Republic of Iraq
Ministry of Higher Education
and Scientific Research
University of Baghdad
College of Dentistry

A potential pathogenic association between periodontal disease and Inflammatory Bowel Disease: Crohn's disease

A Project Submitted to

The College of Dentistry, University of Baghdad, Department of periodontology in Partial Fulfillment for the Bachelor of Dental Surgery.

By :

Om albaneen Ahmed Kamaluddin

Supervised by:

Assist. Lec. Rasha Salah

B.D.S, M.Sc. (periodontology)

2023 A.D. **1444 A.H.**

Certification of the Supervisor

I certify that this project entitled **" A potential pathogenic association between periodontal disease and Crohn's disease "** was prepared by fifth year student **Om albaneen Ahmed Kamaluddin** under my supervision at the College of Dentistry / University of Baghdad in partial fulfillment of the graduation requirements for the bachelor degree in dentistry.

Supervisor's name:

Assist. Lec. Rasha Salah

B.D.S, M.Sc. (periodontology)

Date 27/4/2023

Dedication

I dedicate this work to my special person, the supportive, smart, wonderful brother **Dr.Ameen**.

Acknowledgment

First of all, thank **God** who inspire me to finish this work and for all gifts I have received.

grateful thanks to dean of College of Dentistry, University of Baghdad **Prof. Dr. Raghad A. AL-Hashimi.**

Grateful thanks are express to **Dr. Maha shukri** head of department of periodontics who gave me the opportunity to do this project.

All thanks to my supervisor **Assist. Lec. Rasha Salah** for advising me and helping me in completing this project.

To all doctors in this collage who did they best to make of us a good dentists, just like them.

Thanks from heart for my best friend, the best doctor in this world my brilliant brother **Dr.Ameen**.

• **Table of Content**

• List of figures

• List of abbreviations

1-TDC	1-Tetradecanol complex
BOP	Bleeding on probing
C5aR	Complement 5a receptor
CAL	Clinical attachment loss
CARD	A polymorphic gene involved in the innate immune system
CD	Crohn's disease
CPITN	The community periodontal index of treatment needs
Del-1	is an extracellular matrix protein that is expressed by endothelial cells during embryological vascular development

EIMs	Extraintestinal manifestations
IBD	Inflammatory bowel disease
IL	Interleukin, a family of pro-inflammatory cystine knot cytokines
NOD2	gene (previously known as CARD15) provides instructions for making a protein that plays an important role in immune system
PD	Pocket depth
RvE1	Resolvin E1
Th	T helper cell
UC	Ulcerative colitis
VPI	Visible plaque index

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)**. About one-third of patients with IBD develop extraintestinal manifestations (EIMs) in other organs, such as joints, skin, eyes, and the biliary tract) **(Lankarani KB *et al*., 2013) (Levine JS, Burakoff R. 2011)**.

The oral cavity is also a common site for EIMs in patients with IBD, especially CD **(Lankarani KB *et al*., 2013.)**.

Salivary dysfunction and oral problems are often observed in patients with CD compared with healthy individuals. **(De Vries SAG *et al*., 2018).**

Likewise, the prevalence of periodontitis is significantly higher in patients with CD than in controls without IBD **(She YY *et al*., 2020)**. Shared common pathological and inflammatory processes suggest an association between periodontitis and IBD. However, it is largely unclear if, and how, oral manifestations, such as periodontitis, influence intestinal inflammation in IBD.

The perturbed microbial community in the gut, so-called gut dysbiosis, is a hallmark of IBD. Genetic and environmental factors associated with the risk of IBD may drive the alteration of the gut microbial communities, enriching pathobionts and reducing beneficial bacteria **(Manichanh C *et al*., 2012).**

The dysbiotic microbiota subsequently activates various immune pathways at the mucosal sites, thereby causing or exacerbating intestinal inflammation **(Stecher B. 2015).**

Advances in next-generation sequencing technologies enable high-resolution and quantitative microbiome analysis in IBD. Using these techniques, several studies have identified bacterial taxa that are selectively enriched in patients with IBD. Advanced microbiome analyses have reconfirmed the possible contribution of well-recognized IBD-associated pathobionts, such as members of the large family Enterobacteriaceae, including adherent-invasive E. coli. In addition, several previously under recognized bacterial taxa have been identified as putative pathobionts. Notably, various studies have reported that oral bacteria, such as Fusobacteriaceae, Pasteurellaceae, and Veillonellaceae, are enriched in the mucosal tissues of patients with IBD **(Said HS *et al.*, 2014, Kitamoto S *et al.*, 2020)**.

The abnormal Th1/Th17-shifted immune activation observed in the mucosal tissues of these patients suggests that ectopic colonization by some oral mucosa derived bacteria may elicit the inflammatory immune responses in the gut mucosa.

Indeed, Klebsiella species isolated from the saliva of patients with IBD harbor a potent Th1-inducing capacity when they colonize the colonic mucosa and provoke intestinal inflammation **(Atarashi K *et al.*, 2017)**. Thus, gut colonization by certain oral bacteria, most likely oral disease–associated pathobionts, may contribute to IBD risk.

Despite recognizing the possible contribution of oral pathobionts to the pathogenesis of IBD, the precise mechanisms of how oral manifestations bridge the microbial oral–gut axis remain incompletely understood. In this regard, it has recently reported that periodontitis exacerbates colitis in mice **(Kitamoto S *et al.*, 2020)**.

Oral inflammation induced by periodontitis results in expansion of oral Klebsiella and Enterobacter species, which are ingested and translocated to the gut, in the gut, these oral pathobionts may elicit inflammatory responses in the colonic mucosa **(Kitamoto S *et al.*, 2020)**. In parallel, oral pathobiont-reactive Th17 cells generated in the oral mucosa due to periodontitis migrate to the gut mucosa and aggravate colitis **(Kitamoto S *et al.*, 2020)**.

Thus, oral inflammation can trigger ectopic gut colonization by oral pathobionts, thereby serving as a critical pathogenic factor that elevates the risk of IBD. In this context, patients with IBD display oral dysbiosis likely caused by oral conditions, including periodontitis **(de Vries SAG *et al.*, 2018, Goldinova A *et al.*, 2020)**. However, the effect of oral inflammation or dysbiosis on gut pathophysiology in human IBD remains elusive.

Aims of review

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.

Chapter one: Review of literature

1.1 Crohn's disease

Crohn's disease is a chronic disease that causes inflammation and irritation in the digestive tract. Most commonly, Crohn's affects small intestine and the beginning of large intestine. However, the disease can affect any part of digestive tract, from mouth to anus

Crohn's disease most often begins gradually and can become worse over time.

Researchers estimate that more than half a million people in the United States have Crohn's disease. Studies show that, over time, Crohn's disease has become more common in the United States and other parts of the world **(Kappelman MD *et al.*, 2013) (Molodecky NA *et al.*, 2012)**.

1.1.1 Clinical manifestations of CD

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. CD can occur in all of the layers of the intestine walls **(Matricon *et al.*, 2010)**.

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).**

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)**.

1.1.2 Oral manifestations of CD

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)**

1.1.3 Incidence and prevalence of 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.

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).**

1.1.4 Measuring Crohn's disease

The Harvey-Bradshaw Index consists of a few questions that allow physicians to quickly categorize the severity of Crohn's disease and detect remission. This index is especially useful for data collection. Harvey and Bradshaw first published the index in The Lancet, in 1980, as a shorter, simpler alternative to the standard categorization technique called the Crohn's Disease Activity Index. Patients answer the following five questions, and are given a score based on the severity of their symptoms.

Harvey-Bradshaw Index Questions:

1. Patient's general well-being (for the previous day)

(0 = very well, 1 = slightly below par, 2 = poor, 3 = very poor, 4 =terrible)

2. Abdominal pain (for the previous day)

(0 = none, 1 = mild, 2 = moderate, 3 = severe)

3. Number of liquid stools per day (for the previous day)

(Score 1 per movement)

4. Abdominal mass

(0 = none, 1 = dubious, 2 = definite, 3 = definite and tender)

5. Complications (score 1 per item)

• Joint pain (arthralgia)

• Inflammation of the middle layer of the eye (uveitis)

• Inflammation of fat cells that results in tender red nodules on shins (erythema nodosum).

• Ulcers in the mouth (aphthous ulcers)

• Condition that causes tissue to become necrotic (pyoderma gangrenosum)

• Tear in the tissue that lines the anus (anal fissure)

• A newly formed channel between the end of the bowel and the skin around the anus (fistula)

• Swollen tissue with an accumulation of pus (abscess)

Harvey-Bradshaw Index Score

Remission: <5

Mild Disease: 5-7

Moderate Disease: 8-16

Severe Disease: >16

1.2 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 and 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).**

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**(Brito *et al*., 2013).**

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 $\geq$ 4 mm, higher gingival index and BOP were more frequent in IBD patients.

Common inflammatory mechanisms in the intestinal and periodontal mucosa and the imbalance between proinflamatory and anti-inflammatory mediators were investigated in a study conducted by **Menegat *et al*., (2016)**.

Crohn's disease presence was evaluated both clinically and by laboratory methods using the Harvey Bradshaw index **(Harvey and Bradshaw, 1980)**.

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

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)** 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 rectushad the highest frequency, being found in 94.6% of the patients **(Stein *et al.*, 2010).**

1.3 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 Crohns disease 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)**.

1.4 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)**.

1.5 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)**.

1.6 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 1014 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).**

1.7 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 Bacteroidetesand 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.

1.8 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 variumhave also have 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).

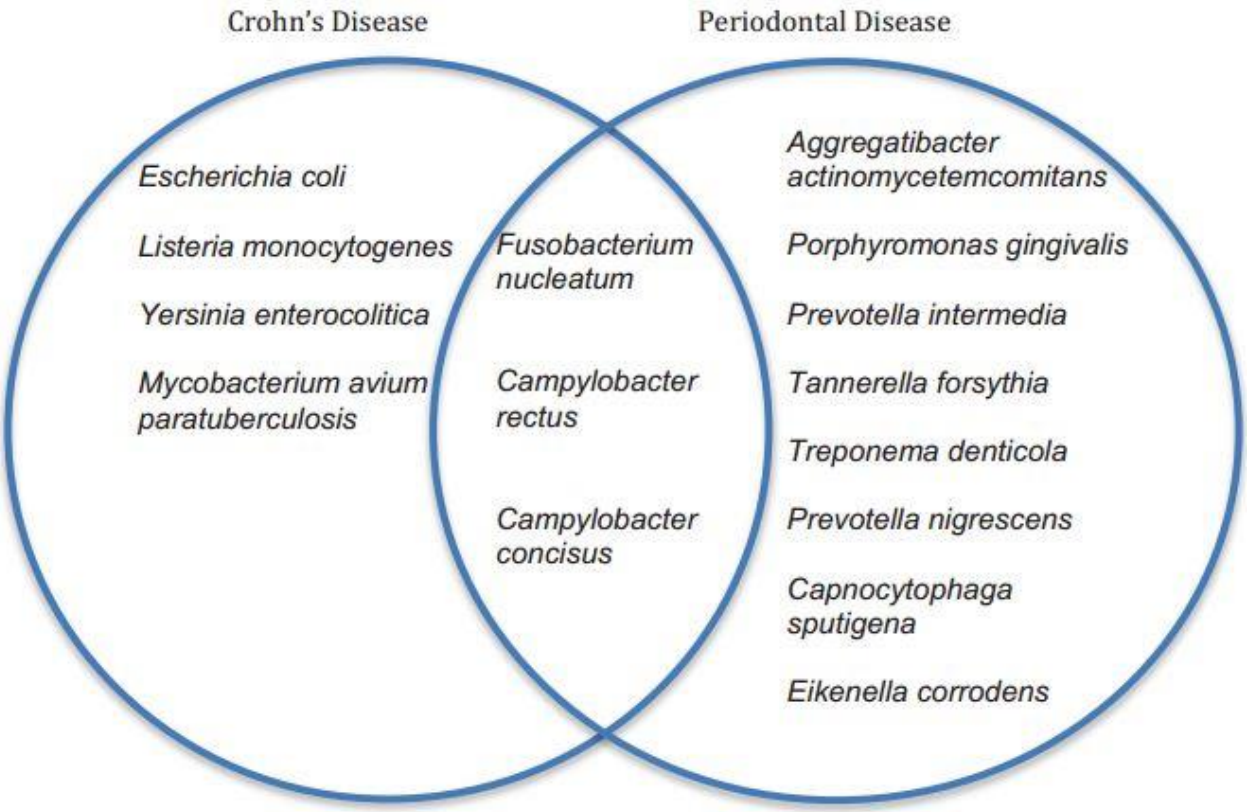

Figure 1. Common pathogenic microbiome of Crohn's disease and periodontal diseases.

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. nucleatumthat contribute to the co-aggregation of periodontal biofilms **(Bradshaw *et al.*, 1998).**

F. nucleatumhas 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).**

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 Wolinellaor Campylobacterspecies 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 rectaare Campylobacter rectus, one of the most common causes of bacterial gastroenteritis **(Tauxe 2002; Man, 2011).**

Campylobacterspecies (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 Ascomycotaand Basidiomycotaphyla dominated the fungal microbiota.

1.9 Conclusion

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. rectusand C. concisusshould 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.

References

- Agossa K, Dendooven A, Dubuquoy L, GowerRousseau C, Delcourt-Debruyne E and Capron M. Periodontal manifestations of inflammatory bowel disease: Emerging epidemiologic and biologic evidence. Journal of Periodontal Research2017; 52:313-324.
- Baer PN. The case for periodontosis as a clinical entity. Journal of Periodontology 1971; 42:516-520.
- Basson A, Trotter A, Rodriguez-Palacios and Cominelli F. Mucosal interactions between genetics, diet, and microbiome in inflammatory bowel disease. Frontiers in Immunology2016; 7:290.
- Chen XT, Chen LL, Tan JY, Shi DH, KeT and Lei LH. Th17 and Th1 lymphocytes are correlated with chronic periodontitis. Immunological Investigations2016; 45:243-254.
- Cholapranee A and Ananthakrishnan AN. Environmental hygiene and risk of inflammatory bowel diseases: A systematic review and meta-analysis. Inflammatory Bowel Diseases2016; 22:2191-2199.
- Darveau R, Hajishengallis G and Curtis M. Porphyromonas gingivalisas a potential community activist for disease. Journal of Dental Research 2012;91:816-820.
- Edwards AM, Grossman TJ and Rudney JD. Fusobacterium nucleatum transports noninvasive Streptococcus cristatusinto human epithelial cells. Infection and Immunity2006; 74:654-662.
- Fisher S, Tremelling M, Anderson C et al., Genetic determinants of ulcerative colitis include the ECM1 locus and five loci implicated in Crohn's disease. Nature Genetics 2008; 40:710-712.

- Flemmig TF, Shanahan F and Miyasaki KT. Prevalence and severity of periodontal disease in patients with inflammatory bowel disease. Journal of Clinical Periodontology1991; 18:690-697.
- Grössner-Schreiber B, Fetter T, Hedderich J, Kocher T, Screiber S and Jepsen S. Prevalence of dental caries and periodontal disease in patients with inflammatory bowel disease: A case-control study. Journal of Clinical Periodontology2006; 33:478-484.
- Gulhane M, Murray L, Lourie R et al., High fat diets induce colonic epithelial cell stress and inflammation that is reversed by IL-22. Scientific Reports2016; 6:28990.
- Han Y, Houcken W, Loos B et al., Periodontal disease, atherosclerosis, adverse pregnancy outcomes, and head-and-neck cancer. Advances in Dental Research 2014; 26:47-55.
- Habashneh RA, Khader YS, Alhumouz MK, Jadallah K and Ajlouni Y. The association between inflammatory bowel disease and periodontitis among Jordanians: A case-control study. Journal of Periodontal Research 2012; 47:293-298.
- Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. Nature Reviews Immunology2015; 15:30-44.
- Harbord M, Annese V, Vavricka SR, et al.The fi rst European evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. Journal of Crohn's and Colitis2016; 10:239-254.
- Harvey RF and Bradshaw JM. A simple index of Crohn's disease activity. Lancet1980; 1:514.

- Jakobsen C, Paerregaard A, Munkholm P and Wewer V. Environmental factors and risk of developing pediatric inflammatory bowel disease – A population based study 2007–2009. Journal of Crohn's and Colitis2013; 7:79-88.
- Khalili H, Higuchi LM, Ananthakrishnan AN et al., Oral contraceptives, reproductive factors and risk of inflammatory bowel disease. Gut2013; 62:1153-1159.
- Kinane DF and Radvar M. The effect of smoking on mechanical and antimicrobial periodontal therapy. Journal of Periodontology1997; 68:467-472.
- Kotsakis GA, Javed F, Hinrichs JE, Karoussis IK and Romanos GE. Impact of cigarette smoking on clinical outcomes of periodontal fl ap surgical procedures: A systematic review and meta-analysis. Journal of Periodontology2015; 86:254-263.
- Koutsochristou V, Zellos A, Dimakou K et al., Dental caries and periodontal disease in children and adolescents with inflammatory bowel disease: A case-control study. Inflammatory Bowel Diseases 2015; 21:1839-1846.
- Kappelman MD, Moore KR, Allen JK, Cook SF. Recent trends in the prevalence of Crohn's disease and ulcerative colitis in a commercially insured U.S. population. Digestive Diseases and Sciences. 2013;58:519–525.
- Lankarani KB, Sivandzadeh GR and Hassanpour S. Oral manifestation in inflammatory bowel disease: A review. World Journal of Gastroenterology 2013; 19:8571-8579.
- Lee S, Lee J, Ha J et al., Clinical relevance of infections with zoonotic and human oral species of Campylobacter. Journal of Microbiology2016; 54: 459-467.

- Molodecky NA, Soon IS, Rabi DM et al., Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012;142(1):46–54.
- Yin W, Ludvigsson JF, Liu Z, Roosar A, Axell T and Ye W. Inverse association between poor oral health and inflammatory bowel diseases. Clinical Gastroenterology and Hepatology 2016; 15:525-531.
- Zhang L, Lee H, Grimm MC, Riordan SM, Day AS and Lemberg DA. Campylobacter concisusand inflammatory bowel disease. World Journal of Gastroenterology 2014; 20:1259-1267.