From The Mouth to the Gut: The Oral Microbiome's Role in Promoting Gastrointestinal Disease

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Abstract

The traditional thoughts about oral microbial health have centered around the risks for dental caries, gingivitis and periodontal disease. There has been however ever-increasing data that oral health has significant implications for gastrointestinal health (GI) with strong evidence links the oral microbiome (which includes bacteria, fungi, virus, archaea), with an ever-increasing spectrum of metabolic, inflammatory and neoplastic diseases. The oral cavity hosts a diverse range of microorganisms that form a complex ecosystem known as the oral microbiome. While traditionally associated with pathologic roles in local conditions like dental caries and periodontal disease, there is growing evidence that disturbances in the oral microbiome can contribute to systemic inflammation and GI disease development, The risks for causality include direct effects of the dysbiotic microbiome, as well as inflammatory cytokine upregulation and metabolic byproducts, all of which can have both local and systemic effects. Altered mucosal integrity can facilitate translocation via systemic spread of these adverse factors directly to tissues and organs well beyond the oropharynx. Awareness of the role of the oral microbiome role maintaining oral health should be a new cornerstone of clinical care to potentially prevent, resolve or mitigate a wide array of systemic GI diseases, including inflammatory bowel disease, colorectal cancer, and metabolic associated inflammatory and fibrotic liver disease.

Keywords: Microbiome; Oral Health; GI Disease; Cancer; IBD; Liver Disease; Cirrhosis

Abbreviations

GI: Gastrointestinal; IBD: Inflammatory Bowel Disease; LPS: Llipopolysaccharide; TLR: Toll-Like Receptor; CVD: Cardiovascular Disease; ORs: Odds Ratios; CIs: Confidence Intervals.

Introduction

Oral health has significant implications for gastrointestinal (GI) health as emerging evidence increasingly links the oral microbiome to various GI diseases. The oral cavity hosts a diverse range of microorganisms that form a complex ecosystem known as the oral microbiome. Dysbiotic changes in this are traditionally associated with local conditions such as dental caries, gingivitis and periodontal disease. There is however, growing evidence that dysbiosis in the oral microbiome can contribute to systemic inflammation and GI disease development [1]. Understanding this connection is important because maintenance of oral health may help prevent, mitigate the onset, prevent, or slow the progression of serious GI conditions, including inflammatory bowel disease (IBD), colorectal cancer, and advanced liver disease.

The pathogenesis of many GI diseases may originate from microbial imbalances or dysbiosis within the oral

microbiome. When the natural balance of oral bacteria is disrupted—whether by poor oral hygiene, diet, or other factors—pathogenic species may flourish, leading to inflammation that can extend beyond the oral cavity. These inflammatory signals and potentially harmful microorganisms or the associated metabolites, can migrate throughout the GI tract, promoting both inflammatory and neoplastic GI diseases. The interconnectedness of oral and gut health highlights the need for a more holistic approach to disease prevention and management [2].

The oral microbiome is not only has not only an identified pathogenic role in GI disease but also, a role as a potentially valuable diagnostic tool. Recent studies suggest that analysing the composition of oral bacteria could help accelerate detection of GI diseases. For example, specific microbial patterns in the mouth may indicate an elevated risk for gastric cancer, serving as a non-invasive early detection strategy. This insight underscores the significance of oral health monitoring as part of comprehensive healthcare and preventive measures [2].

Key Players and General Pathogenesis

The overarching concept for how the oral microbiome plays a role in GI disease involves two main elements: 1) the major players or microbiota and 2) an anatomical understanding of the human body. By disrupting gut barrier function and perpetuating inflammation through the lipopolysaccharide (LPS) and toll-like receptor (TLR) pathway interactions, oral microbiota contributes to the onset and progression of various GI diseases.

The mechanism involved can be thought of as a possible "lock-and-key phenomenon". On one side, there is the LPS, a component of Gram-negative bacterial cell walls, such as those of *Fusobacterium nucleatum* and *Porphyromonas gingivalis*. When oral bacteria translocate to the gut via enteral routes, LPS interacts with TLR4 on gut epithelial cells. This triggers the NF-κB signalling pathway, leading to the release of pro-inflammatory cytokines and damaging the gut barrier integrity, contributing to "leaky gut" and systemic inflammation [3,4].

The TLRs serve as critical immune sensors for microbial components. Oral bacteria and their metabolites stimulate TLRs, particularly TLR4, which governs immune responses. Chronic activation of TLR pathways by dysbiosis caused by oral bacteria has been implicated in conditions such as inflammatory bowel disease (IBD) and colorectal cancer [4,5].

The close anatomical proximity earlier in the GI tract can affect the "downstream" counterparts causing additional impacts. The GI tract is lined by the mucous membrane, beginning at the mouth and ending at the anus owing to an anatomically continuous connection through the GI tract. Moreover, both sites are chemically connected, as saliva and digested food pass through the GI tract. Certain "periodontal pathogens", like *F. nucleatum*, can establish themselves in the gut and exacerbate microbial imbalances, promoting disease progression. For example, approximately 40% of the CRC patients detected identical F. _nucleatum_ strains in both tumor tissue and saliva [6]. They modulate the gut immune environment and favor the growth of pathogenic bacteria, further destabilizing the intestinal ecosystem [7,8]. There have been several key players involved in the oral microbiome that have "downstream" effects into the rest of the GI tract.

The "normal", healthy oral microbiome is composed of genus level organisms: *Streptococcus, Gemella, Veillonella, Haemophilus, Neisseria, Porphyromonas, Fusobacterium, Actinomyces, and Prevotella* which generally coexist in a symbiotic relationship with the host [9]. Specifically, oral cavity has a high abundance of *Firmicutes*. Studies have shown a general increase in *Veillonella, Prevotella, Haemophilus, Neisseria, Campylobacter, Porphyromonas, and Fusobacterium species* in those with dysbiosis, most of which are also associated with periodontal disease conditions [10]. Specific subspecies include A*ggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola, Prevotella intermedia, Campylobacter rectus, Peptostreptococcus anaerobius, and Eikenella corrodens* have also been discussed [10]. While further pathways and full mechanistic principles are still being researched the species of *Fusobacterium nucleatum, Klebsiella species, Porphyromonas gingivalis, Haemophilis parainfluenza, Streptococcus mutans, Aggregatibacter actinomycetemcomitans, Prevotella intermedia, Treopnema dentricola, and Tannerella forsythia* and their general characteristics are summarized in the provided Table 1.

Microbe	Mechanism of Action	Associations
Fusobacterium nucleatum [11,12]	FadH is a proposed virulence factor that affects adherence to intestinal epithelial cells and promoting cell invasion through E-cadherin interaction.	Frequently associated with colorectal cancer, it promotes tumor proliferation, inflammation, and chemoresistance

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Klebsiella spp [13,14]	Adheres by employing adhesions and pili to bind epithelial cells. These bacteria produce a protective capsule and beta-lactamase enzymes, aiding in immune evasion and antibiotic resistance Caspase-11-mediated IL-18 release is a mechanism implicated in colitis triggered by Klebsiella specie	Known to migrate from oral biofilms to the GI tract, causing systemic infections like sepsis and contributing to inflammatory conditions
Porphyromonas gingivalis [13,15]	P. gingivalis can disseminate from the oral cavity to the GI tract through swallowing or bloodstream migration. Once in the gut, it interacts with Peyer's patches and alters immune responses, promoting an imbalance in T-helper 17 (Th17) and regulatory T cells (Treg). This can exacerbate conditions like colitis Disruption of tight junction proteins in the gut, inducing endotoxemia and triggers an inflammatory response in extraoral-organs.	Associated with periodontitis and systemic inflammation; implicated in esophageal and colorectal cancers
Haemophilus parainfluenza [13]	Amassed oral pathonionts. Adheres to mucosal surfaces using pili and adhesins and secretes factors that impair host defenses	Its role in chronic inflammation may influence GI tract conditions
Streptococcus mutans [13,16]	S. mutans expresses surface proteins like PAc, which facilitate adhesion to host tissues and interaction with other microbiota. This may allow transient colonization in the GI tract and interactions with epithelial cells The bacterium produces metabolites, such as lactate and kynurenic acid, which may impact inflammation and microbial composition, particularly in pathological conditions such as tumors or inflammatory diseases	Excessive acid production might dysregulate oral microbiome balance, impacting the gut microbiota
Aggregatibacter actinomycetemcomitans [17,18]	Secretes leukotoxin and cytolethal distending toxin, damaging host cells and impairing immune function	Linked to periodontitis, which can lead to systemic inflammation affecting the GI tract

Table 1: Important microbiota involved in the oral-gut axis.

Together, these mechanisms lay the pathway for oral bacteria-driven inflammation, initiated in periodontal disease and can systematically amplify inflammatory cascades, creating an environment conducive to GI tract diseases [19,20].

Oral-Microbiota and Liver Disease

There is a strong association between liver disease and inflammation arising from impairments in the oral-gut-liver axis. Periodontal disease, also known as gum disease, is a bacterial infection that affects the gums and the tissues that support the teeth. Periodontal diseases have been a major focus of inflammation as they are among the most common type of disease in humans worldwide and can remain overlooked and undertreated [21]. These oral conditions include dental caries, gingivitis, pulp abscesses, and periodontitis. The latter is often used as a model for studying inflammatory oral diseases and is characterized by tissue destruction and alveolar bone resorption [22-

24]. Hajishengallis clearly states that periodontitis is *better understood* if viewed as a "disruption of host-microbe homeostasis" [24]. The altered dysbiosis and causal adverse inflammation, suggests a viable route of treatment that deserves further exploration.

Oral dysbiosis and the related inflammation is often low-grade, but constant and therefore detrimental when not properly treated [25,26]. Recent studies have shown that destruction of gingival tissue that takes place in periodontitis by oral microbial dysbiosis initiates an immune response that releases systemic inflammatory markers such as IL-6, IL-1B, fibrinogen, LPS and C-reactive protein [24,25,27,28]. This chronic low-grade inflammation evolves into a moderate systemic response that often goes unchecked [26]. When concurrent inflammatory processes are present, it is understood that an additive effect occurs that exacerbates underlying conditions such as cardiovascular disease (CVD), type 2 diabetes, non-alcoholic fatty liver disease (NAFLD; now referred to as metabolic dysfunction-associated steatotic

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liver disease (MASLD), and some cancers [25,29-31].

A few mechanisms have been identified to explain how oral dysbiosis eventually leads to liver injury and systemic changes. The induction of adverse inflammatory changes allows pathogenic bacteria and/or their metabolites/cytokines to translocate to the liver via the portal vein. Additionally, oral bacteria and metabolites are swallowed with transits leading to intestinal microbiome dysbiosis. Gut dysbiosis then has various effects including overgrowth of other pathogenic bacteria and changes in microbial composition, changes in pH, and decreased integrity of the intestinal barrier, ultimately allowing pathogenic bacteria and their metabolites, as well as other pro-inflammatory molecules passage to the liver via the portal vein [2,23,30].

Pro-inflammatory mediators interact with hepatic receptors and propagate the cascade of inflammation and fibro genesis with progression to cirrhosis and cancer [28]. Interactions of LPS with TLR4, which is present on Kupffer cells (macrophages in the liver that remove bacteria, viruses, and other foreign materials from the blood), initiates a cascading production of pro-inflammatory molecules. Kupffer cells also will activate hepatic stellate cells (HSCs) and further transdifferentiate into myofibroblasts, which will contribute to increased fibrosis and further damage [28,32]. In this way, the oral microbiome is posited to be a viable target for intervention as it clearly, both directly and indirectly, leads to changes which exacerbate progression of chronic liver disease. This relationship between oral microbiome and liver disease however, does not appear unidirectional. Results from the case-control study by Costa et al. identified a 2-fold increase in the prevalence of periodontitis in patients with liver cirrhosis compared with controls. They suggest that the recognizable risk association between cirrhosis and periodontitis needs further investigation [33]. The inflammatory environment associated with hepatic cirrhosis may be bidirectional, impacting the oral microbiome [34].

Porphyromonas gingivalis is one resident pathogenic bacteria of the oropharyngeal cavity that has been shown to provoke cavities and contribute to periodontal disease. Researchers have also identified the species in the brain, liver, kidney, and GI tract [29,30,35]. One study performed in a rabbit model evaluated periodontal health and nonalcoholic fatty liver disease (NAFLD). Following injection with LPS, one of the pro-inflammatory products of P*. gingivalis*, inflammation was accelerated as well as increased levels of gamma-glutamyl transferase, a surrogate marker for hepatic inflammatory injury [31]. Additionally, compared to controls, greater fibrosis and related progression were also seen. They also indicated that periodontal disease is shown to cause dyslipidemia, which is a risk factor for NAFLD/

MAFLD [31]. Another study in rats analyzed the injection of P *gingivalis*, and demonstrated associated hepatic changes of MAFLD [36]. It is clear that there is complex interplay between the presence of *P. gingivalis* in periodontal disease and its influence on liver disease via multiple mechanisms, ultimately resulting from increased dysbiosis and promoting an inflammatory state.

Notably, there is a high prevalence of periodontal disease among patients with cirrhosis [25]. A study by Bajaj et al, evaluated patients with cirrhosis and minimal hepatic encephalopathy (MSE) [25]. The intervention of referral to a dentist to address oral hygiene and administration of periodontal care resulted in marked improvement in cognitive and quality-of-life scales. Additionally, improvement in the level of endotoxemia (condition where there's too much lipopolysaccharide (LPS) from bacterial cell walls in the blood) following periodontal treatment was evident, versus significant increases in serum endotoxin in the untreated group [25]. Shawcross also explains that when treating patients with cirrhosis, clearance of ammonia does not seem to be the only important target and that there must be other important physiological factors involved [37]. Focusing on causes of systemic inflammation, increased endotoxemia, translocation of bacteria, combined with previous data suggesting that there is invasion of the gut by oral bacteria in patients with cirrhosis, leads to the promising future of novel treatment approaches directed towards the oral biome [25,35,37].

Oral Microbiota and Inflammatory Bowel Disease

The relationship between inflammatory bowel disease (IBD) and poor oral health, particularly periodontitis, is well-documented. Numerous studies indicate that compared to healthy individuals, patients with IBD, exhibit a higher prevalence of periodontal disease, caries, and other oral health problems. The connection likely involves shared inflammatory pathways and the movement of pathogenetic oral bacteria to the gut, where they may exacerbate inflammation and disease severity [38].

Several studies have highlighted the significant role of the "oral-gut axis" in IBD [38-40]. These studies suggest that poor oral health, particularly periodontal disease, can lead to increased intestinal permeability. This abnormal permeability allows for the translocation of oral bacteria and their products, such as LPSs, into the bloodstream and intestinal tissue, whereby initiating or worsening an inflammatory response [41]. *Haemophilus* and *Veillonella* which are known to be oral commensal microbes have been found in the gut mucosa of patients with inflammatory bowel disease [42].

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A large systematic review and meta-analysis showed that patients with active periodontitis are more likely to experience intestinal inflammation and worsened IBD symptoms [43]. Periodontitis was associated with elevated levels of pro-inflammatory cytokines in both the oral cavity and the gut [44]. Notably, immunological biomarkers in the saliva, showed increase in cytokines (like IL-1, IL-6, IL-12, IL-17 and TNF-α), immunoglobulin A, and a lower lysozyme level [45]. A significant correlation was shown between lysozyme and IL-1β levels and the relative abundance of *Streptococcus, Prevotella, Haemophilus* and *Veillonella*. These findings indicate that controlling oral inflammation may be a viable therapeutic target for reducing the overall inflammatory burden in patients with IBD [46].

Further supporting this connection, a 2023 systematic review found that IBD patients had a significantly higher incidence of oral health issues compared to controls, suggesting a bidirectional relationship where gut inflammation could also worsen oral health, thereby creating a vicious cycle of inflammation [47]. A Swedish study showed analysis-based questionnaire where answers from 786 patients showed high prevalence of severe periodontitis (38.5%) was reported, and about 19% of the population had less than 20 remaining teeth and 6.5% a poor oral health-related quality of life [48].

Variations in the composition of the oral microbiota between healthy pediatric patients and IBD patients, suggest that oral microbiota analysis could be used as an adjunct diagnostic tool for IBD [49]. Accordingly, the oral-gut axis represents a critical link in understanding the pathophysiology of IBD. Addressing and promoting oral health may offer novel strategies for managing intestinal inflammation.

Oral Microbiota and Colorectal Cancer

Colorectal cancer (CRC) is the 3rd most common cancer in both men and women within the U.S. It is well established that IBD risk factor for development and progression of CRC and CRC patients show the distinct patterns of microbial compositions in both fecal and intestinal mucosal samples compared to healthy individuals [50].

Oral bacteria such as *Parvimonas ssp, Peptostreptococcus ssp,* and *Fusobacterium ssp*, specifically *Fusobacterium nucleatum (Fn)* have all been detected with patients that have CRC [51,52]. These pathogens can translocate to the gut through swallowed saliva or via bloodstream migration facilitated by periodontal inflammation, with significant adverse effects. *F. nucleatum* adheres to CRC cells via FadA adhesin, promoting tumor proliferation and evading immune surveillance [52]. Furthermore, oral pathogens *Treponema*

denticola and *Prevotella intermedia* were associated with an increased risk of CRC, with odds ratios (ORs) and 95% confidence intervals (CIs) of 1.76 (1.19–2.60) and 1.55 (1.08–2.22), respectively, for the individuals carrying these bacteria compared to non-carriers [53].

From a systemic perspective, gingival inflammation promotes blood flow, which facilitates the translocation of upregulated cytokines and chemokines, as well as of the bacteria and/or metabolic byproducts. Oral dysbiosis often leads to periodontal disease, a state characterized by elevated pro-inflammatory cytokines. These cytokines can disseminate systemically, creating a microenvironment conducive to tumorigenesis. In CRC, inflammatory mediators such as interleukin-6 and tumor necrosis factor-alpha foster cancer cell survival and angiogenesis [54]. Oral bacteria can also modulate immune responses, affecting gut homeostasis. Pathogens like *Prevotella ssp* and *Porphyromonas gingivalis* impair T-cell function and induce immunosuppressive environments, facilitating cancer progression [8]. In C56BL/6 mice models, oral administration of *P. gingivalis* attenuated the intestinal barrier function via downregulating tight junction proteins, leading to significant alteration of gut microbiome and increasing *Clostridiaceae ssp* [55].

H. pylori, well recognized as a gastric pathogen in gastric cancer, has however also been linked as well to the oral microbiome [51]. Although the infection is in the stomach, it also can colonize the oral cavity, serving as a reservoir for gastric reinfection. Oral dysbiosis may facilitate *H. pylori* translocation to the stomach, exacerbating gastritis and increasing cancer risk [51]. The bacterium induces chronic inflammation and DNA damage in gastric epithelial cells, key steps in carcinogenesis [51]. Oral cavity environment also appears to impact treatment response. A randomized controlled trial assessed mitigation of *H pylori* using a triple-therapy approach over a 10-day course, rather than the standard 14-day course. This was combined with periodontal therapy using scaling, root planning/scaling, and oral hygiene instructions, which was associated with a 12% increase in *H pylori* eradication [56].

Advising Our Patients

Clinical gastroenterologists can use the emerging data on the oral-gut microbiome connection to potentially enhance patient outcomes. By understanding the role of oral microbial dysbiosis and the local and systemic effects on GI diseases will be translational from our standard approaches. Moreover, gastroenterologists can incorporate oral health questions into the diagnostic process for GI diseases. restore gut microbial balance in patients whose conditions may be linked to oral dysbiosis [57].

Future Directions

Future research should aim to identify specific oral microbial signatures associated with GI diseases, which could lead to new diagnostic tools or personalized treatment strategies. Integrating oral and gut microbiome profiling in clinical practice may offer a more comprehensive approach to managing gastrointestinal diseases. Promoting preventive oral health measures and developing therapeutics targeting the oral-gut axis could significantly improve patient outcomes and overall gut health.

When considering systemic disease and preventing its progression, maybe we should take a lead from our dental colleagues who have historically and repeatedly emphasized prioritization of oral health. The relevance of oral health in the pathogenesis of GI diseases emphasizes the need for further exploration of the mechanisms linking these distinct, *yet connected*, systems.

Conflict of Interest

DAJ clinical investigator for IsoThrive.

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