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Association between Periodontitis and Inflammatory Bowel Disease- Review of Current Literature on the Biologic Plausibility

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ABSTRACT

Periodontitis, a chronic inflammatory disease of the supporting tissues of teeth, is etiologically associated with a subset of pathogenic organisms that thrive in the anoxic niche provided by the diseased periodontal pockets. These anaerobic gram-negative organisms resident in plaque biofilm and causing an overwhelming chronic inflammatory response in periodontal tissues have also been associated with other systemic chronic inflammatory diseases like cardiovascular, renal, and adverse pregnancy outcomes as per literature being published for the past twenty years or more. This paper aims to provide an overview on the biological plausibility of a strong association between systemic seeding of pathogenic oral bacteria and chronic bowel diseases like Inflammatory Bowel Diseases by reviewing recent literature from open-source journals on the same topic. Knowledge of the association between oral bacteria and gut inflammatory diseases will help in broadening the preventive and therapeutic options available currently by suggesting measures to suppress the systemic hyper-immune response.

Keywords: Campylobacter rectus, Fusobacterium nucleatum, inflammatory bowel disease, immune reaction in inflammatory bowel disease, pathogens in inflammatory bowel disease, periodontitis.

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I. Introduction

Periodontitis, a chronic disease of the supporting tissues around the teeth, and Inflammatory Bowel Disease a chronic disease of the colonic mucosa, reportedly share many similarities in disease development and clinical presentation which is strongly indicative of a shared etiology, viz. chronic inflammation. This persistent chronic inflammation has been reported in the literature to be initiated by a subset of bacteria resident in the oral plaque biofilms as a bacterial community and capable of invasiveness and colonization systemically. Subsequently, systemic seeding of these organisms manifests as selective colonization of the gut mucosa resulting in an exaggerated immune response in susceptible areas, which is clinically expressed as simultaneous alveolar bone loss and erosion of the gut mucosa. In the recent past, new evidence for the biologic plausibility of the chronic inflammation-hyperimmune reaction linkage between periodontitis and inflammatory bowel diseases has been reported in the literature. Hence a literature review from open-source publications on the biologic plausibility of an association between periodontitis and inflammatory bowel disease is reported in this short review, as the confirmation of this paradigm can help prevent both diseases by an earlier intervention at the plaque biofilm level to mitigate the systemic hyper-immune reactions.

II. Literature Review of the Association between Inflammatory Bowel Disease and Periodontitis

Reference [1] first described the association between inflammatory bowel disease and periodontitis due to the altered immune function in one case report where they pointed out that enhanced neutrophil function could prove to be the link between both diseases. Reference [2] reported a hospital-based observational study on the prevalence and severity of periodontitis in inflammatory bowel disease patients and concluded that periodontitis affected more sites per subject in the IBD group in the US population in a case-control study. Reference [3] reported higher prevalence and severity of periodontitis in IBD patients when compared to non-IBD controls in Jordanian patients. Reference [4] also reported that IBD is associated with periodontitis in a Swiss cohort and the increased risk of periodontitis was higher in Crohn's disease subgroup within IBD patients.

Reference [5] did a similar study in the Asian population and interestingly showed a gender predilection for the association. They reported that female IBD patients had a significantly higher risk of developing periodontitis than the non-IBD group in Asians. They concluded that Gender differences could be one of the risk factors for developing periodontitis as females had a higher risk than males in IBD patients in their study. As a follow-up study, [6] studied the same epidemiology of IBD with a focus on the Asian

population and not only confirmed [5]'s findings on gender predilection but also suggested that hormonal influences might play an important factor in this phenomenon of higher risk in female patients for developing periodontitis.

In a recent review [7], they reviewed all the available evidence so far and concluded that the overwhelming epidemiological and biological evidence of similarities between IBD and periodontal diseases makes a strong case in support of a relationship between these two diseases.

Reference [8] referred to the pathogenic interaction between periodontal disease and inflammatory bowel disease where one disease alters the composition of the microbiota and thereby increases the inflammatory response of the other. After a comprehensive analysis of all the epidemiological studies published till then on the two diseases, they attribute the association to be due to an interplay between the immune-inflammatory response and the dysbiotic microbiota resulting in a cyclic impact on both the diseases with each potentiating the other [8].

A systematic review by [9] investigated the association between inflammatory bowel disease (IBD) and oral health. A total of 9 cross-sectional studies including 1297 patients were included in the review and they concluded that IBD was associated with increased risk of periodontitis (95% confidence interval (CI): 257-388 patients; $p < 0.001$) compared to non-IBD patients [9].

Reference [10] summarized the treatments available for inflammatory bowel disease (IBD) and recommended that dentists have a primary responsibility to screen for and refer to a gastroenterologist any early sign of IBD diagnosed while treating oral diseases.

A 2018 retrospective cohort study by [11] from a population-based database derived from the National Health Insurance Research Database (NHIRD) in Taiwan with longitudinal follow-up from 2000 to 2009 of a total of one million participants showed that patients with IBD (Risk Factor:1.82 times), especially more in Crohn's disease (Risk Factor:3.95 times) than in ulcerative colitis, had a higher and increased risk of having periodontitis compared with the non-IBD group even after accounting for all possible confounding factors to minimize bias. The large population subset and the longitudinal design of the study –over nine years if follow-up- makes it all the more relevant that the authors conclude by recommending an intensive regular oral check-up for periodontal status IBD patients in Taiwan [11].

III. Pathophysiology of Inflammatory Bowel Disease and Periodontitis

Inflammatory Bowel Disease refers to idiopathic inflammatory diseases of the intestine, principally Ulcerative Colitis, and Crohn's disease. There is no cure for inflammatory bowel disease and the current medical management of inflammatory bowel disease consists of anti-inflammatory and immunosuppressive agents. Evidence supporting inflammatory dysregulation as a critical factor in the pathogenesis of inflammatory bowel disease and periodontitis has suggested potential underlying relationships in host response characteristics to their autochthonous microbiota in triggering these chronic inflammatory diseases. The general hypothesis of all the reported studies on the association between the two diseases is that patients with inflammatory bowel disease have a greater risk for periodontitis due to an underlying defect in innate immune responses at mucosal surfaces.

The pathogenesis of both inflammatory bowel disease and periodontitis is multifactorial leading to a substantial defect of the mucosal barrier, deregulation of the immune response, and chronic inflammation of the mucosa. The common oral manifestations of inflammatory bowel disease are indurated tag-like lesions, cobblestoning, mucogingivitis, aphthous stomatitis, and pyostomatitis vegetans [12]. Also, severe periodontitis has been observed in individuals with inflammatory bowel disease who suffer from secondary neutrophil impairment [13].

IV. Periodontal Microbiota associated with Inflammatory Bowel Disease

Oral bacteria are considered to be associated with several systemic diseases such as atherosclerotic disease, adverse pregnancy outcomes, rheumatoid arthritis, and respiratory tract infections [14]. Recently, the association of oral bacteria with inflammatory bowel disease (IBD) and colorectal cancer (CRC) has attracted much attention [15]. IBDs, which include Crohn's disease (CD) and Ulcerative Colitis (UC), are chronic relapsing idiopathic inflammatory diseases of the gastrointestinal tract [16]. Inflammatory bowel disease is thought to be associated with both environmental and bacterial factors. The periodontal microbiota reported having a role in IBD include *F.nucleatum, C.rectus,* and *C.concisus. Fusobacterium nucleatum* is a known periopathogen which is also associated with IBD and CRC. *Campylobacter concisus*, which is often found at the site of periodontitis, is also associated with IBD, as in periodontal dysbiosis, there is excessive growth of both pathogenic and/or non-pathogenic periodontal microbiota leading to a disturbance of the biofilm balance and disease initiation [17].

V. *F. nucleatum*- Highly Virulent Invasive Pathogen in Inflammatory Bowel Disease

Fusobacterium nucleatum, a Gram-negative anaerobe, is known as one of the most important periodontopathogens and prevalent abundantly in periodontitis sites.[18] *F. nucleatum* is recognized as an adhesive organism for its remarkable adherence properties and hence understanding its adherence becomes essential to know its role in the pathogenesis of periodontitis. In periodontal infections, *F. nucleatum* coaggregates with several kinds of bacteria, and it contributes to biofilm formation (corn-cob symbiotic union) [19]. *F.nucleatum* has an outer membrane protein RadD, which is an arginine-inhibitable adhesin required for inter-species adherence and associated with the initiation of coaggregation with other biofilm organisms (early colonizers) in the periodontal pocket and especially with *P. Gingivalis*, another known periopathogen [20]. Reference [21] identified a novel adhesin, Fusobacterium Adhesin A, FadA, an outer membrane protein unique to oral Fusobacteria which is required for *F.nulceatum* attachment to epithelial cells as it binds to the surface proteins of the oral mucosal cells. This

FadA is associated with not only colonization in the healthy periodontal environment but also associated with invasion into deeper tissues and systemic dissemination [22].

VI. *F. NUCLEATUM*- SUB-STRAINS CAUSING HYPER-IMMUNE RESPONSE IN INFLAMMATORY BOWEL DISEASE

Another important pathologic characteristic of *F. nucleatum* is synergistic virulence in mixed infections as reported by [23], as when *F. nucleatum* and *P. gingivalis*, were simultaneously injected into mice, larger abscesses were formed compared to mice mono-injected with each bacterium. Reference [24] reported that *F. nucleatum* septicemia in ulcerative colitis patients is associated with portal vein thrombosis indicative of this organism's virulence. Although *F. nucleatum* is a heterogeneous oral pathogen normally resident in anoxic deep periodontal pockets, it was reported by [25] to be also present in biopsy tissue harvested from the colon in inflammatory bowel disease patients, especially the more invasive *F. nucleatum* strains. Reference [26] reported in 2011 that these highly invasive *F. nucleatum* strains stimulated ramped up production of inflammatory mediators like MUC2 mucin and TNFα suggesting a possible role for these specific substrains in the hyper-immune response seen in chronic inflammatory conditions like Periodontitis and IBD. Reference [27] compared the genes between actively-invading and passively-invading *F. nucleatum* strains and reported that the active invaders had much larger genomes and encoded FadA-related adhesins containing a MORN2 domain which translates to higher invasiveness of gut mucosa by the periodontopathic bacteria and resultant more robust hyperimmune response systemically. Hence based on these literature findings *F. nucleatum* and especially a specific few sub-strains with high virulence properties, can be plausibly linked with an invasion of gut mucosa and producing an enhanced inflammatory response of the colonic tissues leading to inflammatory bowel diseases.

VII. *C. RECTUS* - THE INVERSE RELATIONSHIP BRIDGE ORGANISM CAUSING AN AUTO-IMMUNE RESPONSE IN INFLAMMATORY BOWEL DISEASE

Another often implicated organism in chronic inflammatory diseases like Periodontitis and IBD is Campylobacter rectus, a Gram-negative oral anaerobe associated with plaque biofilms in periodontal pockets. Reference [28], on patients with Crohn's disease, reported a high frequency of periodontopathic bacteria isolated from colonic tissue samples with *A. actinomycetemcomitans, P. gingivalis, P. intermedia, T. forsythia* and especially *C. rectus*. They also reported that C.rectus, can not only impair neutrophils but also significantly upregulate both mRNA and protein levels of Il-6 and TNF-alpha leading to a systemic pro-inflammatory response due to its invasiveness. They conclude that trigger effects for autoimmune responses or cross-tolerance to *C. rectus* are possible mechanisms involved in the pathogenesis of both the diseases and especially the periodontal manifestations of Crohn's disease [28]. Hence *C. rectus* is an organism of interest in the chronic inflammatory diseases paradigm as it can be an inverse relationship bridge between colonic multiplication and periodontal manifestation.

VIII. HYPER-IMMUNE RESPONSE PARADIGM IN INFLAMMATORY BOWEL DISEASE AND PERIODONTITIS

Reference [29] reported in one of the very first studies in 1986 that they focused on the periodontal manifestations of inflammatory bowel disease for three major reasons:

i. the similarities in the pathogenesis of the diseases and
ii. the simultaneous occurrence of the diseases, and
iii. the unusual microflora found associated with periodontal disease in IBD patients.

They conclude that as indicated by the clinical measurements, the degree of inflammation of the gingiva of the affected inflammatory bowel disease patients seems greater than that of age- and sex-matched periodontal disease patients [29].

Reference [30] reporting on the immuno-pathogenic link between periodontitis and inflammatory bowel disease postulated that endogenous infection with local hypersensitivity causes periodontal disease, reflecting 'frustrated' immune elimination mechanisms entertained by antigens from dental plaque. This perturbation of a tightly controlled cytokine network, with abnormal crosstalk between several cell types, explains the progressive immunopathology of chronic inflammatory mucosal diseases in general and specifically the association between periodontitis and bowel disease [30].

As discussed above, the bacterial provocation and hyper-immune response paradigm and its biological plausibility through the presence of very specific sub-strains of organisms like *F. nucleatum* and *C. rectus* intimately involved in the initiation of this hyper-responsive state have been repeatedly affirmed by many other studies independently, leading to the conclusion that there is a very strong association between IBD and Periodontitis and hence management of one disease can lead to prevention or alleviation of the other disease synergistically. More rigorously conducted large scale trials would provide the proof of concept beyond the biological plausibility and validate this association beyond doubt.

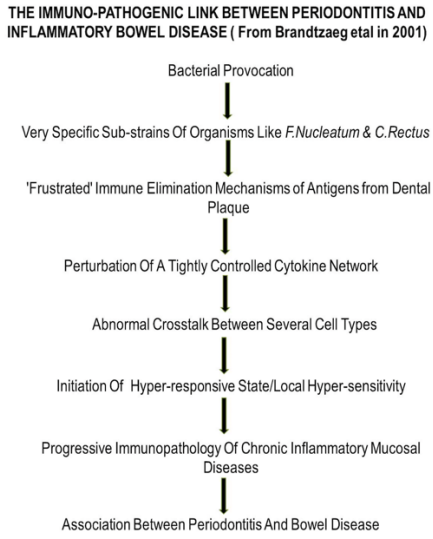

Fig. 1. The Biological Plausibility Paradigm Flowchart.

TABLE I: HUMAN MODEL STUDIES INCLUDED FOR THE REVIEW OF LITERATURE

S. No	Reference	Method	Principal Findings
1	Reference [2]	The periodontal status of 107 consecutive patients seeking treatment for inflammatory bowel disease was assessed. There was no control group and results were compared with the assessment of Oral Health of United States Adults	IBD patients revealed a 11.9% higher prevalence (P less than or equal to 0.01) but 0.6 mm lower severity (P less than or equal to 0.01) of periodontal disease.
2	Reference [28]	147 Caucasian patients with CD (age range: 18-59)	Patients with Crohn's disease have an increased prevalence but only moderate severity of periodontal disease
3	Reference [29]	Total of 20 patients with inflammatory bowel disease (IBD)	The data suggest that unusual microorganisms colonizing the oral cavity of IBD patients potentially play a role in the pathogenesis of IBD
4	Reference [11]	A total of 993,232 outpatients between 2000-2009 from NHIRD sub-datasets from National Health Insurance Research Database (NHIRD) in Taiwan. In IBD cohort, 27 IBD patients (7 Crohn's disease and 20 ulcerative colitis) with catastrophic illness registry were identified. 108 controls were selected as non-IBD cohort. The median follow-up period was 3.00 years in the IBD group and 3.15 years in the non-IBD group.	After adjusting for several confounding factors, IBD group had higher risk for developing periodontitis than non-IBD group (adjusted HR: 1.82; 95% CI: 1.09–3.03). To further stratification with subtype, Crohn's disease group had significantly higher risk of periodontitis (adjusted HR: 3.95; 95% CI: 1.59–9.82).
5	Reference [4]	In a prospective 8-month study, systematic oral examinations were performed in 113 patients with IBD, including 69 patients with CD and 44 patients with ulcerative colitis.	In only the CD subgroup, high clinical activity was associated with 1 periodontitis marker, the loss of attachment at sites of maximal periodontal pocket depth
6	Reference [9]	A total of 9 cross-sectional studies including 1297 patients were included.	IBD was associated with increased risk of periodontitis (332 more patients per 1000 patients; 95% confidence interval (CI): 257-388 patients; $p < 0.001$) compared to non-IBD patients

IX. CONCLUSION

Converging and reproducible evidence is now abundantly available on the role played by a few specific periodontal pathogens in contributing to the initiation, amplification, and perpetuation of inflammatory bowel disease. The microbial dysbiosis in the plaque biofilm with the proliferation of pathogens and a concomitant change in the flora with the more aggressive substrains being disseminated widely leading to a systemic hyperimmune response is the biologically plausible pathway linking Periodontitis and IBD. As such, both Dental professionals and Gastroenterologists should be educated on the relationship between these two diseases as a regular oral check-up for periodontal status might serve as an early warning sign and a cost-effective diagnostic screening tool for inflammatory bowel diseases. Also, meticulous plaque control monitored by periodontists can be recommended to help in the prevention of more such systemic inflammatory diseases in the future. More and rigorous research on these issues with large, randomized trials on diversified genetic populations is needed for us to come to a definitive conclusion on the interconnectedness of the human microbiome and the systemic dysfunction caused by its dysbiosis.

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