**Mini Review**  **Open Access**

# Oral Bacteria and Bowel Diseases – Mini Review

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## Abstract

Oral bacteria are considered to be associated with several systemic diseases. Recently, their association with inflammatory bowel disease (Crohn's disease and ulcerative colitis) and colorectal carcinoma has attracted much attention. In this mini-review, the association of oral bacteria with these diseases is briefly summarized.

*Fusobacterium nucleatum* is known as a periodontopathic bacterium, and it is also associated with inflammatory bowel disease and colorectal carcinoma. *Campylobacter concisus*, which is found at the site of periodontitis, is associated with inflammatory bowel disease. *Streptococcus mutans* is a famous cariogenic bacterium, but a highly-virulent strain of this bacterium is also associated with inflammatory bowel disease.

In this way, both periodontopathic bacteria and cariogenic bacteria are associated with bowel diseases. Further epidemiological studies are necessary to reveal the cause and effect relationship between oral bacterial and bowel diseases.

**Keywords:** Oral bacteria; Inflammatory bowel diseases; Colorectal carcinoma

## Introduction

Oral bacteria are considered to be associated with several systemic diseases such as atherosclerotic disease, adverse pregnancy outcomes, rheumatoid arthritis, and respiratory tract infections [1].

Recently, the association of oral bacteria with inflammatory bowel disease (IBD) and colorectal cancer (CRC) has attracted much attention. IBDs, which include Crohn's disease (CD) and ulcerative colitis (UC), are chronic relapsing idiopathic inflammatory diseases of the gastrointestinal tract [2]. IBD is thought to be associated with both environmental and bacterial factors. Epidemiological studies suggested that environmental factors play an important role in the increased incidence of IBD. On the other hand, colitis did not occur in germ-free animal models of IBD, and intestinal inflammation in patients with CD was resolved after faecal stream diversion [3,4].

In this mini-review, the association of oral bacteria and these diseases will be briefly summarized (Table 1).

| Oral bacteria | Intestine disease | Important findings | Reference |
|---|---|---|---|
| *Fusobacterium nucleatum* | IBD | *F. nucleatum septicemia* in UC patient is associated with portal vein thrombosis | 11 |
| | | Highly invasive strains of *F. nucleatum* may be a biomarker of IBD | 12 |
| | | Highly invasive strains of *F. nucleatum* stimulates MUC2 mucin and TNFα | 13 |
| | | Comparison of genes between actively-invading and passively-invading Fusobacterium | 14 |
| | CRC | Associatiton of *F. nucleatum* with CRC | 15 |
| | | Associatiton of *F. nucleatum* with CRC and lymph node metastasis | 16 |
| | | *F. nucleatum* recruit tumor-infiltrating immune cells | 17 |
| | | *F. nucleatum* modulates E-cadherin/β-catenin signalling via Fad A | 18 |
| | | Polymicrobial signature of anaerobic bacteria is associated with CRC | 19 |
| | | *F. nucleatum* is associated with progression from adenoma to CRC. | 22 |
| | | *F. nucleatum* and Clostridium is associated with CRC | 20 |

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|---|---|---|---|
| | | *F. nucleatum* is associated with shorter survival of CRC patients | 23 |
| | | Effect of *F. nucleatum* on human immunity and molecular alteration | 24 |
| Campylobactr concisus | IBD | *C. concisus* and antibodies to this bacterium were detected in CD | 29 |
| | | High rate of *C. concisus* isolation from older children and adults | 30 |
| | | Isolation of immunoreactive proteins from *C. concisus* | 32 |
| | | IBD patients are colonized with specific oral *C. concisus*, which underwent natural recombination | 31 |
| | | Isolation of zonula occuden toxin (Zot) gene from *C. concisus* | 33 |
| | | *C. concisus* Zot is associated with barrier defect of intestine. | 34 |
| | | Autophagy of *C. concisus* is in part associated with intracellular survival. | 35 |
| | | Increased gastric pH and reduced intestinal bile may be useful for *C. concisus* colonization. | 36 |
| | | Genetic recombination is common in oral and enteric *C. concisus* | 37 |
| *Streptococcus mutans* | IBD | Crohn's disease patients had more caries experience compared to normal population | 40 |
| | | Lactobacillus count and the number of decayed tooth surface were higher in the Crohn's disease | 41 |
| | | Crohn's disease patients had more mutants streptococci counts than non-disease control | 42 |
| | | Collagen binding protein-positive *S. mutans* is considered to be a risk factor for ulcerative colitis | 43 |
| | | More *S. mutans* was detected in Crohn's disease patients, not in ulcerative colitis | 44 |
| | | Crohn's disease patients had higher DMFs score and *S. mutans* counts compared to control | 45 |
| | | Both CD and UC patients had more dental treatment, but it was more pronounced for CD | 47 |

**Table 1:** Oral bacteria and bowel diseases; important findings in literature review. IBD: Inflammatory bowel disease; CRC: Colorectal carcinoma.

### Fusobacterium nucleatum

*Fusobacterium nucleatum*, which is a Gram-negative fusiform bacterium, is known as one of the most important periodontopathogens [5]. It is commonly detected at the site of periodontitis. In animal experiments, *F. nucleatum* shows synergistic virulence in mixed infections. When *F. nucleatum* and *Porphyromonas gingivalis*, another important periodontopathogen, were simultaneously injected to mice, larger abscesses were formed compared to mice mono-injected with each bacterium [6]. *F. nucleatum* coaggregates with several kinds of bacteria [7], and it contributes to biofilm formation. *F. nucleatum* has an outer membrane protein RadD, which is associated with coaggregation [8]. Han et al. identified an adhesion FadA that is unique to oral Fusobacteria [9]. FadA may be associated with colonization in the periodontal environment and is considered to be associated with invasion [10] and systemic dissemination [9].

### F. nucleatum and IBD

Verna et al. reported that *F. nucleatum* septicemia in UC patients is associated with portal vein thrombosis [11]. *F. nucleatum* is a heterogeneous oral pathogen, and it also resides in the human gut mucosa. In the inflamed biopsy tissue from IBD patients, more invasive *F. nucleatum* strains are found [12]. Dharmani reported that highly invasive *F. nucleatum* strains stimulated MUC2 mucin and TNFα production [13]. McGuire et al. compared the genes between actively-invading and passively-invading Fusobacteria [14]: Active

invaders had much larger genomes and encoded FadA-related adhesins containing a MORN2 domain.

### F. nucleatum and colorectal carcinoma

Two reports on *F. nucleatum* and CRC were reported in 2012 by different authors in the same journal. Kostic reported the association of *F. nucleatum* with CRC [15], and Castellarin reported the positive association with lymph node metastasis [16]. Kostic et al. examined the effect of *F. nucleatum* on tumorigenesis by using a mouse model [17]. This bacterium increased tumor multiplicity and selectively recruited tumor-infiltrating myeloid cells. FadA is a unique adhesin of *F. nucleatum*, and the effect of the protein on carcinogenesis was examined. Rubinstein et al. demonstrated that *F. nucleatum* adhered to, invaded and induced oncogenic and inflammatory responses through FadA [18]. They also reported that FadA bound to E-cadherin and activated α-catenin signaling. *F. nucleatum* coaggregates with several microorganisms, which contributes to the progression of periodontitis [18].

In colorectal carcinoma, *F. nucleatum* is found to co-reside with other gram negative bacteria, such as *Campylobacter* [19]. Fukugaiti et al. reported that *F. nucleatum* and *Clostridium difficile* are detected in CRC patients [20].

*F. nucleatum* is also known to associate with colorectal adenomas [21]. Flangan et al. reported that *F. nucleatum* is associated with the progression from adenomas to CRC and suggested that detection of *F. nucleatum* may be useful as a diagnostic and prognostic determinant

in CRC patients [22]. As for prognosis, *F. nucleatum* is reported to be associated with the worse clinical outcome of CRC [23]. The mechanism of CRC progression by *F. nucleatum* is not fully understood, but Nosho et al. reported the effect of this bacterium on T cell immunity [24].

## Campylobacter concisus

*Campylobacter concisus* is a Gram-negative, highly fastidious, spiral, and microaerophilic bacterium [25]. *C. concisus* has been isolated from human gingiva and is linked with periodontal lesions, including gingivitis and periodontitis [26]. Aspartate aminotransferase (AST) is markedly elevated in gingival crevicular fluid from sites with severe gingival inflammation and progressive attachment loss, and C. concisus is often isolated from AST positive sites [27].

## Campylobacter concisus and IBD

Campylobacter species, such as *C. jejuni*, have been recognized as important pathogens of bowel diseases [28]. Zhang et al. demonstrated that a significantly higher presence of *C. concisus* and significantly higher levels of IgG antibodies specific to *C. concisus* are present in children with CD than in controls [29], and this bacterium is now recognized as an emerging pathogen of the human gastrointestinal tract. They also detected *C. concisus* from the saliva of healthy individuals and IBD patients [30]. They suggested that an individual may harbor multiple *C. concisus* strains in the oral cavity and that some oral *C. concisus* strains may colonize the lower gastrointestinal tract and be involved in IBD. Ismail et al. reported that patients with IBD were colonized with specific oral *C. concisus* strains, which underwent natural recombination and obtained invasiveness [31].

The virulence factors of *C. concisus* were further investigated, and the association of immunoreactive proteins [32] and zonula occludens toxin [33,34] with IBD was reported. Survival of *C. concisus* in host cells and tissues were also investigated. Autophagy usually contributes to the clearance of intracellular organisms, which is true for *C. concisus*. However, some strains of *C. concisus* were found to utilize autophagy for intracellular survival [35]. Ma et al. reported that increased gastric pH and reduced intestinal bile may be beneficial for *C. concisus* to colonize the intestine [36]. Recently, the genes of *C. concisus* are being investigated. Mahendran et al. reported the genetic relatedness and population structure of oral and enteric *C. concisus* species [37]. The relationship between oral and enteric strains of *C. concisus* will be investigated in the future.

## Streptococcus mutans

*S. mutans* is a Gram-positive oral bacterium. The bacterium metabolizes different kinds of carbohydrates, and creates an acidic environment, which is associated with tooth decay. *Streptococci* are also known as the cause of infectious endocarditis [38]. Recently, a highly-virulent strain of *S. mutans* was reported to be associated with hemorrhagic damage in the murine brain [39], and this bacterium attracts much attention in the field of general medicine.

## Streptococci and bowel diseases

Sundh et al. examined the microbial features of saliva and reported the association of dental caries and Crohn's disease [40,41]. Among the oral bacteria, *S. mutans* was found to be most associated with Crohn's disease [42]. Kojima et al investigated the effect of a highly-virulent

strain of *S. mutans* on dextran sodium sulfate-induced mouse colitis [43]. The specific strain of *S. mutans*, which produced a collagen-binding protein, aggravated colitis. They reported that this highly-virulent strain of *S. mutans* was also associated with human IBD. The relationship between dental caries and IBD was further investigated. Brito et al. reported that *S. mutans* was detected in Crohn's disease but not in ulcerative colitis [44]. It was confirmed that Crohn's disease patients had higher decayed –missing-filled surfaces (DMFs) scores and *S. mutans* counts compared to the control [45]. Johannsen et al. reported that both CD and UC patients had received more dental treatment, but this was more pronounced for CD [46].

## Conclusion

Oral bacteria are divided into two categories: cariogenic bacteria and periodontopathic bacteria [47]. Most of the periodontopathic bacteria are Gram-negative anaerobic and have many virulence factors associated with soft tissues and bone. It is not surprising that they affect not only the periodontal environment but also the intestine. Some of the periodontopathic bacteria, such as *F. nucleatum* and *C. concisus*, are associated with IBD and CRC. On the other hand, *S. mutans* is considered to be a cariogenic bacterium, and it is interesting that this bacterium also affects soft tissues of the gastric organ. The oral cavity and the intestine are not neighboring organs, but the bacteria of these organs seem to be closely associated. However, there is also the possibility that oral bacteria can only harbor bowel disease sites, and this point should be clarified. Further work by dental and medical doctors may reveal that dental and periodontal treatments decrease the incidence of IBD and CRC.

## Acknowledgement

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