The Association between Inflammatory Bowel Disease and Periodontal Conditions: Is There a Common Bacterial Etiology?

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Abstract

Introduction: The gastrointestinal system is strongly associated with the oral mucosa including periodontal tissues. Inflammatory bowel disease (IBD) has two common forms: Crohn's disease (CD) and ulcerative colitis (UC). Local inflammation in periodontal diseases (PD) has an impact on inflammatory diseases in various parts of the body. The existence of periodontitis in IBD patients suggests the possibility that the two inflammatory conditions may have common pathogenic pathways. Both diseases are multifactorial conditions in which genetic and environmental factors initiate and maintain the chronic inflammatory response.

Aim: The aim of this review was to determine the current state of understanding of the characteristics and mechanisms underlying the association between IBD and periodontal diseases, with emphasis on the role of microorganisms.

Methods: A computer-assisted MEDLINE search was performed to find the relevant articles concerning IBD and periodontal diseases published until September 2016.

Results and conclusion: A number of studies have showed an association between PD and IBD. Both diseases share genetic and environmental etiological factors. The precise role of intestinal bacteria remains vague. The periodontal microbiota that might be involved in the association of these diseases are *Fusobacterium nucleatum, Campylobacter rectus* and *Campylobacter concisus*. Fungal and viral microbiota dysbiosis should also be evaluated as common pathogenic pathways in IBD and periodontal disease.

Keywords: Crohn's disease, ulcerative colitis, periodontal diseases, inflammatory bowel disease, bacteria

Introduction

The gastrointestinal system is strongly related to periodontal and dental tissues both in adults and children (Mantegazza *et al.*, 2016). One gastrointestinal disorder encompasses inflammatory bowel disease (IBD), which has two common forms: Crohn's disease (CD) and ulcerative colitis (UC). These are conditions common in western countries based on an immune-mediated inflammation of the gastrointestinal tract that can be both chronic and relapsing (Loftus, 2004).

Local inflammation in periodontal diseases has an impact on systemic autoimmune or inflammatory diseases (Leech and Bartold, 2015; Scannapieco and Cantos, 2016). The existence of periodontitis in IBD patients suggests the possibility that the two inflammatory conditions may have common pathogenic pathways (Brito *et al.*, 2008; Oz *et al.*, 2010; Figueredo *et al.*, 2011; Menegat *et al.*, 2016). Both diseases are multifactorial conditions in which genetic and environmental factors initiate and maintain the chronic inflammatory response. The aim of this review is to determine the current state of understanding of the characteristics and mechanisms underlying the association between IBD and periodontal diseases, with emphasis on the role of microbial etiology. The role of other factors common to both IBD and periodontal diseases is briefly discussed.

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Clinical manifestations of UC and CD

Ulcerative colitis affects the rectum, colon, and caecum mucosa, presenting as continuous areas of inflammation and ulceration. The symptoms are abdominal pain/cramping, diarrhea, blood in stool, fatigue, low-grade fever, weight loss, and a decrease in appetite (Head and Jurenka, 2003). In contrast, CD affects the entire gastrointestinal system from mouth to anus; it especially has an impact on the terminal ileum and colon. In CD, there are healthy parts of the intestine alternating with inflamed areas. Ulcerative colitis affects only the innermost lining of the colon, whereas CD can occur in all of the layers of the intestine walls (Matricon *et al*., 2010). Crohn's disease has similar clinical gastrointestinal manifestations to those in UC. At least one of the extra-intestinal manifestations of IBD is observed in up to 50% patients, including arthropathy, arthritis, osteoporosis, and hepato-pancreato-biliary, neurological, cardiovascular, pulmonary, urogenital, eye and skin or oral diseases (Harbord *et al.,* 2016).

According to Plauth *et al.* (1991), the most common types of oral manifestations of CD are edema, ulcer, and polypoid papulous hyperplastic mucosa. Oral symptoms in CD are especially localized in gingiva, lips, buccal mucosa, and vestibular sulcus. Manifestations include indurated tag-like lesions, gingival swelling, mucogingivitis, lip swelling with vertical fissures, and deep linear ulcers. Nonspecific oral lesions include glossitis, recurrent aphthous stomatitis, pyostomatitis vegetans, and angular cheilitis, (Lankarani *et al*., 2013; Pereira and Munerato, 2016). Oral lesions in UC are less frequent than in CD, and almost all of the nonspecific oral lesions common in CD can also occur in UC. Oral manifestations of UC are mostly seen as aphthous ulcers or superficial hemorrhagic ulcers and angular cheilitis. Pyostomatitis vegetans is the only condition that occurs more frequently in UC than in CD (Lankarani *et al*., 2013).

Incidence and prevalence of UC and CD

The occurrence of IBD is high in developed and western countries, such as Canada and northern European nations, though recent studies have revealed that incidence of these diseases is increasing in eastern countries and the Asia Pacific area, possibly due to generalized behavioral and environmental changes. Crohn's disease has an incidence of 6.3 per 100,000 population, and a prevalence of 174 cases per 100, 000. The incidence of UC is 8.1 per 100,000, with a prevalence of 214 cases per 100,000 (Loftus *et al.,* 2007). In a study from Hungary where the prevalence of IBD is high, it is estimated to be 0.34% for UC and 0.20% for CD (Kurti *et al*., 2016). In a recent 28-year follow-up study in Finland, the mean annual incidence of IBD among pediatric patients dramatically increased from 7/100,000 (1987-1990) to 23/100,000 (2011-2014; Virta *et al*., 2016).

The link between PD and IBD

Periodontal diseases and IBD have been considered to be linked and to partly share a common etiopathogenesis of chronic mucosal inflammation according to early studies by Lamster *et al.* (1978), Van Dyke *et al.* (1986), and Engel *et al.* (1988). Severe periodontal disease is a characteristic feature in Crohn's patients (Lamster *et al*., 1978). The prevalence and severity of periodontitis in patients with IBD have been studied (Flemmig *et al*., 1991; Grössner- Schreiber *et al.,* 2006; Brito *et al.,* 2008; Stein *et al.,* 2010; *Table 1*). Crohn's disease subjects presented with fewer sites with dental plaque and bleeding on probing (BOP), deeper pocket depth (PD) and more periodontitis when compared with systemically healthy controls (Brito *et al.,* 2008). Moreover, UC patients had significantly increased clinical attachment loss (CAL) than CD patients (Brito *et al.,* 2008). In 2013, Brito *et al.* conducted a study on a subset sample population of their preceding study (Brito *et al.,* 2008; Brito *et al.,* 2013). Forty-five patients diagnosed with periodontitis (15 patients with CD, 15 with UC and 15 systemically healthy controls) were re-invited for microbiological sampling of subgingival plaque. Although there was no difference in PD, CAL, or BOP among groups, patients with CD harbored higher numbers of *Bacteroides ureolyticus, Campylobacter gracilis, Prevotella melaninogenica, Staphylococcus aureus, Streptococcus mitis, S. anginosus, S. intermedius, and S. mutans* compared to UC patients. All of these microorganisms, except for *S. mitis*, were higher in CD compared with healthy controls (Brito *et al*., 2013). In a recent review (Agossa *et al*., 2016), the epidemiological and biological evidence of similarities between IBD and periodontal diseases makes a case in support of a relationship between these two diseases. Twelve cross-sectional or case-control studies and five animal studies were critically reviewed. Spontaneous or chemically induced colitis led to alveolar bone loss in animal studies. Human studies showed that at a minimum one periodontal site with PD ≥ 4 mm, higher gingival index and BOP were more frequent in IBD patients. Additionally, patients with UC had more severe forms of periodontitis compared with CD patients (Agossa *et al*., 2016).

Common inflammatory mechanisms in the intestinal and periodontal mucosa and the imbalance between pro-inflammatory and anti-inflammatory mediators were investigated in a study conducted by Menegat *et al.* (2016). Crohn's disease and UC presence was evaluated both clinically and by laboratory methods using the Harvey-Bradshaw index (Harvey and Bradshaw, 1980) for CD and Truelove and Witts score for UC (Truelove and Witts, 1955). The Harvey-Bradshaw index was used for data collection purposes. It consists of only clinical parameters according to general well-being or complications. A score of less than 5 represents clinical remission, while Truelove and Witts index measures mild, moderate and severe disease related to bowel movements, blood in stools, pyrexia, pulse rate, anemia, and erythrocyte sedimentation rate.

Table 1. Clinical studies evaluating the correlation between periodontal status and inflammatory bowel diseases

Author, year	Study type	Subjects	Methods	Main findings
Menegat *et al.*, 2016	Cross-sectional	28 patients diagnosed with chronic periodontitis, CD and UC	Gingival and intestinal biopsies (3 pairs of samples matched for the same patient)	Higher PD ≥ 7 mm in CD. Higher IL-10,17A,17F, 22, 25, 33, INF-¡ in gingival tissue
Yin *et al.*, 2016	Prospective cohort	20,162 participants 209 diagnosed as IBD	Tooth loss Dental plaque Oral mucosal lesions	Presence of dental plaque decreased the risk of CD Loss of 5-6 teeth of 6 Ramfjord teeth examined was associated with the lower risk of UC
Pereira and Munerato, 2016	Case report	One patient with UC One patient with CD	Evaluated oral manifestations with UC and CD	Angular cheilitis, erosive and crusty lesions on the lip Aphthous ulcers, hyperplastic cobblestone lesions Superficial hemorrhagic ulcers
Koutsochristou *et al.*, 2015	Case-control	55 children and adolescents with IBD (36 with CD and 19 with UC) 55 age-matched systemically healthy controls	DMFT Simplified gingival index (GI-S) Plaque control record (PCR) index CPITN	GI-S was 60% higher in patients with IBD compared with controls while 9% had at least 1 site with pocket probing depth 4 or 5 mm. Plaque scores in the IBD group were not significantly higher compared with controls
Schulz *et al.*, 2014	Cross-sectional	142 patients with CD	Plaque index PD, CAL BOP Genetic test for TNF-α genotypes of rs1800629 and rs361525	Genetic tendency was present in oral soft tissue alterations in CD No significant differences in PI and BOP found according to different genotype, allele, and haplotype Significant association between genetic pattern and PD, as well as CAL, was determined for rs361525
Brito *et al.*, 2013	Case-control	15 periodontitis patients with CD 15 periodontitis patients with UC 15 systemically healthy periodontitis patients	Microbiological sampling from subgingival plaque	No difference in PD, CAL, BOP among groups Patients with CD harbored higher numbers of *Bacteroides ureolyticus, Campylobacter gracilis, Prevotella melaninogenica, Staphylococcus aureus, Streptococcus mitis, S. anginosus, S. intermedius, S. mutans* compared with UC patients
Vavricka *et al.*, 2013	Case-control	113 patients with IBD (69 CD, 44 UC) 113 matched healthy controls	DMFT index Papilla bleeding index PD, CAL BOP	Gingivitis higher in patients with CD and UC, and periodontitis was more common in patients with IBD. Having an inflammatory bowel disease increased the risk for periodontitis significantly (OR, 3.92)

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Habashneh *et al.*, 2012	Case-control	101 with UC 59 with CD 100 with no IBD	Plaque index, gingival index PD, CAL Gingival recession	Plaque index and gingival index in patients with UC or CD were significantly higher than those in subjects with no IBD Periodontitis was higher in patients with CD and UC compared to subjects without IBD in the age groups < 36 and 36 - 45 years old
Figueredo *et al.*, 2011	Cross-sectional	15 patients with CD and periodontitis 15 patients with UC and periodontitis 15 systemically healthy patients with periodontitis	PD, CAL, BOP, plaque presence GCF from shallow (PD ≤ 3 mm) and deep (PD ≥ 5 mm) sites; blood samples	IL-4 in GCF was lower in shallow sites of IBD patients Serum IL-18 was higher in IBD patients
Stein *et al.*, 2010	Cross-sectional	147 patients with CD	Plaque index, gingival index, PD, CAL, CPITN Subgingival microbial sampling, DNA probe CARD 15 genotyping	36.7% had oral soft tissue lesions; 57.8% had PD values 4 - 5 mm. *C. rectus* had the highest frequency
Brito *et al.*, 2008	Case-control	99 CD patients 80 UC patients 74 age-matched systemically healthy controls	Presence of plaque BOP, PD, CAL	CD subjects had fewer sites with dental plaque and BOP, deeper PD and more periodontitis when compared with systemically healthy controls
Grössner- Schreiber *et al.*, 2006	Case-control	46 patients with CD 16 patients with UC 59 matched healthy controls	DMF-S index, dentine caries, plaque index , BOP PD CAL .	Higher number of oral lesions 63% of patients with IBD had at least one site with CAL > 5 mm; not statistically different compared to controls

CD, Crohn's disease; UC, ulcerative colitis; PD, probing depth; IBD, inflammatory bowel disease; DMFT, decayed, missing, filled teeth; CPITN, community periodontal index of treatment needs; CAL, clinical attachment loss; BOP, bleeding on probing; GCF, gingival crevicular fluid

Pocket depth, CAL, BOP and visible plaque index (VPI) were measured in patients undergoing colonoscopy. Twenty-four gingival samples from inflamed sites and 12 samples from intestine were collected at the same time. Only three biopsy pairs were matched and analyzed for cytokine content. The authors found significantly higher percentage of PD ≥ 7 mm in CD patients; higher levels of IL-17A, 1L-17F, IL-22, IL-25, IL-33, INF-g, and IL-10 were also found in pooled gingival tissues (from both CD and UC patients) compared to intestinal tissues.

In another report, oral soft tissue alterations including gingival swelling (27.2%), hyperplastic lesions on the buccal mucosa (20.4%), leukoplakia (2%), lichen planus (2.7%), candidiasis (3.4%), and aphthous ulcers (4.1%) were seen in 54 out of 147 patients with CD (36.7%; Stein *et al.,* 2010). There were no relevant differences between the mutant and wild-type caspase recruitment domain-containing protein 15 (CARD15), also known as nucleotide-binding oligomerization domain-containing protein 2 (NOD2) gene subgroups. CARD15/NOD2 is the first susceptible gene for CD (Huang and Chen, 2016). Regarding the clinical parameters PI, GI, mean PD, mean CAL, BOP and all CPITN (community periodontal index of treatment needs) values, there were no significant differences between the different genetic subgroups of the patients. Of the patients 57.8% had PD values between 4 - 5 mm, whereas 31.3% of the patients had at least one site with PD ≥ 6 mm. Among all the subgingival bacterial plaque samples obtained from patients, *Campylobacter rectus* had the highest frequency, being found in 94.6% of the patients (Stein *et al.,* 2010).

Cofactors common in PD and IBD

The possible etiological factors of IBD are: aspects intrinsic to the host such as genetic susceptibility; environmental factors, such as smoking, western type diet, antibiotics, vitamin D, excessive hygiene; and a shift from protective microorganisms to pathogenic ones (Cholapranee and Ananthakrishnan, 2016). Autoimmunity takes part in the etiology of IBD (particularly CD) and periodontal diseases. It results from an interaction of genetic predisposition and factors that trigger disease (Huang and Chen, 2016). Periodontal diseases result from an imbalance between microorganisms and host response. Similar to IBD, genetics, microbial infection, and environmental factors are also considered in disease pathogenesis (Batista da Silva and Bissada, 2013). It is hypothesized that chronic intestinal inflammation in IBD is triggered by 'western lifestyle factors' and remission and exacerbation periods are observed in a genetically susceptible host (Rogler *et al.,* 2016). Pediatric-onset disease of IBD is more severe and more extensive than the adult-onset variety, similar to aggressive forms of periodontal diseases beginning around puberty (Baer, 1971).

Host factors

Three conditions should be taken into account for understanding the disease pathways of both periodontal and IBD diseases: genetic susceptibility; autophagy; and epithelial barrier alterations. Some of the genes involved in IBD pathogenesis are related to the innate immune system (TLR, NOD2; Huang and Chen, 2016). The role of the CARD15/NOD2 CD susceptibility gene in bacterial peptidoglycan recognition supports the association between enteric bacteria and mucosal inflammation in IBD and periodontal diseases. Other genes are associated with homeostatic mechanisms such as autophagy (IRGM, ATG16L1; Huang and Chen, 2016), which is an evolutionarily conserved degradation process in response to metabolic stress or changing environment. Autophagy induction involves formation of autophagosomes, which fuse with lysosomes and degrade encapsulated intracellular components, such as long-lived and misfolded proteins, as well as intracellular organelles. Autophagy plays a wide variety of physiological and pathophysiological roles and has been implicated in the regulation of immunity and inflammation. Diminished and ineffective autophagic response to intracellular pathogens has been questioned for both IBD and periodontal diseases (Hooper *et al.*, 2016). Furthermore, in IBD, the intestinal mucosal layer exhibits broad epithelial damage, crypt abscesses and a huge number of neutrophils. Similar to the gingival sulcus epithelium, an atypically permeable mucosal membrane permits excessive microbial translocation into the submucosa of IBD patients (Matricon *et al.*, 2010).

Environmental factors

Smoking is the environmental factor most studied and identified in IBD cohort analyses. The relationship between IBD and periodontal diseases and the link to smoking of both diseases is significant because chemicals in cigarette smoke may modulate cytokines and disturb cell immunity. In a recent review by To *et al.* (2016), 33 studies investigating the association of smoking and CD were subjected to meta-analysis. The course of CD was more complex in active smokers versus nonsmokers and there was a 56 - 85% rise in flares of disease activity. Smoking has been extensively studied as a risk factor for periodontitis, and numerous studies have shown the relationship between cigarette smoking and worsening of clinical parameters of periodontitis (Bergström and Eliasson, 1987; Kinane and Radvar, 1997; Kotsakis *et al.,* 2016). Moreover, the prevalence of periodontitis among adults is higher in smokers (Eke *et al.,* 2016). In both IBD and periodontal diseases, smoking affects the composition of the microbiota, damages host response by various mechanisms both local and systemic, causes oxidative stress in tissues and causes a defect in Th1/Th2/Th17 immune responses (Torres de Heens *et al.,* 2008; Özdemir *et al.,* 2016; Chen *et al.*, 2016).

Diet and food additives have also been associated with IBD clinical presentation, risk of flares, and increased incidence. Emulsifiers in processed fatty foods promote IBD (Roberts *et al.,* 2010). Dietary components are etiological factors in plasma cell gingivitis and orofacial granulomatosis (Reed *et al.,* 1993). A bidirectional association has been suggested among nutrition, dietary intake, and oral health (Neiva *et al.,* 2003; Varela-Lopez *et al.,* 2016). Saturated fat-rich diets increase oxidative stress, and the intensity and duration of inflammation. Therefore, such diets should be avoided by both periodontal disease and IBD patients (Basson *et al*., 2016; Verala-Lopez *et al.,* 2016).

Another confounding factor is hygiene. The 'hygiene hypothesis' for IBD proposes that excessive hygiene in childhood related to reduced contact with enteric bacteria may lead to an insufficiently stimulated mucosal immune system, consequently leading to susceptibility to uncontrolled inflammation in adulthood. An inverse relationship between contact with farm animals, pets, sharing bedrooms, number of siblings, and IBD was found (Cholapranee and Ananthakrishnan, 2016). However, in a case-control study involving IBD patients diagnosed before age 15, it was shown that sharing a bedroom was related to developing IBD and that association could be related to an increased threat of infections due to crowded living environments (Jakobsen *et al.,* 2013). Although the causal relation of oral hygiene with periodontal diseases was very well established several decades ago, there still is a debate about the role of oral hygiene in IBD patients. In a cohort study, 20162 participants were followed for 40 years; among them were 209 individuals diagnosed with IBD whose tooth loss and plaque scores were recorded. The presence of dental plaque was associated with a lower risk of CD (Yin *et al.,* 2016). Yin *et al.* (2016) claimed that these studies on the relationship between good oral health and IBD support the hygiene hypothesis, but there is still discussion on this association (Hujoel *et al*., 2016).

Oral contraceptive use has also have been described as a risk factor for IBD and may cause flares of the disease (Khalili *et al*., 2013). Females develop IBD slightly more than males (Kurti *et al.,* 2016). Possible mechanisms for female sex bias in IBD are pregnancy-associated events, hormone signaling, and skewing of X chromosome. Activation of CD is associated with a high level of estrogen due to puberty or oral contraceptive use. In comparison, periodontal diseases, especially gingivitis, reach a peak at puberty because of hormonal activity, and estrogen deficiency leads to bone loss in periodontitis (Baer, 1971).

Comparison of bacterial etiology of PD and IBD

Advances in microbiological techniques and utilization of 16S rDNA in sequencing technologies have permitted the detailed description of bacterial etiology of both diseases. Intestinal and periodontal microbiota plays a crucial part in human health and disease and microbial composition can affect the host response towards pathogenic bacteria and vulnerability to diseases. The human gut contains a huge number of microorganisms, up to 10^{14} bacteria, mainly anaerobic, and encompassing 500 - 1,000 species (Savage, 1977; Xu and Gordon, 2003; Qin *et al*., 2010). Pathogenic microflora associated with periodontitis has been investigated by many researchers since the nineteenth century (Wade, 2011; Slots, 1976; Newman and Socransky, 1977; Moore *et al*., 1982; Loesche *et al*., 1985). Detailed information on these organisms is available in recent reviews by Wade (2011), and Teles *et al.* (2013).

Dysbiosis/disruption of tolerance

The composition of the mucosal bacteria is thought to be essential in stimulating immune and inflammatory diseases (Peterson *et al*., 2015). The host-microbiota system in the body works in symbiosis, in which different organisms living together benefit from each other. A common feature of both periodontitis and IBD is that they may occur as a result of dysbiosis, which is a modification of the resident bacteria, or of misrecognition of the resident bacteria by the host immune system (Nibali *et al*., 2014). Environmental factors such as antibiotic use or genetic defects may lead to changes in microbial metabolism, and an increase in the number of pathogenic bacteria. In IBD dysbiosis leads to effector immune cell activation or deficient regulatory cell activity in response to intestinal bacteria, or a disruption in the equilibrium between protective versus damaging intestinal microbiota. Inflammatory bowel disease patients harbor a reduced diversity of commensal bacteria, particularly in the phyla *Bacteroidetes* and *Firmicutes*, including the clinically pertinent *Faecalibacterium prausnitzii*, and an increased presence of *Escherichia coli* (Packey and Sartor, 2009). Commensal enteric microbiota modulate the immune system, which may lead to onset and chronicity of IBD. If commensal gut microbiota undergo a change in composition, it would deliver constant immunological stimuli leading to immune system anomalies and may have an impact on systemic conditions and inflammatory diseases such as periodontitis (Blasco-Baque *et al*., 2016; Forbes *et al*., 2016). In a longitudinal prospective study (Shaw *et al*., 2016), 19 pediatric IBD patients (15 CD, 4 UC) were followed regularly. Healthy family members of patients and unrelated subjects were recruited as controls. Differences in microbiome diversity, microbial dysbiosis, and inflammation were evaluated. Higher dysbiosis was seen in IBD patients with higher calprotectin levels (indicator of inflammation in the intestine). However, it remains uncertain whether dysbiosis directly induces IBD or is an outcome of the altered intestinal environment (Round and Mazmanian, 2009).

Inflammatory bowel disease as a polygenic disease could happen as a result of different defects in successfully managing the commensal and pathogenic microbiota. These genes are mainly associated with mucosal barrier function, antimicrobial recognition and function, or immune regulation (Fisher *et al.*, 2008). In a human study by Li *et al.* (2012) the occurrence of NOD2 risk alleles was associated with increased numbers of *Actinobacteria* and *Proteobacteria*. Yet, it is possible that dysbiosis is not causally linked to the pathogenesis of IBD but rather a consequence of these genetic variations (Becker *et al.*, 2015). Alterations in the gut microbiota might still contribute to prolonging intestinal inflammation.

The development and persistence of dysbiotic oral microbiota can mediate inflammatory diseases at local as well as in anatomically distant parts of the body (Hajishengallis, 2015). The interest on the role of dysbiotic periodontopathic bacteria is rising (Roberts and Darveau, 2015; Hajishengallis, 2015). Instead of individual pathogens, it is proposed that a synergy of diverse periodontitis-associated bacteria is implicated in disease. In dysbiosis, there is excessive microbial growth of pathogenic and/or non-pathogenic periodontal microbiota or a change in the influence of bacterial species leading to disturbance of the biofilm balance (Hajishengallis *et al.*, 2012; Hajishengallis *et al.*, 2014). Studies have shown that *Porphyromonas gingivalis*, by manipulating the host immune response, may induce dysbiotic communities, acting as a keystone pathogen (Darveau *et al.*, 2012). However, in the absence of a keystone pathogen, a genetic deficiency such as endothelial cell-derived protein (Del-1), that regulates neutrophil recruitment, causes inflammatory bone loss and alterations to the murine commensal microbiota (Eskan *et al.*, 2012) may be a factor. Therefore, it is conceivable that periodontitis could be initiated in the absence of bacteria acting as keystone pathogens (Hajishengallis and Lamont, 2012). Moreover, treatment of *P. gingivalis*-colonized mice with a complement 5a receptor (C5aR) antagonist leads to the eradication of *P. gingivalis* from the periodontium and overturns the dysbiotic alterations (Hajishengallis *et al.*, 2011). In a rabbit model of periodontitis, Hasturk *et al.* (2007a) used resolvin E1 (RvE1) as treatment for the control of inflammation. This therapy led to removal of the Gram-negative pathogens from the microbial flora and a return to pre-disease homeostasis of both the resident flora and the host (Hasturk *et al.*, 2007a). In the same model of periodontitis, the authors also reported reduction of inflammatory cell infiltration and periodontal bone loss when treating with a monosaturated fatty acid, 1-tetradecanol complex (1-TDC; Hasturk *et al.*, 2007b). These studies describe the role of inflammation creating dysbiosis during periodontitis in susceptible individuals. Similarly, in bowel diseases, diet high in fat and sugar causes bowel inflammation, which leads to dysbiosis of the intestinal microbiota (Luck *et al.*, 2015; Gulhane *et al.*, 2016). The alterations in the composition of the intestinal microbiota were reversed by using 5-aminosalicylic acid, which is an anti-inflammatory drug (Luck *et al.*, 2015). In another study using obese mice, the cytokine IL-22, which promotes tissue regeneration, improved the integrity of the mucosal barrier, decreased inflammation, and reversed microbial changes associated with obesity (Gulhane *et al.*, 2016). Therefore, the role of host inflammation and keystone pathogens in causing dysbiosis needs to be further evaluated.

The role of pathogenic microbiota

Inflammatory bowel disease microbiota has been the focus of interest in several studies; however, to date there are still some debates on the definite etiological microbial factors of IBD. The species that have been associated with IBD are: *Escherichia coli*, *Listeria monocytogenes*, *Yersinia enterocolitica*, *Clostridium difficile, Mycobacterium avium paratuberculosis, Salmonella sp., Campylobacter sp., Fusobacterium sp.* (Becker *et al.*, 2015). *Mycobacterium avium paratuberculosis* was the first bacterium to be suggested as an IBD pathogen (Sanderson *et al.*, 1992; Hermon-Taylor, 2001) although there still is debate on the theory that *Mycobacterium avium paratuberculosis* is the cause of CD (Quirke, 2001). *Clostridium difficile* in patients with IBD is associated with severe infection and should be treated with caution (Stoica *et al.*, 2015). Additionally, adherent-invasive *Escherichia coli* and *Fusobacterium varium* have also been associated with IBD (Ohkusa *et al.*, 2003; Petersen *et al.*, 2009).

Fusobacterium species are normally commensal microbes in both the oral and gut environments. Strauss *et al.* (2011) isolated *Fusobacterium* (based on 16S rRNA gene sequence) from 63.6% of individuals with gastrointestinal disease matched to 26.5% of healthy controls. In 50% of the IBD patients, *Fusobacterium nucleatum* was isolated and in 4.5% of the patients, *F. varium* was identified (*Figure 1*). *F. nucleatum* strains originating from disease biopsy tissue from CD subjects were found to have a significantly increased ability to invade intestinal epithelial cells in comparison to strains from healthy tissue from either IBD patients or healthy controls. *F. nucleatum* invasiveness can cause a subsequent infiltration of bacteria through the epithelial barrier into the lumen. *F. nucleatum*, by its ability to adhere to non-invasive bacterial species, can potentially shuttle those bacterial species across the epithelium (coinvasion phenomenon; Edwards *et al.*, 2006). These findings are consistent with the proposed roles as 'bridging bacteria' of *F. nucleatum* that contribute to the co-aggregation of periodontal biofilms (Bradshaw *et al.*, 1998). *F. nucleatum* has been shown to 'facilitate the survival of obligate anaerobes in aerated environments,' and has been suggested as one of the important indicators for attachment by later colonizers in periodontal disease (Bradshaw *et al.*, 1998, Shaw *et al.*, 2016).

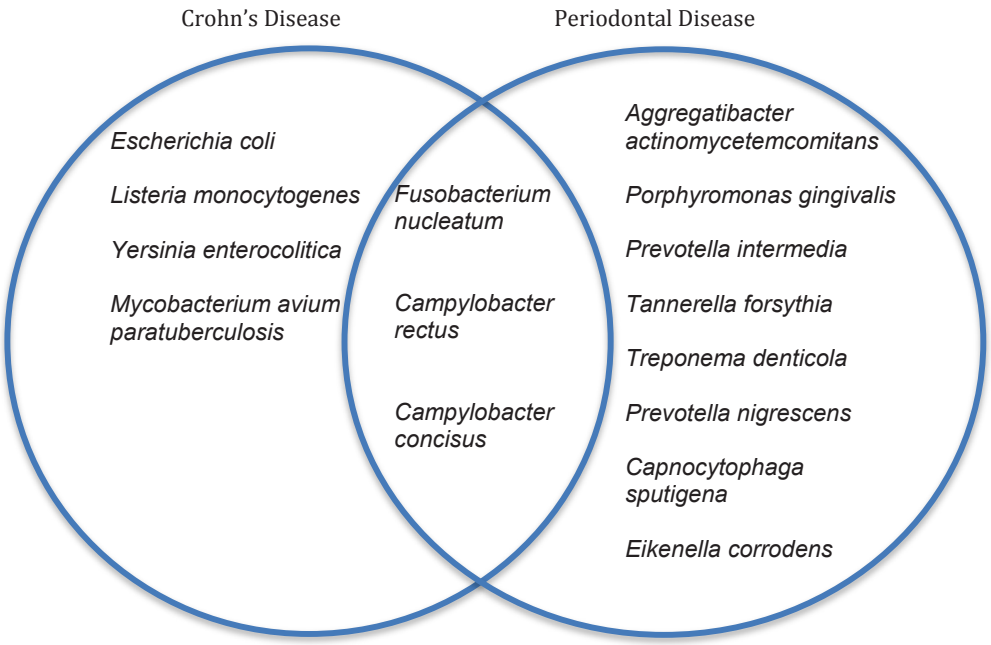

Figure 1. Common pathogenic microbiome of Crohn's disease and periodontal diseases.

In support of a potential role of periodontal pathogens in IBD, Van Dyke *et al.* (1986) reported that the majority of small motile Gram-negative rods were *Wolinella* or *Campylobacter* species in the periodontal biofilm of IBD patients. In 1988, Engel *et al.* found *Wolinella recta* in IBD patients using whole-cell DNA probes. In the new taxonomy, *Wolinella recta* are *Campylobacter rectus*, one of the most common causes of bacterial gastroenteritis (Tauxe 2002; Man, 2011). *Campylobacter* species (*C. concius*, *C. showae*, *C. hominus*, *C. gracilis*, *C. rectus*, *C. jejuni*, *C. curvus*, *C. ureolyticus*) were reported to be at higher prevalence in intestinal samples from IBD patients. Those species colonize primarily the oral cavity (Lee *et al.*, 2016). *C. concisus,* which is commonly present in the human oral cavity, was detected in abundance both in intestinal biopsies and fecal samples of patients with IBD in comparison to healthy controls (Zhang *et al.*, 2014).

Although bacteria play an important role in IBD, there are emerging data suggesting the role of fungi and viruses in IBD pathogenesis. Sokol *et al.* (2016) found that the diversity ratio of bacteria to fungi was increased in CD and flares of disease. Fungi from *Ascomycota* and *Basidiomycota* phyla dominated the fungal microbiota.

Summary and future directions

A number of studies have showed an association between PD and IBD. Both diseases share genetic and environmental etiological factors. Despite the advances in molecular typing methods, the precise role of intestinal bacteria remains elusive. Two theories are suggested: the presence of an unidentified persistent pathogen either endogeneous, exogeneous or metastatic, and the disruption of beneficial species of intestinal flora by harmful ones. The periodontal microbiota might have a role in these theories; *F. nucleatum, C. rectus* and *C. concisus* should be further evaluated in periodontal-gut microbiome research. In IBD and periodontal disease, microbial dysbiosis must be assessed as common pathogenic pathways that may affect each other. However, further investigations are needed to determine if IBD and periodontitis dysbiosis could be the result of inflammation generated by genetic and environmental alterations of the host. Converging and reproducible evidence should make a clear case for the potential role of periodontal pathogens in contributing to initiation, amplification, and perpetuation of IBD. Microbial colonization on mucosal surfaces of the intestine is different than colonization in the lumen (Li *et al.*, 2015). Microorganisms on gut mucosa are found in proximity to the intestinal epithelium and might affect the host immune system more than luminal/fecal microbes (Forbes *et al.*, 2016). Many studies of the gut microbiota use stool material for patient profiling, and because luminal/stool microbes might be more relevant for metabolic interactions, sampling gut microbiota from stool rather than biopsy may not adequately reflect the totality of viable microbes within the gut (Forbes *et al.*, 2016). Sampling of microbiota from different parts of intestine in IBD patients is important to interpret the results of the studies, as ileal and colonic IBD have different microbiological niches. Involved and uninvolved parts of intestine also yield different information regarding the causal relationship. All these factors should be considered in future studies to determine the role of microbial etiology in both chronic inflammatory intestinal and periodontal diseases.

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