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REVIEW ARTICLE

Gum-gut axis: The potential role of salivary biomarkers in the diagnosis and monitoring progress of inflammatory bowel diseases

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Abstract The gut mucosa is an extension of the oral mucosa, and both are directly linked. There is emerging evidence that pathogenic oral microbiome contributes greatly to the risk of developing Inflammatory Bowel Disease (IBD). Dysbiosis of the oral microbiota can interfere with the host immune system's ability to respond normally, thereby increasing the development of periodontitis which raises the risk of IBD, cancer, rheumatoid arthritis, cardiovascular disease, and other complex disease processes. Salivary biomarkers are possibly important for determining the incidence, severity, and remission of IBD. Nevertheless, clinical translation of biomarker knowledge from lab to clinical practice needs further studies that identify biomarkers related to the transitional phase between healthy and unhealthy. In this review, the bidirectional pathway between the gut and the oral cavity was investigated and several aspects were discussed.

Contents

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1. Introduction

Human gut microbiota (GM) comprises intricate and dynamic communities of microorganisms that are important for health and survival. According to reports, the GM is stable and diversified under physiologically normal settings, with Bacteroidetes and Firmicutes serving as the two main dominating groups. They are the main controllers of body homeostasis, including both gut and extra-gut effects by influencing many physiological functions such as metabolism, inflammation, and hematopoiesis. Any change to the GM community structure not only leads to gut disorders but also influences other organs and may result in concurrent disease. Recently, the GM has been defined as a 'vital organ' in respect to its involvement with other organs; thus, creating a connection of bi- or multidirectional cross talk axis between different body organs through immune, humoral, neural, endocrine, and metabolic pathways (Forkosh and Ilan, 2019; Nicholson et al., 2012). Multiple signaling pathways and direct chemical interactions allow for this crosstalk between the host and the microorganisms (Wells et al., 2011). A multidirectional communication system between the host cellular pathways and numerous microbial species is called the host-microbe metabolic axis (El Aidy et al., 2015). Changes in GM have been associated with numerous disease conditions in humans; but the exact interaction mechanism between the gut and other organs is not yet completely understood.

In this review, the bidirectional pathway between the gut and the oral cavity was explored and various aspects were discussed. Particular emphasis was placed on the connection between periodontal disease and inflammatory bowel disorders (IBD). It covered how periodontal bacteria and inflammatory mediators affect the start and progression of IBD. The fact that the oral cavity serves as the access point to the gut and is also in contact with the nasal cavity and facial skin (Braga and Squier, 1980) makes it well-connected to these tissues especially to the gut where oral microbiota could easily translocate to the gut. This translocation could result in inflammatory disease of the oral cavity, under certain conditions, modifying gut microbiota or dysbiosis, which can then impact the course of IBD (Fig. 1 summarizes the effect of oral cavity microbiome on gut microbiota).

1.1. Oral microbiome in health and diseases

The microbiota of the oral cavity and the gut have distinctive bacterial diversity (Donaldson et al., 2016; Lloyd-Price et al., 2017; Welch et al., 2019). Each of these anatomical regions contains microhabitats with diverse bacterial communities that might not be effectively represented by standard sample techniques (Donaldson et al., 2016; Welch et al., 2019). Both gut microbiota and oral microbiota can potentially be either beneficial or pathogenic and are balanced by the normal host defense mechanisms (Lamont and Hajishengallis, 2015). Alterations in oral or gut microbiota could result in dysbiosis due to the expansion of harmful microorganisms.

The oral cavity microbiome is a complex environment with more than 700 bacterial species as well as various viruses and fungi. This complex ecosystem colonizes teeth surfaces and all mucosal surfaces. Oral microbiome on hard surfaces usually exists as a biofilm, which is defined as arranged residents of microorganisms that are attached to a surface and trapped in an extracellular polymeric matrix (Chattopadhyay et al., 2019). Basically, they are layers of goop-like material made of exopolysaccharides (EPS), within which bacteria tend to have increased resistance to antibiotics and innate host defense (Avila et al., 2009; Chung and Khanum, 2017). On the tooth surface, this biofilm is called dental plaque (Hojo et al., 2009; Perez-Chaparro et al., 2014). Comparable to the gut microbiota, oral microbiota can be either anaerobic or aerobic with certain dominating species, for example *Fusobacterium*, *Veillonella*, and *Streptococci*. While most of the gut microbiota are extracellular, certain oral pathogenic bacteria, such as *Porphyromonas gingivalis* (*P. gingivalis*), can be intracellular and more pathogenic. Oral pathogens can be useful as an early diagnostic and prognostic biomarker, or be modified for beneficial functions (Avila et al., 2009; Chattopadhyay et al., 2019). It has been demonstrated that the salivary microbiota, which includes bacteria shed from the oral cavity, is unique, temporally stable, and significantly influenced by diet and lifestyle. It is associated with local bacterial changes of the supragingival and subgingival microbiota. In addition, salivary microbiota has been associated with certain reported characteristics of dental caries and periodontitis.

Bacteria play an essential role in periodontal disease which is manifested by a progressive destruction of tooth supporting structures. Various commensal bacteria colonize the oral cavity including the tooth structure. The crevice between the tooth structure and the gingiva, the so-called gingival sulcus, is somewhat unique where bacteria are secluded from continuous exposure to the oral environment in a subgingival biofilm commonly referred to as dental plaque (Curtis et al., 2020). In periodontitis, alterations in the oral cavity microbiota may impact systemic disease through the blood circulation (Georges et al., 2022). Subgingival pathogenic bacteria and its components can reach the blood circulation through the ulcerous pocket, which leads to low-grade inflammation and influences gut microbiota. Additionally, swallowing the periodontitis-associated salivary microbiota could be another pathway linking periodontitis with many systemic diseases. It is believed that swallowed pathogenic oral microbes may disrupt the balance of the gut microbiota leading to dysbiosis which mediates the effect of periodontitis on systemic diseases (Bao et al., 2022; Donoff et al., 2014; Elad et al., 2019).

Usually, Gram-negative bacterial species, such as *P. gingivalis*, *Tannerella forsythia*, *Treponema denticola* and *Aggregatibacter actinomycetemcomitans*, are considered major offenders of periodontal damage. *P. gingivalis*, in particular, which is considered a main pathogen in periodontitis, can profoundly

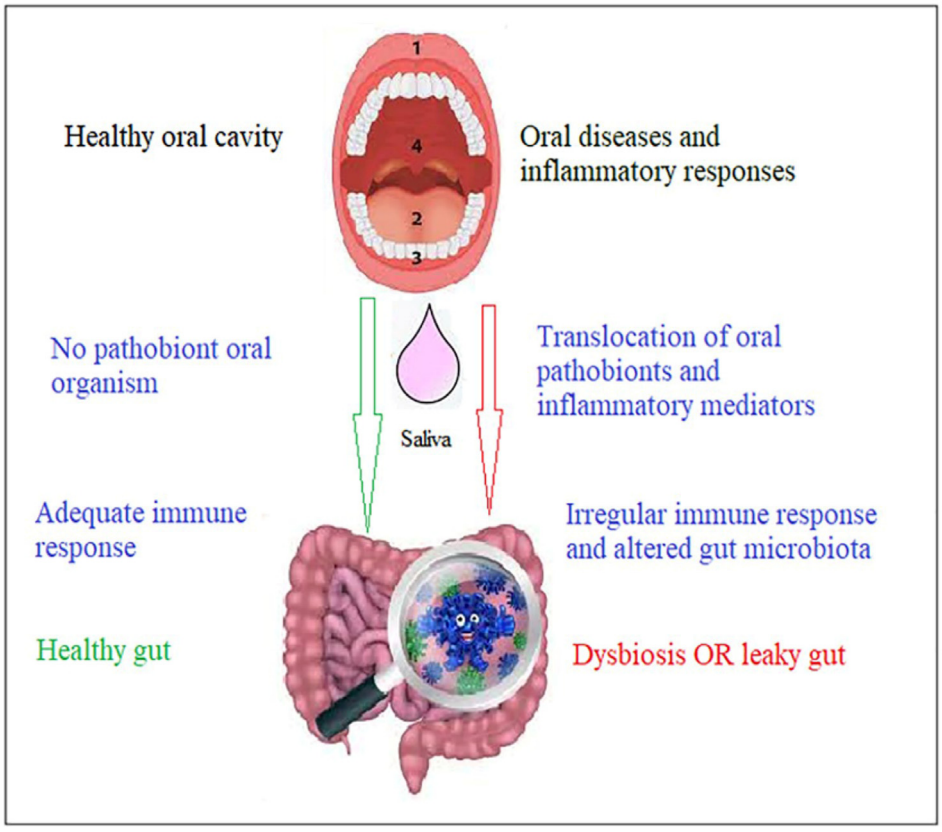

Fig. 1 The effect of oral cavity microbiome on gut microbiota.

affect the oral environment, even if it constitutes an insignificant portion of the subgingival microbiota. Also, Gram-positive bacteria, for instance *Filifactor alocis*, *Parvimonas micra* and *Eubacterium nodatum*, play a role in periodontal pathogenesis (Könönen and Kumar, 2015). Within this biofilm, bacteria communicate with each other through a phenomenon known as "quorum sensing" that affect gene expression involved in bacterial survival, virulence, and biofilm formation (Agarwal et al., 2014). It is believed that a shift in the abundance of certain bacterial species within the biofilm, leads to dysbiosis, which initiates the inflammatory destruction of tissues or periodontitis (Curtis et al., 2020). In general, commensal subgingival biofilm bacteria are dominated by gram-positive cocci and rods (Listgarten, 1976), while in microbial dysbiosis gram negative spirochetes, rods and filamentous bacteria increase in abundance (Theilade et al., 1966). *P. gingivalis*, can threaten the host immune response, disrupting the host-microbe homeostasis in the oral cavity and stimulating a dysbiotic condition, even when present at low amounts (Hajishengallis and Lamont, 2014). Moreover, *P. gingivalis* uses the virulence factor gingipain, a cysteine protease enzyme to catabolize proteins, such as hemin acquired from hemoglobin. Together, these findings suggest that IBD, one of the more well-known inflammatory illnesses, has the oral cavity microbiota playing a significant role in its etiology. (Brennan and Garrett, 2019; Lim et al., 2020).

Recently, Radaic and Kapila (Radaic and Kapila, 2021) introduced the term "Oralome" to describe each and every interaction that takes place between the host and the oral microbiota. For instance, it is well known that the oral microbiota is crucial for the synchronization and protection of commensal oral microbiota as well as for the establishment of an appropriate oral immune response and protection of the host against pathogenic microorganisms (Gao et al., 2018; Idris et al., 2017). However, the host immune response must maintain a balance between pathogen-killing inflammation and guarding against unfavorable immunological reactions against the host's own tissue and commensal bacteria. In fact, inducing a violent immune response against microbes that pose no risk or harm would be pointless, metabolically inefficient, and might be damaging to host tissues (Sultan et al., 2018). In exchange, some oral commensals can act as a pathogen killer and have coordinated roles in initiating the antagonistic action against a pathogen to prevent the colonization and integration of pathogens, a phenomenon referred to as colonization resistance (He et al., 2014). *Streptococcus salivarius*, for example, combats the primary etiological agent of pharyngitis, *Streptococcus pyogenes*, blocking its colonization and proliferation in the pharyngeal mucosa, hence preventing pharyngitis (Cosseau et al., 2008; Devine et al., 2015; Guglielmetti et al., 2010). This reciprocal defense is one sign that the host immune system has developed to sustain and tolerate some helpful microorganisms (Baker and Edlund, 2019).

1.2. The gum-gut axis

The connections between oral disease and prevalent chronic diseases are generating more and more interest. (Byrd and

Gulati, 2021) hypothesized that gum-gut axis presents a bidirectional pathway, playing a crucial part in chronic inflammation which is believed to be involved in the etiological mechanism of non-communicable chronic diseases such as diabetes mellitus, cardiovascular diseases, pulmonary diseases, neurological disorders, and cancer.

The average person produces and swallows ~1.5 L of saliva per day, holding a massive number of oral inhabitant bacteria (Humphrey and Williamson, 2001; Nasidze et al., 2009). Interestingly, ingested oral bacteria poorly inhabit the healthy intestine (Seedorf et al., 2014); however, patients with diverse illness conditions, including IBD, have been found to have higher numbers of oral-originated bacteria in their gut microbiota (Olsen and Yamazaki, 2019).

Bartlett et al. (2020) studied the role of gut-oral cavity intermucosal axis in patients with IBD. In an intriguing experiment, dextran sodium sulfate (DSS) was used to produce gut dysbiosis or leaky gut in specific-pathogen-free (SPF)-ligature mice imitating a periodontitis phenotype and normal healthy controls mice (HC). Prior to receiving DSS, periodontitis SPF mice displayed oral dysbiosis compared to controls, an elevated T helper 1 (Th1) response, and significantly increased immunological infiltration of T helper 17 (Th17), B cells, and T cells. In comparison to control mice, periodontitis SPF-ligature DSS animals produced greater IL-17A and interferon gamma (IFN-γ) after DSS therapy and had more inflammation in their gut mucosa (Kitamoto et al., 2020). When SPF-ligature DSS mice's oral and gut microbiota were compared, it was observed that particular oral-originating bacteria were present in both. Among these, *Klebsiella spp*. and *Enterobacter spp*. from the bacterial family *Enterobacteriaceae* were primarily identified in the oral cavity of periodontitis rodent models as well as in overgrowth in the gut while they were not discovered in controls (Bartlett et al., 2020; Kitamoto et al., 2020). DSS-treated mice were more likely to have oral-derived pathobiont migration to the gut, supporting the "oral-gut axis" hypothesis. This was demonstrated by increased inflammation and infiltration of gut immune cells brought on by periodontitis ligatures. According to Atarashi et al. (2017), bacterial species that make up a small fraction of the oral microbiota can expand and occupy the gut, and a subset of these oral species can cause the buildup of intestinal Th1 inflammatory cells.

Recent research has suggested a paradigm that connects oral microbiota to IBD, where periodontitis has been demonstrated to cause an increase in specific oral pathobionts such *Klebsiella* species (Kitamoto et al., 2020). This increase in pathobionts contribute to gut inflammation through a couple of mechanisms, first by direct translocation of bacteria to the gut where they induce Th 1 cells accumulation (Atarashi et al., 2017) and inflammasome mediated IL1 secretion (Kitamoto et al., 2020; Seo et al., 2015). The second mechanism is through primed of Th17 in the oral mucosa that translocate, via lymphatics, to the gut mucosa and gets activated by orally derived *Klebsiella* (Kitamoto et al., 2020).

1.3. Saliva as an emerging diagnostic tool to study gum-gut axis

Currently, common practice for clinical diagnosis of IBD involves blood, stool, endoscopic imaging and histological examination (Maaser et al., 2019). A biological marker (biomarker), according to the National Institutes of Health Biomarkers Definitions Working Group, is defined as "A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (Biomarkers Definitions Working Group, NIH, 2001). They have been researched in relation to diagnosing IBD, assessing prognosis, tracking severity and progression, and distinguishing between its subtypes Ulcerative colitis (UC) and Crohn's disease (CD) (Chen et al., 2020; Nijakowski et al., 2021). IBD biomarkers are typically based on blood or stools (Said et al., 2014). Fecal calprotectin (FC) and fecal lactoferrin (FL) are utilized as biomarkers during the therapy of IBD in clinical practice, as well as serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) (Di Ruscio et al., 2017; Soubières and Poullis, 2016). Despite promising results, there is no current biomarker that is sensitive and specific enough to preclude the need to perform invasive endoscopy procedures (Soubières and Poullis, 2016). The convenience of saliva collection and handling has triggered research directed towards identifying useful IBD biomarkers.

In general, salivary IBD biomarkers can be grouped into: oxidative status markers, inflammatory cytokines, microRNAs and other biomarkers (Nijakowski and Surdacka, 2020). Interesting findings have been reported with regards to several salivary biomarkers including IL-1β, IL-6, IL-8, TNFα (Bartlett et al., 2020; Nijakowski and Surdacka, 2020; Said et al., 2014), antioxidants (e.g., glutathione), ferric reducing antioxidant power (FRAP), increased lipid peroxidation and its byproducts such as malondialdehyde (MDA) (Szczeklik et al., 2018), MicroRNAs (miRNAs) (e.g., miR-101, miR-21, miR-31, miR-142-3p, miR-142-5p) (Schaefer et al., 2015), Salivary exosomal proteasome subunit alpha type-7 (PSMA7) (Zheng et al., 2017), α-amylase (Xu et al., 2018), calprotectin (also named migration inhibitory factor-related protein 8/14 or S100A8/A9) (Majster et al., 2019), myeloperoxidase, catalase, and TNF-R1 (Nijakowski et al., 2021).

The pattern of salivary IBD biomarkers expression is not simple and straightforward but rather complex. In fact, it is affected by whether the saliva is stimulated or unstimulated, they could increase or decrease in relation to IBD activity and have different patterns during active versus remission. Furthermore, differential expression of biomarkers could be encountered in UC compared to CD. For example, calprotectin was elevated 4.0 folds in stimulated saliva sample of IBD patients compared to controls with statistical significance, while unstimulated saliva was slightly higher but not statistically significant (Majster et al., 2019). Some biomarkers are elevated in patients with IBD such as IL-1β (Nijakowski and Surdacka, 2020), α-amylase (Xu et al., 2018), and MDA (Szczeklik et al., 2018) while others are reduced such as glutathione and FRAP (Szczeklik et al., 2018). Some biomarkers showed different levels during active disease compared to remission, such as the levels of PSMA7, which were considerably higher in IBD patients compared to healthy controls; while its levels were much reduced in IBD patients in remission compared to active cases (Zheng et al., 2017). Differential expression of biomarkers between CD and UC has been shown in the levels of TNF-R1 and catalase activity which were significantly reduced in UC compared to CD patients (Nijakowski et al., 2021).

The expression of salivary IBD biomarkers and the microbiota's composition were also found to be correlated. Increased concentrations of the inflammatory cytokines IL-6, IL-8, TNF-, and IL-1 as well as secretory IgA were shown to be correlated with the relative abundance of the bacterial genera *Prevotella*, *Haemophilus*, *Streptococcus*, and *Veillonella* that are linked to IBD disease (Said et al., 2014). Such findings could aid in the future development of more non-invasive IBD diagnostic techniques.

This variability in IBD salivary biomarkers expression merit further investigation to elucidate association of various biomarkers with different IBD subtypes, disease activity, and remission. Such extensive research should culminate in generating a model with multiple salivary indicators that can offer a precise representation regarding IBD status. In addition, salivary biomarkers associated with newly reported role of oral microorganisms and inflammatory cells in aggravating existing IBD (Atarashi et al., 2017; Kitamoto et al., 2020) could be carefully investigated, particularly through identifying culprit pathobionts at the strain level. These biomarkers could add value to the above suggested panel of biomarkers as a potential severity level indicators in the model.

1.4. Gut and oral microbiome-based diagnostics and biomarkers in IBD patients

Patients with IBD have been found to have significant changes in their gut and oral cavity bacterial populations. Chronic inflammatory responses have been linked to microbial dysbiosis in the gut of IBD patients, which may be made worse by a decline in bacteria known to produce short chain fatty acids (SCFAs) and an increase in *Enterobacteriaceae* (Mottawea et al., 2016; Olbjørn et al., 2019; Said et al., 2014). Comprehensive evidence on this dysbiosis has been documented by metagenomic profiling microbiome research, which have found higher abundance of common oral bacteria in the gut microbiomes of IBD patients (e.g., *Veillonella, Haemophilus, Eikenella* spp.) whereas many SCFAs producers were reduced (Olbjørn et al., 2019; Shaw et al., 2016). Additionally, Mottawea et al. (2016) have found that IBD patients had higher levels of H_2S producers. These findings support the possibility of using specific bacterial species and their metabolites (e.g LPS, SCFAs, and H_2S) as microbiome-based diagnostic biomarkers in IBD patient. Although salivary microbial alterations have not been studied extensively, available evidence suggests an association between certain aberrations in salivary microorganisms and IBD especially in terms of relative microbial abundance. In a recent study, Abdelbary et al. (2022) were able to show that IBD patients' saliva contained more *Veillonella* and *Prevotella* on a relative basis than did those of healthy people. Conversely, IBD-free individuals had higher levels of salivary *Neisseria*, *Streptococcus*, *Haemophilus*, and *Fusobacterium* (Abdelbary et al., 2022). *Prevotella* was more prevalent, and *Neisseria* was less prevalent in active CD compared to remission phase and healthy controls (Zhang et al., 2020). Additionally, Said et al. (2014) found that IBD patients had significantly higher levels of salivary *Prevotella* and *Veillonella* than healthy controls, but lower levels of salivary *Streptococcus* and *Haemophilus* were seen in IBD. Furthermore, as compared to healthy controls, IBD patients had higher levels of the salivary bacteria *Saccharibacteria* (TM7), *Absconditabacteria* (SR1), *Leptotrichia*, *Atopbium*, and *Bulleidia*, whereas their levels of the bacteria *Streptococcus* and *Rothia* were much lower. (Qi et al., 2021). Interestingly, differences in relative salivary microorganisms' abundance have been noticed between CD and UC where *Streptococcaceae* and *Enterobacteriaceae* are elevated in UC while *Veillonellaceae* (*Veillonella*) is raised in CD. On the other hand, it has been noted that *Neisseria* and *Haemophilus* are becoming less prevalent in CD, as well as *Lachnospiraceae* and *Prevotella* in UC (Xun et al., 2018). Recent evidence confirms the idea that relative abundance rather than absence/presence of certain oral microorganisms is a promising approach to use to diagnose IBD and furthermore to differentiate between its subtypes CD and UC, however, additional investigations are crucial to determine precisely how to use oral microorganisms for the diagnosis of IBD. In addition, IBD as a "multimicrobial" disease has no single causative microorganism; more severe disease is associated with decreased gut microbial diversity and growth or decline in certain taxa. Therefore, to improve our understanding of this condition, future research should cover the entire community (Aldars-García et al., 2021).

2. Conclusion

Despite the clear interaction between gum and gut through the gum-gut axis, additional research work is needed in the area of pathogenesis of oral and gut diseases in order to improve our understanding of how they influence one another through a bidirectional pathway. It is evident that treatment of periodontitis and gingivitis could be of great help in improving oral and gut dysbiosis, and related chronic diseases.

While oral manifestations are not commonly the primary target for therapy in many chronic diseases like IBD, it may provide an easily accessible site to aid in the early diagnosis and intervention. The search for a group of salivary biomarkers for IBD could positively impact the management of IBD by providing a safe and easy sample collection method. However, much work needs to be carried out to determine all the potential salivary biomarkers and their precise role in IBD.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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