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Pathogenic associations between oral and gastrointestinal diseases

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Abstract

Both periodontitis and inflammatory bowel disease (IBD) are complex chronic conditions characterized by aberrant host immune response and dysregulated microbiota. Emerging data show an association between periodontitis and IBD, including direct and indirect mechanistic links between oral and intestinal inflammation. Direct pathways include translocation of pro-inflammatory microbes from the oral cavity to the gut and immune priming. Indirect pathways involve systemic immune activation with possible non-specific effects on the gut. There are limited data on the effects of periodontal disease treatment on IBD course and vice-versa, but early reports suggest that treatment of periodontitis decreases systemic immune activation and that treatment of IBD is associated with periodontitis healing, underscoring the importance of recognizing and treating both conditions.

Keywords

periodontal disease; oral-gut axis; microbiome; pathobiont; immunology; inflammatory bowel disease

Clinical and epidemiologic context of periodontal disease and inflammatory bowel disease

The oral-gut axis is an area of emerging interest because of the high burden of oral disease and recent discoveries elucidating the interplay between inflammation, the microbiome (see Glossary), and chronic disease in these related sites[1, 2]. Prior epidemiologic research has identified associations between oral health and a variety of medical conditions[3]. In this

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review, we will focus on the relationship between periodontitis and inflammatory bowel disease (IBD).

Periodontal disease is characterized by chronic inflammation affecting the bone and tissues around the tooth. This develops initially as gingivitis, a reversible inflammation of the gums and soft tissues around the tooth, and it progresses to involve the bone, cementum, and periodontal ligament. The causes of periodontitis are multifactorial but lead to chronic inflammation with progressive tissue destruction, exposing deeper structures to the oral microbiome, which leads to further host immune activation.

Periodontitis is one of the most prevalent conditions worldwide[4]. There is limited high-quality data on the international prevalence and trends in periodontal disease. The global prevalence of periodontitis is estimated to be 11.2% and increases with age[3–7]. There is significant variation in prevalence and incidence by region and country. The variability may be attributable to individual-level differences, availability of oral care, methodologic differences between studies, and a lack of nationally representative samples in most countries.

Despite these research challenges, data suggest that the prevalence of severe tooth loss (i.e. edentulism) is decreasing while the prevalence of advanced periodontitis is increasing, likely because of increasing longevity and improved preventive dental care that limits tooth loss[4, 5, 8].

In the US, an estimated 42% of all community-dwelling adults aged 30 years and older have periodontal disease, and 7.8% of the population has severe periodontitis[6]. Longitudinal Scandinavian data show that overall rates of periodontal disease are improving in highly developed countries, though the percentage of the population with severe disease has remained stable[9–14]. In China, Japan, and India, periodontal disease incidence has increased over the past three decades, and in South Korea and Thailand, the incidence has decreased[15]. There are limited data for other regions.

IBD is a set of idiopathic chronic inflammatory disorders affecting the GI tract. It includes two main types, Crohn’s disease (CD) and ulcerative colitis (UC). The pathogenesis of IBD is multifactorial, involving both host and environmental factors, such as genetics, diet, stress, and the microbiome[16]. CD is characterized by chronic transmural mucosal inflammation that can occur throughout the GI tract from mouth to anus, at times in a discontinuous pattern. Inflammation in UC is limited to the mucosa and occurs in a contiguous fashion in the colon, starting at the rectum, though there can be some involvement of the terminal ileum. The mouth is a common extra-intestinal site of IBD involvement, suggesting a role for the oral-gut immune and microbiome axis in pathogenesis. Previously, CD was felt to be a Th1 cell-predominant process, whereas UC was Th2-driven, though work on Th17 cells has led to a more complex understanding of these diseases[17].

In the US, IBD affects an estimated 1.3% of adults[18]. Globally, the incidence of IBD varies but has been increasing[19, 20]. In the past 25 years, IBD incidence in highly developed countries has risen slowly or plateaued[21, 22]. However in Asia, IBD incidence has increased dramatically, with some countries reporting rates that doubled or tripled in the

same time frame[23, 24]. The highest age-standardized prevalence of IBD is in high-income areas of North America (422.0 cases per 100,000), whereas the lowest is in the Caribbean (6.7 per 100,000 population)[20].

The mechanisms by which periodontal disease may cause or exacerbate chronic gastrointestinal (GI) diseases are complex. We will discuss the epidemiologic evidence supporting an association between periodontitis and IBD, emerging research on the pathways behind these associations, controversies in the field, and future directions.

Associations between periodontal disease and IBD

On an epidemiologic level, multiple studies have demonstrated a strong association between IBD and periodontal disease (Table 1). Three recent meta-analyses found that periodontitis is associated with both CD and UC, with pooled odds ratios of 1.7–3.6 for CD and 2.4–5.4 for UC[25–27]. This association is seen both in adults as well as children and adolescents with IBD[28]. Individuals with IBD are more likely to have had dental treatments and have worse perceived oral health than healthy controls[29, 30]. This may be based on a greater need for dental procedures among individuals with IBD as compared to those without IBD, as was found in a Swedish cohort study[31].

However, a major challenge in understanding the causal pathways implicated is that most epidemiologic studies of periodontal disease and IBD have been cross-sectional rather than longitudinal. Some of the larger cohort studies on this topic report mixed results. A retrospective cohort study in Korea showed that periodontal disease was associated with an increased risk of a new diagnosis of UC but not of CD[32]. In a 20,000-patient retrospective cohort from Sweden, poor dental hygiene and tooth loss were associated with lower risk of IBD; loss of 5–6 teeth was associated with a 50% lower risk of developing IBD, and high dental plaque burden was associated a 70% lower risk of development of CD, though plaque burden was not associated with UC[33]. In a Taiwanese cohort study of individuals with periodontitis, there was an increased risk of development of UC (adjusted hazard ratio 1.56) but not of CD[34]. Taken collectively, these studies suggest a link but that standardized prospective studies are needed.

Association between oralization of the gut microbiome and IBD

The link between periodontal disease and IBD is further supported by the changes seen in both the oral and gut microbiome of individuals with IBD[35, 36]. When compared to healthy controls, individuals with IBD have altered gut and salivary microbiomes, often referred to as dysbiosis. This is accompanied by failures of mucosal immunity and a loss of symbiotic relationships between bacteria and the human host, which leads to inflammation and illness[16]. One characteristic of the dysbiotic gut microbiome in IBD is a greater resemblance to the oral microbiome or “oralization” of the gut microbiome[37]. This includes enrichment of typically oral bacteria such as *Fusobacteriaceae*, *Pasteurellaceae*, *Klebsiella* spp. and *Veillonellaceae* and loss of more typical gut bacteria, like *F. prausnitzii* [2, 37–39]. Patients with IBD also experience salivary dysbiosis, with increased Bacteroidetes, which is associated increased salivary inflammatory cytokines[38]. Small

studies have reported that salivary dysbiosis in IBD may correlate with IBD activity, suggesting a reciprocal relationship[40, 41].

Mechanisms

The mechanisms of oral-gut microbiome interaction in IBD are an area of active clinical and translational investigation. Current hypotheses are based off observations from translational research in humans and animal models of IBD. The working theory is that there are both direct and indirect pathways of oral-gut interaction that depend on both the microbiome and immune cell activation to synergistically promote inflammation in susceptible individuals (Figure 1). These may operate in a series of steps that gradually establish the conditions necessary for ectopic bacterial colonization and promote a hyperactive immune response[36].

Underlying factors that may predispose to increased intestinal inflammation from periodontitis are not fully understood. However, a disruption or instability of the healthy microbiome is necessary to allow for ectopic gut colonization by oral pathobionts. Host genetic variants can alter immune response to pathogens, increase susceptibility to colonization with specific bacteria, and change the threshold for dysbiosis as opposed to self-resolution in response to an acute change[42–44]. Data from the spontaneous ileitis SAMP1/YitFc mouse model suggests that there may be genetic factors involved in the immune response that predispose to both IBD and periodontitis, as these mice exhibit severe periodontitis that correlates with intestinal inflammation[45]. This is supported by additional work that has identified shared susceptibility loci in both periodontitis and IBD, such as NOD2[43, 46]. Environmental factors such as diet, tobacco use, medications, and individual behaviors (e.g. dental care) may also contribute[47, 48].

In susceptible individuals, oral inflammation leads to large blooms of pathobionts, such as *Klebsiella* and *Enterobacter* species, that are swallowed and colonize the gut, displacing healthy gut microbes. IBD may increase the amount of oral bacterial exposure, as individuals with IBD and periodontitis harbor larger populations of oral pathobionts than healthy controls[40, 49, 50]. Possible reasons for altered oral microbiota in IBD include oral involvement of disease with ulceration and other histologic findings plus changes in salivary function[51]. Preexisting intestinal inflammation facilitates the colonization process by creating an environment that is more favorable to oral bacteria colonization, less diverse, and more unstable[41, 52].

The underlying conditions that lead to translocation of oral bacteria to the intestine and allow their survival in there are important active areas of study. Stomach acid and enzymes are potent antibacterials, but some bacteria can tolerate low pH environments and enzymatic exposure for limited periods of time [53]. Additionally, if there is a significantly large bacterial input, such as with the proliferation of oral pathobionts seen in periodontitis, some may survive through strain-specific features [54] or by protection within biofilms[55]. Finally, there may be hematogenous spread of bacteria as well.

Ectopic colonization of the gut by oral pathobionts activates the inflammasome and leads to local tissue damage. Data from mouse models have shown that the salivary microbiota from humans with periodontitis is pro-inflammatory in mice treated with dextran sulfate sodium (DSS)[56]. One mechanism is through more epithelial permeability, which increases antigen exposure and immune activation[57]. In addition, saliva from CD and UC patients can cause intestinal inflammation in mice lacking an anti-inflammatory cytokine (interleukin (IL)-10) through *Klebsiella* spp.-induced dendritic cell signaling and Th1 activation[58]. In response to oral bacteria, there is CD4+ T cell accumulation in the intestinal mucosa of these mice, as is seen in humans with CD.

While some of these T cells may be in direct response to the presence of pathobionts, there are thought to be other mechanisms as well. Pathogenic T cells may arise from lymph nodes that drain the oral cavity and then transmigrate to other lymphoid tissues, such as those in the gut. A second source is through hematologic spread, by which T cells sensitized to oral pathobionts in the mouth can then home to the gut in response to the presence of similar bacteria. Prior work has shown that Th17-skewed T cells reactive against oral pathobionts arise in the mouth in response to periodontitis[59]. These are imprinted with intestinal tropism and migrate to the inflamed intestinal mucosa, where they are then activated by ectopic oral pathobionts, leading to further inflammation.

Though less-investigated than the T cell responses, periodontitis also causes neutrophil activation. Gingival calprotectin is associated with more aggressive periodontitis and is elevated in individuals with IBD when compared to healthy controls[60, 61]. In individuals with periodontitis, systemically circulating neutrophils have cytokine hyper-reactivity and impaired chemotaxis[62–64]. Hyper-reactive neutrophils in patients with periodontitis exhibit a type I interferon (IFN) pattern of cytokine expression. These primed and systemically circulating neutrophils express up-regulated phagocytic receptors and activity and have elevated reactive oxygen species (ROS) production[63]. When coupled with impaired chemotaxis, this may cause increased collateral damage to host tissues through increased transit time, though this has not yet been demonstrated in the gut. Thus, non-T immune cells, such as neutrophils, may also contribute to the oral-gut axis in the context of IBD.

An additional hypothesized mechanism linking IBD and periodontitis is through trained immunity[65]. Periodontitis can cause bacteremia and systemic circulation of bacterial components. In a mouse model simulating periodontitis-induced *P. gingivalis* bacteremia, this led to bone marrow changes in response to elevated serum IL-6[66]. Though the focus of the prior study was on bone loss, the finding of bone marrow-level effects of systemic inflammation from oral pathobionts suggests that these effects may also include effects on hematopoietic stem and progenitor cells (HSPCs) via inflammatory cytokine signaling[67]. HSPCs are essential for the production of neutrophils, dendritic cells, and macrophages, all of which have been implicated in IBD pathogenesis, though an experimental link between periodontitis and IBD via HSPCs has not yet been experimentally investigated.

Controversies

The main controversies in understanding the role of periodontitis in IBD are about causality, confounding, and the direction of the effect. Animal models indicate that oral inflammation and dysbiosis can promote intestinal inflammation in a susceptible host[59], however this has not been conclusively demonstrated in humans. As described previously, there are many epidemiologic studies that show an association between IBD and periodontitis, but there is a lack of well-designed prospective research to help understand whether periodontitis more often is a consequence of IBD or is a cause, if periodontitis can precipitate IBD flares, or if the association between the two conditions is the product of confounding by shared genetic, environmental, or immunologic risk factors (Table 2). The presence of incipient periodontitis may contribute to worse outcome in some CD patients[37]. However, in that study, patients enrolled were relatively few and heterogeneous in diagnosis, disease activity, and treatment. Therefore, prospective studies with more controlled study populations are required to assess the impact of periodontitis on IBD. A retrospective cohort study using the national Taiwanese health insurance database showed that individuals with CD were 36% more likely to develop periodontitis than individuals without IBD, highlighting the need for studies examining the association in both directions[68].

Clinical implications

The clinical impact of both periodontal disease and IBD are substantial (see Clinician's Corner). Emerging evidence around the interplay of these conditions highlights the importance of diagnosis and treatment of both. However, clinical data in this area are still lacking. There are no trials of the treatment of periodontal disease and IBD-related outcomes, but translational research suggests that periodontal disease treatment can reduce inflammation and improve oral microbiome composition. Prospective studies have shown that periodontal disease treatment reduced IFN-α levels, neutrophil IFN-signaling genes, and neutrophil ROS production[63, 69]. A similar study showed that neutrophil chemotaxis was improved by periodontal disease treatment, but there was no reduction in cytokine production[64]. Periodontitis treatment through mechanical biofilm removal leads to fewer disease-associated bacteria and decreases in inflammatory markers[70].

There are also no trials of IBD treatment and periodontal disease outcomes. However, a small study showed that treatment of IBD with an anti-TNF-alpha biologic was associated with an increased probability of periodontal disease healing[71]. This is an important finding, because it emphasizes the role of aberrant immune activation in both periodontal disease and IBD and its contribution to poor tissue healing. A study of individuals IBD but without identified periodontitis who were started on treatment for IBD showed improved salivary immunoglobulin A and myeloperoxidase in individuals with UC who responded to therapy, suggesting that there may be improvement in oral host defenses with IBD treatment[72].

Concluding Remarks

Epidemiologic, translational, and basic science research are beginning to illuminate the oral-gut connections behind periodontal disease and IBD. While it remains to be discovered the underlying pathways behind these links, a picture is emerging that incorporates the complex interplay between environmental, host, and microbiome factors. There is a need for future clinical innovation and rigorous study design to better understand this important area.

There is a need for large-scale, prospective observational and interventional studies to better characterize the natural history of periodontitis in individuals with IBD, the temporal relationship between periodontitis and IBD development and flares, and the effects of periodontal disease treatments and IBD treatments on disease outcomes. Further basic science research is needed to evaluate the role of neutrophils and other immune cell types in the oral-gut axis, interrogate the role of non-bacterial components of the microbiome, and clarify the mechanisms behind the observed associations (see Outstanding Questions).

Use of salivary biomarkers for IBD is an emerging area of research[73]. These include cytokines, microRNAs, oxidation markers and other molecules including calprotectin[73]. Prior microbiome research has also shown that the salivary microbiome can distinguish between individuals with and without IBD, with one study reporting an average area under the curve for saliva of 0.73[40]. Currently, no salivary IBD biomarkers are available for commercial testing.

In addition to bacteria, the microbiome is comprised of a diverse community of other organisms, including viruses and fungi (i.e. the virome and mycobiome). The investigation of their role in IBD and periodontitis is another important area for future research. Viruses and fungi have the potential to both directly interact with the host immune system and to modify the bacterial microbiome[74, 75]. IBD and periodontitis are associated with shifts in viral diversity and virome composition[76–78]. To date, studies have not examined the impact of these changes on the relationship between IBD and periodontitis.

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Glossary:

Dextran sulfate sodium
a chemical irritant used for mouse models of colitis. Mice administered dextran sulfate sodium in their drinking water develop colonic inflammation. The model is simple, widely used, and has similarities to human ulcerative colitis. However, it is an irritant colitis rather than a spontaneous autoimmune colitis.

Dysbiosis
a state of imbalance or altered microbial composition of a microbiome from what is found in a healthy state, often associated with disease or illness.

Inflammasome
a complex intracellular immune complex of multiple proteins that is activated in response to pathogens or other stressors.

Inflammatory Bowel Disease
an idiopathic chronic inflammatory disease of the gastrointestinal tract. Inflammatory bowel disease is typically subdivided into two major types: Crohn's disease and ulcerative colitis, which are distinguished by histopathologic features and the areas of intestinal involvement.

Microbiome
the community of microbes that reside in an environment, including bacteria, fungi, viruses, and other organisms.

Pathobiont
a microbe that does not cause disease under normal circumstances but can be pathogenic under specific conditions or for susceptible hosts.

Periodontitis
chronic inflammation affecting the bone and tissues around the tooth triggered by bacterial infiltration. Periodontitis is a serious condition that is thought to be the consequence of untreated less severe acute inflammation of the gums.

Th1/Th2/Th17 cell immune response
broad categorizations of T-helper cell (Th) inflammatory responses. These responses are based on the types of cytokines produced and the immune function of the cells. Th1 cells typically produce interleukin (IL)-2 and interferon-γ (IFN-γ) and are involved in cell-mediated immunity. Th2 cells produce IL-4, IL-5, and IL-13 and are involved in antibody-mediated immunity. Th17 cells produce IL-17 and are important for activating the immune response.

Trained immunity
increased immunologic responsiveness to pathogens resulting from epigenetic and metabolic changes following early microbial exposures. Trained immunity arises through priming of bone marrow hematopoietic progenitor cells. These give rise to myeloid cells, which include basophils, dendritic cells, eosinophils, macrophages, and neutrophils. Trained immunity is adaptive in fighting reinfection, but it may increase chronic inflammation and cause or exacerbate autoimmune diseases.

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Clinician's Corner:

- Both periodontitis and inflammatory bowel disease (IBD) are complex chronic conditions characterized by aberrant host immune response and dysregulated microbiota.
- Emerging data show that periodontitis is associated with IBD, with higher rates of aggressive periodontitis among IBD patients even in adolescence and childhood. Recent studies have shown mechanistic links between periodontitis and intestinal inflammation. The inflammation and altered oral microbiome of periodontitis can worsen intestinal inflammation through direct and indirect immune activation. Oral bacteria are swallowed and may ectopically colonize the gut, leading to a pro-inflammatory gut microbiota that leads to inflammation and tissue damage. In addition, oral inflammation primes T cells which travel to the gut, leading to additional inflammation via a CD4+ T cell response.
- There are limited data on the effects of periodontal disease treatment on IBD course and vice-versa, but early reports suggest that treatment of periodontitis decreases systemic immune activation and that treatment of IBD is associated with periodontitis healing.
- In light of these newly recognized pathways and the high rates of periodontal disease among patients with IBD, it is important that dental assessments be included as part of comprehensive IBD and preventive health maintenance.

Outstanding Questions:

- Does the treatment of periodontitis reduce the risk of developing inflammatory bowel disease or reduce flares?
- Does the treatment of inflammatory bowel disease reduce the risk of aggressive periodontitis?
- What is the effect of preventive dental hygiene procedures on inflammatory bowel disease development and flares?
- How do genetic and environmental factors contribute to both periodontal disease and inflammatory bowel disease?
- What is the temporal relationship between oral and gut inflammation in IBD and periodontitis?
- What environmental, immunologic, and microbiologic characteristics promote translocation and survival of oral bacteria in the intestine?
- T cells have been relatively well studied, but what is the role of other immune cells in inflammation of the oral-gut axis?
- What is the role of trained immunity in periodontitis and inflammatory bowel disease?
- What specific factors make the oral microbiome in periodontitis pro-inflammatory in the intestinal environment? Is it specific to the presence of particular bacterial species or are there community-level metabolic or other features that drive immune activation?
- Is there a role for non-bacterial components of the microbiome in exacerbating oral-gut axis inflammation?
- Are there oral biomarkers with clinical utility for both periodontitis and inflammatory bowel disease?

Highlights:

- Inflammatory bowel disease and periodontitis are associated in epidemiologic studies.
- Both complex conditions involve microbial and host immune system interactions that create chronic inflammation and tissue damage in susceptible individuals.
- Emerging evidence shows a link between oral inflammation and gut inflammation through direct and indirect mechanisms, including hematologic and lymphatic trafficking of activated T-cells and enteric transmission of inflammatory bacteria.
- There is a need for prospective interventional research to determine the clinical implications of these findings.

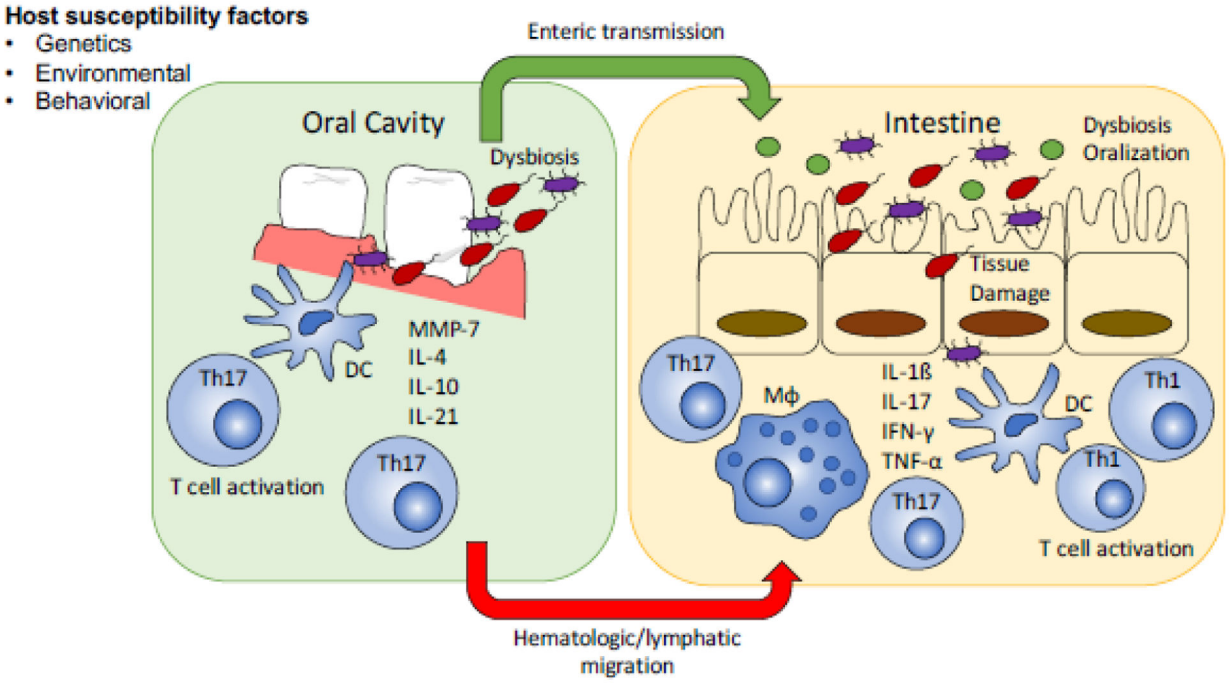

Figure 1. Mechanisms of periodontal and intestinal inflammation.

In the setting of host factors that increase susceptibility periodontal disease with altered microbial communities and activation of inflammatory T cells through dendritic cell signaling can lead to intestinal inflammation. This occurs through enteric transmission of inflammatory microbes that lead to *in situ* T cell activation and through hematogenous and lymphatic migration of activated T-cells to the gut.

Abbreviations: DC=dendritic cell, IFN=interferon, IL=interleukin, MMP=matrix metalloprotease, Mϕ=macrophage, Th=T-helper, TNF=tumor necrosis factor.

Table 1.

Studies of Periodontitis and IBD

Country	Design	IBD patients (n)	Healthy controls (n)	Periodontitis measures	Findings	Reference
Taiwan	Cohort	6,657 (CD)	26,628	Billing codes	CD patients at increased risk of developing periodontitis (HR 1.36)	[68]
Sweden	Cohort	3,161 (CD) and 2,085 (UC)	5,246	Dental care utilization	CD and UC patients had higher numbers of dental procedures following diagnosis, including more total procedures and fillings.	[31]
Korea	Cohort	9,950,548 overall (IBD and no IBD)		Oral screening exam	Periodontitis associated with increased risk of UC development (aHR 1.091) but not CD (aHR 0.879).	[32]
Taiwan	Cohort	27,041 periodontal disease	108,149 no periodontal disease	Billing codes	HR of IBD in both groups similar (HR 1.01), but increased risk of UC in periodontitis group after adjustment (aHR 1.56)	[34]
Sweden	Cohort	20,162 overall (IBD and no IBD)		Oral exam at study entry	Tooth loss at baseline associated with lower risk of IBD development (HR 0.56). More plaque associated with lower CD risk (HR 0.32)	[34]
Brazil	Cross-sectional case-control	179 (99 CD and 80 UC)	74	DMFT, PPD, CAL, BOP, plaque index	More IBD patients had periodontitis than controls (81.8% CD, 90% UC, 67.6% controls).	[79]
Japan	Cross-sectional case-control	60 (18 CD and 42 UC)	45	BOP, caries, PPD	No difference in periodontitis or caries between IBD and control groups.	[37]
Germany	Cross-sectional case-control	62 (IBD type not specified)	59	DMFS, caries, plaque index, BOP, PPD, CAL	No difference in DMFS between groups but more dental caries and CAL in IBD group.	[80]
Jordan	Cross-sectional case-control	160 (59 CD and 101 UC)	100	PPD, GR, LA, BOP, plaque index, gingival index	Higher prevalence of periodontitis in IBD group <45 years old and in adjusted analysis (OR for CD 4.9, OR for UC 7.0), and more severe periodontitis in IBD group.	[81]
Greece	Cross-sectional case-control	55 (36 CD and 19 UC)	55	DMFT, gingival index, plaque index, periodontitis treatment needs	DMFT, gingival inflammation both higher in IBD. No difference in plaque index. Higher periodontal treatment needs in IBD group.	[28]
Italy	Cross-sectional case-control	110 (IBD type not specified)	110	DMFT, PAI	DMFT and prevalence of apical periodontitis similar between IBD and control groups but higher PAI in IBD group.	[82]
Spain	Cross-sectional case-control	54 (28 CD and 26 UC)	54	RPL, PAI, RFT	More RPL in IBD group (35.2% vs 16.7%), no difference in number of teeth with apical periodontitis or number of RFT	[83]
Germany	Cross-sectional case-control	59 (30 CD and 29 UC)	59	DMFT, PPD, BOP, CAL	IBD patients had higher CAL, more severe periodontitis, and more gingival bleeding.	[84]
Sweden	Cross-sectional case-control	150 (71 CD with prior intestinal	75	DMFT, DMFS, salivary flow, dental plaque	CD with prior resection had higher DMFS and more plaque than controls.	[85]

Country	Design	IBD patients (n)	Healthy controls (n)	Periodontitis measures	Findings	Reference
		surgery and 79 CD no surgery)				
Netherlands	Cross-sectional case-control	229 (148 CD, 80 UC, 1 IBD undetermined)	229	DMFT, DPSI	DMFT higher in IBD group. DMFT higher for CD than controls but not for UC. DPSI not different between IBD and control groups, but more IBD patients edentulous	[86]
Switzerland	Cross-sectional case-control	113 (69 CD and 44 UC)	113	DMFT, PPD, PBI, LA, PPD, BOP	Worse DMFT, PBI, LA-PPD, BOP in IBD. In CD group, clinical activity (HBI) associated with worse LA-PPD; perianal disease associated with BOP.	[87]
Greece	Cross-sectional case-control	30 (15 CD and 15 UC)	47	Appearance of periodontitis, gingivitis, BOP, other lesions	Higher rates of oral lesions in IBD group (87% CD, 93% UC, 55% control group). More periodontitis and BOP in CD compared to controls.	[88]
China	Cross-sectional case-control	389 (265 CD and 124 UC)	265	DMFT, DMFS, PPD, CAL, BOP, GR, gingival index, plaque index, CAL	DMFS increased in IBD vs controls (OR 4.27 for CD, 2.21 for UC). Higher risk of dental caries, probing pocket depth ≥5mm, CAL ≥4mm in IBD group.	[89]
Studies of perceived oral health and behaviors						
United States	Cross-sectional case-control	880 (IBD type not specified)	72,741	Oral health questionnaire	Self-reported periodontal disease not associated with IBD. Poorer self-rated oral health and eating limitations due to teeth more common in IBD group (OR 1.15 and 1.22, respectively)	[30]
Sweden	Cross-sectional case-control	1,598 (all CD)	748	Oral health questionnaire	IBD patients rate worse oral health and greater need for dental treatment after controlling for age, smoking, gender, and education.	[29]
United States	Cross-sectional case-control	83 (57 CD and 26 UC)	54	Oral health questionnaire	Higher frequency of brushing and flossing at disease onset in IBD patients. More frequent dental visits, more caries.	[90]

Abbreviations: BOP=bleeding on probing; CAL=calculus index; CD=Crohn's disease; DMFS=decayed missing filled surfaces; DMFT=decayed missing filled teeth; DPSI=Dutch Periodontal Screening Index; GR=gingival recession; HR=hazard ratio; aHR=adjusted hazard ratio; IBD=inflammatory bowel disease; LA=loss of attachment; OR=odds ratio; PAI=periapical index; PBI=papilla bleeding index; PPD=probing pocket depth; RFT=root filled tooth; RPL=radiographic radiolucent periapical lesions; UC=ulcerative colitis

Table 2.

Risk factors for IBD and Periodontitis

Category	Examples
Environmental	Diet/nutrition
	Tobacco use (Crohn's disease only)
	Medications
	Stress
Genetic	NOD2
	IL-10
	IL-1
	Autophagy genes
	Peroxidase genes
Microbiome	Dysbiosis
	Hygiene hypothesis
	Mucosal microbial load
Immunologic	Immunodeficiencies

Abbreviations: IL=interleukin; NOD2=Nucleotide Binding Oligomerization Domain Containing 2