Association Between Periodontal Disease and Inflammatory Bowel Disease (IBD): A Clinical Evidence-based Review

Benso Sulijaya[1,2]*, Alma Mutiarani[3], Amaliyatus Silmi[3], Mutiara Medikasari[3], Naila Zhafirah[3]

1. Department of Periodontology, Faculty of Dentistry, Universitas Indonesia, Jakarta, Indonesia.
2. Dental Division, Universitas Indonesia Hospital, Depok, West Java, Indonesia.
3. Dental Profession Program, Faculty of Dentistry, Universitas Indonesia, Jakarta, Indonesia.

Abstract

This article purpose to find out the relationship between periodontitis and IBD further.

Literature searches were conducted from articles published in PubMed using keywords "periodontal disease AND periodontitis AND inflammatory bowel disease", and then the findings were comprehensively summarized and elaborated.

The pathogenesis of both diseases, both periodontitis and IBD, are multifactorial, leading to defects in mucosal defenses, deregulation of the immune response, and chronic inflammation of the mucosa. The prevalence of periodontal disease in IBD patients continues to increase. In addition, induction of periodontitis appears to result in dysbiosis in the intestine and alter the function of the intestinal epithelial barrier.

There are complex pathogen interactions between periodontal disease and IBD. Therefore, patients with IBD have a higher susceptibility to periodontal disease.

Review (J Int Dent Med Res 2023; 16(3): 1336-1341)

Keywords: Periodontal disease, periodontitis, inflammatory bowel disease.

Received date: 21 April 2023. **Accept date:** 23 May 2023

Introduction

The most prevalent disease affecting people today is certainly periodontal disease, a chronic condition. Gingivitis is a warning sign of reversible inflammation in the gums and soft tissues around teeth that is brought on by an immune reaction to biofilms that develop on the surface of the teeth.[1] Periodontitis, an inflammatory condition of the tooth's supporting tissues brought on by microorganisms, damages periodontal ligaments and alveolar bones with increased probing depths, recessions, or both, which may end in tooth loss or alveolar bone resorption.[2,3]

Inflammatory bowel disease (IBD) is defined as a chronic intestinal inflammation that is caused by host-microbial interactions in a genetically vulnerable person.[4] This inflammatory condition consists of two major form, known as Crohn's disease and Ulcerative colitis.[5] The multifactorial etiology of periodontitis and inflammatory bowel disease (IBD) includes a significant mucosal barrier failure, dysregulation of the host immune response, and persistent mucosal inflammation. indurated lesions, cobblestone, mucogingivitis, aphthous stomatitis, and pyostomatitis vegetans are common oral symptoms of IBD. Furthermore, people with IBD who have secondary neutrophil abnormalities have been seen to have severe periodontitis.[5] Current research aims at regarding the relationship between IBD and periodontitis. This article purpose to find out the relationship between IBD and periodontitis further.

Corresponding author:
Benso Sulijaya, DDS., MDS(Perio-Consultant)., Ph.D.
Department of Periodontology, Faculty of Dentistry, Universitas Indonesia, Salemba Raya No. 4, Jakarta Pusat, 10430, Indonesia.
E-mail: bensosulijaya@gmail.com, benso.sulijaya87@ui.ac.id

Materials and methods

Literature searches were conducted by 2 reviewers (A.M. and A.S.), independently. Article published in PubMed within the past 10 years with full text written in English available were included. Keywords used were "periodontal disease AND periodontitis AND inflammatory bowel disease". Paper selection and data extraction were performed by aforementioned reviewer. Also, additional articles were manually searched and included from citations of the selected papers. We focused on the articles

describing: 1) gingival epithelial barrier, 2) pathogenesis of periodontal disease, 3) association between periodontal disease and IBD. Based on article abstracts, irrelevant topics, and non-English written articles were excluded. Further evidence and findings reported were discussed in the form of narrative review.

Results

Gingival Epithelial Barrier

In various areas, including the oral cavity, respiratory system, and digestive system, the interaction of epithelial cells with the external environment serves as a defense against physical, chemical, and microbiological illnesses. The term "leaky gut" refers to the intestinal epithelial barrier's dysfunction, which makes it easier for pathogenic agents to enter the host and cause a variety of gastrointestinal illnesses. Chronic gastrointestinal inflammation known as IBD is linked to intestinal epithelial barrier failure brought on by microorganisms. The most prevalent oral ailment in people is periodontitis, a chronic inflammatory disease of the mouth cavity. The gingival epithelium serves as a structural barrier between the underlying tissue and the outside environment, acting as the first line of defense against foreign infections. Periodontal disease's onset and development are linked to "leaky gum," a disruption of epithelial cell adhesion.[4]

The surface of the teeth, gums, and buccal mucosa are colonized by more than 700 kinds of bacteria, making the oral cavity the second-largest microbial population in the body. Gum tissue epithelial cells will be exposed to a lot of bacteria on a constant basis. By disrupting the epithelial barrier, the virulence factors of several periodontopathogens can stretch the gingival tissue.[4]

The gastrointestinal epithelium is made up of a layer and a columnar epithelial cell, unlike the oral epithelium. The primary cellular secretion in the intestinal epithelium that produces and secretes mucin into the intestinal lumen are goblet cells. The secretion of immunoglobulins and the absorption of nutrients are both related to enterocytes. Antimicrobial peptides can be created and produced by panet cells. An effective physical and chemical barrier against microbial invasion is provided by these specialized epithelial cells. [4]

The oral epithelium, in contrast to the gastrointestinal epithelium, is made up of a stratified squamous epithelium that is split into the three parts known as the oral epithelium (OE), sulcular epithelium (SE), and junctional epithelium (JE) depending on the cell morphology. The OE is a keratinized epithelium that acts as a strong physical barrier to prevent the invasion of microbes. SE and JE, in contrast, are non-keratinized epitheliums that are semipermeable and facilitate the transfer of macro-substances into the underlying connective tissue through the gingival sulcus. The junction structures that join epithelial cells help to reinforce an effective barrier against bacterial invasion. By weakening the cell-to-cell junction structures, a number of bacteria and their products can disrupt the epithelial barrier, leading to the collapse of the barrier and the production of periodontal inflammation and periodontal immune response. [4]

When left untreated, gingivitis, a reversible inflammation of the gingiva, can turn into periodontitis. Pathogen buildup in the pocket is followed by epithelial cell release of chemotactic cytokines, which causes neutrophils to be deposited in the JE. The epithelial barrier is broken as a result of proteolytic enzymes released by neutrophils. When the epithelium breaks down, pathogens and their byproducts can enter the area between epithelial cells and the lamina propria. This allows them to cause tissue to deteriorate and bone resorption by releasing pro-inflammatory cytokines. An elevated level of gingival inflammation brought on by PMN migration, mononuclear leukocytes (such as T- and B-lymphocytes), and gingival crevicular fluid moving through the intercellular gaps are factors that lead to localised disruption of the JE. [4]

Microbes can interact with epithelial barrier function through direct and indirect ways. The bacteria or their products manipulate genes or proteins involved in barrier function, which mediates the direct effect. In contrast, the cells immunoregulatory reactions to microorganisms mediate the indirect effect. In response to microorganisms, epithelial cells generate pro-inflammatory cytokines and chemokines that cause immune cells to secrete inflammatory mediators like IFN- and TNF locally. By inhibiting the growth of harmful organisms, which indirectly alter the epithelial barrier function, anti-microbial

peptides and secretory antibodies both contribute significantly to maintaining microbiota homeostasis. [4]

Microbes can interact with epithelial barrier function through direct and indirect ways. The bacteria or their products manipulate genes or proteins involved in barrier function, which mediates the direct effect. In contrast, the cells immunoregulatory reactions to microorganisms mediate the indirect effect. In response to microorganisms, epithelial cells generate pro-inflammatory cytokines and chemokines that cause immune cells to secrete inflammatory mediators like IFN- and TNF locally. By inhibiting the growth of harmful organisms, which indirectly alter the epithelial barrier function, anti-microbial peptides and secretory antibodies both contribute significantly to maintaining microbiota homeostasis. Connexin-43, a gap junction protein, can be decreased in human gingival epithelial cells by *A. actinomycetemcomitans*. T. denticola, together with *P. gingivalis* and *T. forsythia*, is one of the main pathogens in chronic periodontitis. ZO-1 protein degradation allowed *T. denticola* to breach the epithelial barrier and enter the epithelium layer. In addition to dangerous bacteria, the oral cavity contains helpful bacteria. The best anti-microbial defenses were provided by *Lactobacillus* species such *L. paracasei, L. plantarum, L. rhamnosus*, and *L. salivarius* against infections that interfered with the epithelial barrier. The sialic acid-binding protein Hsa is present in *Streptococcus gordonii*, which makes it easier for the bacteria to adhere to oral surfaces and support biofilm homeostasis. [4]

The most well-known bacteria associated with gastrointestinal disorders in the gut is *Escherichia coli* (*E. coli*). Additionally, some microbes are regarded as helpful bacteria because of how well they affect the function of the gut epithelial barrier. Lactic acid is produced by *Lactobacillus* species that are prevalent in the gastrointestinal tract. As probiotics, these microorganisms are frequently utilized. Some *Lactobacillus* species boost the genes (*occludin, ZO-1, ZO-2,* and *cingulin*) linked to tight junction formation and suppress TEER disruptions. One of the bacterial species found in the human intestine is the *Bifidobacterium* genus. In the colonic tissue, *B. longum* is related to an increase in tight junction protein (claudin-1 and occludin). [4]

Pathogenesis of Periodontal Disease

Based on their virulence and close ties to the disease's site, the oral anaerobic bacterial red complex of *P. gingivalis, T. denticola*, and *T. forsythia* has historically been considered the primary cause of periodontitis. According to a novel pathogenesis model for periodontitis, synergistic and polymicrobial dybiosis, which upsets the ecological balance of biofilms and threatens the homeostasis of periodontal tissue, rather than individual pathogens, are to blame for the illness. An imbalance in the relative quantity or impact of microbial species with various roles that work together to generate pathogenic organisms that can cause disease in the mouth or extraoral tissue of vulnerable people is what is known as periodontal microbiota dysbiosis. [1]

The change from symbiotic microbial communities made up primarily of facultative bacteria like *Actinomyces* and *Streptococci* to dysbiotic microbial communities made up of anaerobic bacteria from the phylum *Firmicutes, Proteobacteria, Spirochaetes, Bacteroidetes*, and *Synergistetes* is associated with the transition from periodontal health to a disease. The oral dysbiosis microbiota has evolved to grow in an inflammatory environment and is enriched by virulence factors. Subgingival fissures, biofilms, gingival crevicular fluid, and the epithelium around cervical teeth are the primary homes of bacteria linked to periodontitis. Bacteria face difficulties in the subgingival environment, which is full of immunological and inflammatory mediators. Controlling immunoinflammatory circumstances is necessary for maintaining host-microorganism equilibrium in the periodontium and maintaining periodontal health. However, in periodontitis, the host's immune response is erratic because of microbial interference or a malfunction in the immunoregulatory system of the host, therefore ineffective in halting bacterial development and the pathogenesis cycle. Dysbiosis and inflammation can reinforce one another in a self-sustaining pathogen cycle caused by an unchecked host immunological response, creating a positive feedback loop. [1]

Association Between Periodontal Disease and Inflammatory Bowel Disease

Impact of Periodontal Disease on IBD

For more than 20 years, additional chronic inflammatory disorders have been linked to periodontitis. Periodontitis is thought to affect IBD because the inflammation it causes can lead

to low-grade systemic inflammation. Pro-inflammatory cytokines have been linked to a number of processes, including atherosclerosis, by inducing acute phases in the liver. Ingestion of P. gingivalis can alter the intestinal microbiota, which increases epithelial permeability and results in intestinal endotoxemia, which results in systemic inflammation. This is because vast numbers of oral bacteria are eaten by saliva into the intestine. [2]

Study	Participant	Findings
Flemmig *et al.*[8] (1991)	107 IBD patients (46 with CD and 61 with UC).	IBD patients presented an 11.9% higher prevalence, but lower severity.
Grossner-Schreiber *et al.*[9] (2006)	62 patients with IBD (46 with CD and 16 with UC) and 59 healthy controls.	IBD patients had more sites with attachment loss (at least 4 and 5 mm), although periodontal disease was not clearly different.
Brito *et al.*[10] (2008)	179 patients with IBD (99 with CD and 80 with UC) and 74 controls.	CD and UC patients had higher prevalence of periodontitis than controls.
Habashneh *et al.*[11] (2012)	160 patients with IBD (59 with CD and 101 with UC) and 100 control patients.	Patients with IBD have higher prevalence, severity, and extent of periodontitis compared with non IBD group.
Vavricka *et al.*[12] (2013)	113 patients with IBD (69 with CD and 44 with UC) and 113 controls.	Gingivitis and periodontitis markers were higher in patients with IBD than in healthy control.
Koutsochristou *et al.*[13] (2015)	55 children and adolescents with IBD and 55 controls.	More gingival inflammation and increased periodontal treatment needs were observed in children and adolescents with IBD

Table 1. Relationship Between Periodontitis and IBD[2]. CD: Crohn's disease; UC: Ulcerative colitis; IBD: Inflammatory bowel disease.

A study used P. gingivalis, F. nucleatum, and P. intermedia to infect the periodontal tissue of mice as a model of periodontitis. The mice were given healthy meals that were either normal or diabetogenic, high in fat, and carbohydrate-free, after which the periodontal and gut microbiota were examined for alterations. It was discovered that periodontitis in mice fed a typical diet was linked to straightforward alterations in the gut microbiota, including an increase in the *Actinobacteria* and *Deltaproteobacteria* Groups. Changes in the gut flora were also seen in mice fed high-fat, carbohydrate-free diets. Due to the constant flow of saliva into the gastrointestinal system and the numerous opportunities for salivary bacteria to enter the intestine, another study claims that salivary microbiota may somewhat influence the development of gut microbiota. According to the findings mentioned above, a complex interaction between the immune system's inflammatory response and a dysbiotic microbiota under the influence of environmental and genetic variables accounts for the pathogenesis of both periodontitis and inflammatory bowel disease. [2, 6-7]

Impact of IBD on Periodontal Disease

Extra-intestinal symptoms, which may affect the eyes, joints, skin, liver, pancreas, blood, and mouth, are what define IBD's clinical presentation.[3] These extra-intestinal indications may start before or continue for many years after the intestinal symptoms. In 1969, pyostomatitis vegetans, gingival hyperplasia, papillomatosis of the oral mucosa, vesicular eruptions like pemphigus vegetans, periodontitis, and caries were among the first oral signs of Crohn's disease (CD) to be identified. Additionally, conditions including lip swelling, cobblestone lesions on the palate and oral mucosa, vesicles, erosion, ulcers, polypoid lesions, and necrotic areas can have an impact on the oral and gingival mucosa. [2]

It has been investigated through a few epidemiological studies if patients with IBD may have a higher prevalence of periodontal disease. IBD did not increase susceptibility to periodontal disease, according to a study that found there was no significant difference in periodontal health between the IBD group and the control group. Periodontal examinations, however, were only partially performed in this study. Another study indicated that IBD patients had greater rates of periodontal disease severity and periodontitis, as well as a higher prevalence of periodontal disease when employing a complete mouth periodontal examination. Patients with Ulcerative Colitis can see these changes more clearly than those with Crohn's disease.[2] Some summaries of epidemiological studies regarding the relationship between periodontitis and IBD can be seen in the Table.1.

The oral microbiome is a significant subject that has been investigated as a potential cause causing the altered susceptibility to periodontal disease in IBD patients.[14] As reported recently, periodontitis causes higher number of tooth loss in higher staging and grading.[15] Further, the periodontal microflora of patients with IBD was examined in a study, and it was discovered that these patients had a microflora that was primarily made up of small, movable, Gram-negative rods, which is most consistent with the species *Wolinella*. Another study found that pediatric CD patients' oral microbiome had less overall diversity than UC patients did. In

individuals with IBD, there was a substantial variation in the makeup of salivary microbiota, according to a study. The genus *Prevotella* was found in much higher concentrations in the salivary microbiome of IBD patients, according to the investigators. Changes in the microbiota of the tongue, buccal mucosa, and saliva were seen in animal models of colitis. Additionally, compared to the tongue and buccal mucosa, the microbial community in saliva was more susceptible to alteration. Regardless of the level of periodontal loss, different species, including Campylobacter gracilis and Treponema denticola, were found in inflamed regions in patients with CD, UC, and controls. These differences were more prominent in CD patients. These species could be damaging to the relationship between microbes and hosts.[2]

In patients with IBD and periodontitis, the inflammatory immune response is a significant contributor to tissue destruction. The inflammatory response is therefore thought to play a significant role in raising the risk of periodontitis in IBD patients. The study examined the expression of IL-1, IL-4, IL-6, IL-10, IL-12p40, IL-12p70, IL-18, and INF- in the GCF and serum of individuals with IBD and untreated periodontitis. Comparing UC patients to control patients, there was a considerable drop in IL-4 in the inflammatory area without any tissue damage. Other cytokines, however, showed equal expression in GCF across all groups. When compared to controls, IL-18 levels in serum are noticeably greater in CD and UC patients. Similar to the findings for gingival fluid, it was discovered that there were no significant differences in the expression of the cytokines (IL-1, IL-4, IL-6, IL-10, IL-21, IL-22, IL-23, IL-25, IL-31, IL-33, IL-17A, IL-17F, IFN-s, sCD40L, and TNF) between CD and UC when evaluating the patient's gingival tissue. The relevance of greater levels of IL-4, IL-10, and IL-21 and a tendency toward higher levels of IL-1 suggest that IBD activities may exacerbate the inflammatory response in the gingival tissue of IBD patients with periodontitis. [2]

Studies have focused on the changes in saliva in IBD patients. Patients with IBD, particularly those with active disease, have been reported to have elevated levels of pro-inflammatory cytokines. IL-6 levels in saliva were higher in CD patients than in UC patients. individuals with active CD have higher levels of salivary IL-1, IL-6, and TNF than individuals with inactive or under control CD. Additionally, CD patients have a marked decline in overall antioxidant capacity as well as an uptick in TGF-(1), nitric oxide, and lipid peroxidation. TGF- and nitric oxide levels in UC patients are higher than in the control group. Additionally, CD and UC patients had lower levels of lysozyme and higher levels of IgA and LL37 in their saliva. Comparing UC patients to CD patients, salivary inflammation is a little more common in UC patients. Although studies of salivary changes may help to explain why IBD patients have a higher prevalence of periodontitis, more research is still required to determine how these changes can impact the onset and/or progression of periodontal disease. In addition to salivary alterations, IBD patients have also been researched for neutrophil behavior, which is crucial in the etiology of periodontitis. Patients with active IBD have peripheral neutrophils that are more metabolically active than people without IBD. [2]

Conclusions

IBD and periodontitis have been linked for more than 20 years. Both periodontitis and IBD have a complex etiology that results in compromised mucosal defenses, dysregulated immunological responses, and persistent mucosal inflammation. In patients with inflammatory bowel illness, periodontal disease is more common. Additionally, it appears that the induction of periodontitis alters the function of the intestinal epithelial barrier and causes dysbiosis in the intestine. Inflammatory bowel disease (IBD) and periodontal disease have intricated pathogen interactions. As a result, periodontal disease is more likely to affect IBD patients.

Declaration of Interest

The authors report no conflict of interest.

References

1. Hajishengallis, G. Periodontitis: from microbial immune subversion to systemic inflammation. Nature Publishing Group 2015; 15(1), 30–44. https://doi.org/10.1038/nri3785
2. Lira-junior, R., Figueredo, C. M., Lira-junior, R., & Figueredo, C. M. Periodontal and inflammatory bowel diseases: Is there evidence of complex pathogenic interactions ?, World J Gastro 2016; 22(35): 7963–7972. https://doi.org/10.3748/wjg.v22.i35.7963
3. Newman, M. G., & Takei, H. H. (n.d.). Newman and Carranza's Clinical Periodontology.
4. Takahashi, N., Sulijaya, B., Yamada-Hara, M., Tsuzuno, T.,

Tabeta, K., & Yamazaki, K. Gingival epithelial barrier: regulation by beneficial and harmful microbes. Tissue Barriers. 2019;7(3): 1–10. https://doi.org/10.1080/21688370.2019.1651158
5. Yu, H., Chen, T., & Chang, Y. ScienceDirect Inflammatory bowel disease as a risk factor for periodontitis under Taiwanese National Health Insurance Research database. J Dent Sci 2018;13(3): 242–247. https://doi.org/10.1016/j.jds.2018.03.004
6. Sulijaya B, Yamada-Hara M, Yokoji-Takeuchi M, Matsuda-Matsukawa Y, Yamazaki K, Matsugishi A, et al. Antimicrobial function of the polyunsaturated fatty acid KetoC in an experimental model of periodontitis. J Periodontol. 2019;90(12):1470–80.
7. Mulhall H, Huck O, Amar S. Porphyromonas gingivalis, a Long-Range Pathogen: Systemic Impact and Therapeutic Implications. Microorganisms. 2020;8(6):869.
8. Flemmig T.F, Shanahan F., Miyasaki K.T. Prevalence and severity of periodontal disease in patients with inflammatory bowel disease. J Clin Periodontol 1991; 18: 690-697 [PMID: 1960238 DOI: 10.1111/j.1600-051X.1991.tb00111.x]
9. Grössner-Schreiber B., Fetter T., Hedderich J., Kocher T., Schreiber S., Jepsen S. Prevalence of dental caries and periodontal disease in patients with inflammatory bowel disease: a case-control study. J Clin Periodontol 2006; 33: 478-484 [PMID: 16820035 DOI: 10.1111/j.1600-051X.2006.00942.x]
10. Brito F., de Barros F.C, Zaltman C., Carvalho A.T, Carneiro A.J, Fischer R.G, Gustafsson A., Figueredo C.M. Prevalence of periodontitis and DMFT index in patients with Crohn's disease and ulcerative colitis. J Clin Periodontol 2008; 35: 555-560 [PMID: 18400026 DOI: 10.1111/j.1600-051X.2008.01231.x]
11. Habashneh R.A, Khader Y.S, Alhumouz M.K, Jadallah K., Ajlouni Y. The association between inflammatory bowel disease and periodontitis among Jordanians: a case-control study. J Periodontal Res 2012; 47: 293-298 [PMID: 22050539 DOI: 10.1111/ j.1600-0765.2011.01431.x]
12. Vavricka S.R, Manser C.N, Hediger S., Vögelin M., Scharl M, Biedermann L, Rogler S, Seibold F, Sanderink R, Attin T, Schoepfer A, Fried M, Rogler G, Frei P. Periodontitis and gingivitis in inflammatory bowel disease: a case-control study. Inflamm Bowel Dis 2013; 19: 2768-2777 [PMID: 24216685 DOI: 10.1097/01. MIB.0000438356.84263.3b]
13. Koutsochristou V, Zellos A, Dimakou K, Panayotou I, Siahanidou S, Roma-Giannikou E, Tsami A. Dental Caries and Periodontal Disease in Children and Adolescents with Inflammatory Bowel Disease: A Case-Control Study. Inflamm Bowel Dis. 2015; 21: 1839-1846 [PMID: 25985243 DOI: 10.1097/MIB.0000000000000452]
14. Sulijaya B, Athallah S.F, Sunarto H, Natalina, Lessang R. Tooth Loss Observation in Patients with Periodontitis in Recall Period based on the Staging and Grading System of a World Classification 2017. J Int Dent Med Res. 2022; 15(4):1-7.
15. Hajishengallis G, Darveau RP, Curtis MA. The keystone-pathogen hypothesis. Nat Rev Microbiol. 2012;10(10):717–25.