IL-22, IL-23, IL-25, IL-31, IL-33, IL-17A, IL-17F, sCD40L, and TNF-α in gingival tissue and intestinal mucosa of patients having both periodontitis and IBD was measured. Twenty eight patients with periodontitis (18 with CD and 10 with UC) were selected. Gingival and intestinal biopsies were collected and cytokines expression was evaluated. It has been reported that the expression of IL-17A, IL-17F, IL-22, IL-25, IL-33, IL-10, and INF-γ was significantly increased in gingival tissue in comparison with intestinal mucosa of patients with periodontitis and IBD.[35]

In an *in vitro* study, the anti-inflammatory potential of green and black tea extracts using models related to PD and IBD was investigated. It was reported that all tea compounds tested exhibited comparable effects, including the capacity to reduce the secretion of pro-inflammatory mediators. The anti-inflammatory properties of tea polyphenols suggested that they may represent promising preventive or therapeutic agents.[50]

CONCLUSION

As a conclusion, it can be stated that there are few cross sectional and cohort studies in the literature related with PD and IBD which demonstrates a common immunoptahogenic mechanisms. Not only host response, also common bacterial etiology may take part in both diseases. Mostly investigated mechanisms are cytokine involvement especially in gingival crevicular fluid in patients with periodontitis and IBD.

There are limited reports regarding the therapeutic effects of cytokine inhibitors on gingival, periodontal, and oral mucocutaneous diseases, which could be due to their restricted indication for severe systemic conditions, high costs, and many adverse effects.

REFERENCES

1. Hinrichs JE, Kotsakis G. Classification of Diseases and Conditions Affecting the Periodontium: In Carranza's Clinical Periodontology. Newman MG, Takei H, Klokkevold PR, Carranza FA, Eds. 12th ed. USA: Elsevier Health Sciences; 2012. p.45-67.

2. Mariotti A. Dental plaque-induced gingival diseases. Ann Periodontol 1999;4:7-19.

3. Caton JG, Armitage G, Berglundh T, Chapple IL, Jepsen S, S. Kornman K, *et al*. A new classification scheme for periodontal and peri-implant diseases and conditions–Introduction and key changes from the 1999 classification. J Periodontol 2018;1:S1-S8.

4. Zelkha SA, Freilich RW, Amar S. Periodontal innate immune mechanisms relevant to atherosclerosis and obesity. Periodontol 2000 2010;54:207-21.

5. Schenekein H. Academy Reports- Pathogenesis of Periodontal Disease. J Periodontol 1999;70:457–70.

6. Page RC, Schroeder HE. Pathogenesis of inflammatory periodontal disease. A summary of current work. Lab Invest 1976;34:235–49.

7. Page RC, Offenbacher S, Schroeder HE, Seymour GJ, Kornman KS. Advances in the pathogenesis of periodontitis: summary of developments, clinical implications and future directions. Periodontol 2000 1997;14:216–48.

8. Kinane DF, Bartold PM. Clinical relevance of the host responses of periodontitis. Periodontol 2000 2007;43:278-93.

9. Holt SC, Bramanti TE. Factors in virulence expression and their role in periodontal disease pathogenesis. Crit Rev Oral Biol Med 1991;2:177-281.

10. Madianos PN, Bobetsis YA, Kinane DF. Generation of inflammatory stimuli: how bacteria set up inflammatory responses in the gingiva. J Clin Periodontol 2005;6:57-71.

11. Akçam M. Çocukluk çağı inflamatuar barsak hastalıkları. Türkiye Klinikleri J Pediatr Sci 2012;8:56-60.

12. Kliegman, R, Nelson, WE. Nelson textbook of pediatrics. 18th ed. Philadelphia: Saunders; 2007.

13. Geissler, C, Powers HJ, Garrow JS. Human nutrition. 11th ed. Edinburgh; New York: Elsevier/Churchill Livingstone; 2005.

14. Gasche C, Scholmerich J, Brynskov J, D'Haens G, Hanauer GB, Irvine EJ, *et al*. A simple classification of Crohn's disease: report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998. Inflamm Bowel Dis 2000;6:8-15.

15. Silverberg MS, Satsangi J, Ahmad T, Arnott IDR, Bernstein CN, Brant SR, Caprilli R, *et al*. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol 2005;19A:5A-36A.

16. Walker, W.A. Pediatric gastrointestinal disease: pathophysiology, diagnosis, management. 5rd ed. Hamilton, Ont.;Lewiston, NY: B.C. Decker; 2008.

17. Gollop JH, Phillips SF, Melton LJ, Zinsmeister AR. Epidemiologic aspects of Crohn's disease: a population based study in Olmsted County, Minnesota, 1943-1982. Gut 1988;29:49-56.

18. Tozun N, Atug O, Imeryuz N, Hamzaoglu HO, Tiftikci A, Parlak E. Clinical characteristics of inflammatory bowel disease in Turkey: a multicenter epidemiologic survey. J Clin Gastroenterol 2009;43:51-7.

19. Gahl WA, Brantly M, Kaiser-Kupfer MI, Iwata F, Hazelwood S, Shotelersuk V, *et al*. Genetic defects and clinical characteristics of patients with a form of oculocutaneous albinism (Hermansky Pudlak syndrome). N Engl J Med 1998;338:1258-64.

20. Roe TF, Coates TD, Thomas DW, Miller JH, Gilsanz V. Brief report: Treatment of chronic inflammatory bowel disease in glycogen storage disease type Ib with colony stimulating factors. N Engl J Med 1992;326:1666-9.

21. Seymour GJ, Gemmell E. Cytokines in periodontal disease: where to from here?. Acta Odontol Scand 2001;59:167-73.

22. Jaedicke KM, Preshaw PM, Taylor JJ. Salivary cytokines as biomarkers of periodontal diseases. Periodontol 2000 2016;70:164-83.

23. Shapira L, Wilensky A, Kinane DF. Effect of genetic variability on the inflammatory response to periodontal infection. J Clin Periodontol 2005;6:72-86.

24. Munro CL, Grap MJ, Jablonski R, Boyle A. Oral health measurement in nursing research: state of the science. Biol Res Nurs 2006;8:35-42.

25. Giannobile WV, Beikler T, Kinney JS, Ramseier CA, Morelli T, Wong DT. Saliva as a diagnostic tool for periodontal disease: current state and future directions. Periodontol 2000 2009;50:52-64.

26. Jaedicke KM, Taylor JJ, Preshaw PM. Validation and quality control of ELISAs for the use with human saliva samples. J Immunol Methods 2012;377:62-5.

27. Siew NgC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, *et al*. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet 2018;390:2769-78.

28. Kinane, DF, Stathopoulou PG, Papapanou PN. Periodontal diseases. Nat Rev Dis Primers 2017;3:17038.

29. Nesse W, Abbas F, Van Der Ploeg I, Spijkervet FKL, Dijkstra PU, Vissink A. Periodontal inflamed surface area: quantifying inflammatory burden. J Clin Periodontol 2008;35:668-73.

30. Pietropaoli D, Del Pinto R, Corridoni D, Rodriguez-Palacios A, Di Stefano G, Monaco A, *et al*. Occurence of spontaneous periodontal disease in the SAMP1-Yitc murine model of Crohn disease. J Periodontol 2014;85:1799-805.

31. Agossa K, Dendooven A, Dubuquoy L, Gower-Rousseau C, Delcourt-Debruyne E, Capron M. Periodontal manifestations of inflammatory bowel disease: Emerging epidemiologic and biologic evidence. J. Periodontal Res 2017;52:313–24.

32. Khan SA, Kong EF, Meiller TF, Jabra-Rizk MA. Periodontal Diseases: Bug Induced, Host Promoted. PLoS Pathog 2015;11:e1004952.

33. Menegat JSB, Lira-Junior R, Siqueira MA, Brito F, Carvalho AT, Fischer RG, *et al*. Cytokine expression in gingival and intestinal tissues of patients with periodontitis and inflammatory bowel disease: An exploratory study. Arch Oral Biol 2016;66:141-6.

34. Koutsochristou V, Zellos A, Dimakou K, Panayotou I, Siahanidou S, Roma-Giannikou E, *et al*. Dental Caries and Periodontal Diseases in Children and Adolescents with Inflammatory Bowel Disease: A case-Control Study. Inflamm Bowel Dis 2015:21;1839-46.

35. Figueredo CM, Brito F, Barros FC, Menegat JSB, Pedreira RR, Fischer RG, *et al*. Expression of cytokines in the gingival crevicular fluid and serum from patients with inflammatory bowel disease and untreated chronic periodontitis. J Periodont Res 2011;46:141–6.

36. Brito F, Zaltman C, Carvalho ATP, Fischer RG, Persson R, Gustafsson A, *et al*. Subgingival microflora in inflammatory bowel disease patients with untreated periodontitis. Eur J Gastroenterol Hepatol 2013;25:239-45.

37. Schulz S, Reichert S, Streetz K, Trautwein C, Reichert Y, Glaser C, *et al*. Tumor necrosis factor and oral inflammation in patient with Crohn disease. J Periodontol 2014;85:1424-31.

38. Stein JM, Lammert F, Zimmer V, Granzow M, Reichert S, Schulz S, *et al*. Clinical periodontal and microbiologic parameters in patients with Crohns disease with consideration of the CARD15 genotype. J Periodontol 2010;81:535-45.

39. Chu CQ, Wittmer S, Dalton DK. Failure to suppress the expansion of the activated CD4 T cell population in interferon gamma-defificient mice leads to exacerbation of experimental autoimmune encephalomyelitis. J Exp Med 2000;192:123-8.

40. Zhang GX, Gran B, Yu S, Li J, Siglienti I, Chen X, *et al*. Induction of experimental autoimmune encephalomyelitis in IL-12 receptor-beta 2-defificient mice: IL-12 responsiveness is not required in the pathogenesis of inflammatory demyelination in the central nervous system. J Immunol 2003;170:2153-60.

41. Brito F, de Barros FC, Zaltman C, Carvalho ATP, Carneiro AJV, Fischer RG, *et al*. Prevalence of periodontitis and DMFT index in patients with Crohn's disease and ulceratice colitis. J Clin Periodontol 2008;35:555-60.

42. Kelsen J, Bittinger K, Pauly-Hubbard H, Posivak L, Grunberg S, Baldassano R, *et al*. Alteration of the subgingival microbiota in pediatric Crohn's disese studied longitudinally in discovery and validation cohorts. Inflamm Bowel Dis 2015;21:2797-805.

43. Andersen KM, Selvig KA, Leknes KN. Altered healing following mucogingival surgery in a patient with Crohns disease: a literature review and case report. J Periodontol 2003;74:537-46.

44. Habashneh RA, Khader YS, Alhumouz MK, Jadallah K, Ajlouni Y. The association between inflammatory bowel disease and periodontitis among Jordanians: a case control study. J Periodontal Res 2012;47:293-8.

45. Vavricka SR, Manser CN, Hediger S, Vögelin M, Scharl M, Biedermann L, *et al*. Periodontitis and gingivitis in inflammatory bowel disease: a case control study. Inflamm Bowel Dis 2013;19:2768-77.

46. Figueredo CM, Martins AP, Lira-Junior R, Menegat JB, Carvalho AT, Fischer RG, *et al*. Activity of inflammatory bowel disease influences the expression of cytokines in gingival tissue. Cytokine 2017;95:1-6.

47. Bunte K, Beikler T. Th17 Cells and the IL-23/IL-17 Axis in the Pathogenesis of Periodontitis and Immune-Mediated Inflammatory Diseases. Int J Mol Sci 2019;20:3394.

48. She Y, Kong X, Ge Y, Liu ZY, Chen J, Jiang J, *et al*. Periodontitis and inflammatory bowel disease: a meta-analysis. BMC Oral Health 2020;20:67.

49. Cotti E, Mezzena S, Schirru E, Ottonello O, Mura M, Ideo F, *et al*. Healing of Apical Periodontitis in Patients with Inflammatory Bowel Diseases and under Anti–tumor Necrosis Factor Alpha Therapy. J Endod 2018;44:1777-82.

50. Ben Lagha A, Grenier D. Tea polyphenols inhibit the activation of NF-κB and the secretion of cytokines and matrix metalloproteinases by macrophages stimulated with *Fusobacterium nucleatum*. Sci Rep 2016;6:34520.