REVIEW ARTICLE

Annals of Agricultural and Environmental Medicine 2024, Vol 31, No 1, 1–7
www.aaem.pl

Relationship between periodontal diseases and non-specific inflammatory bowel diseases – an overview. Part I

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Goździewska M, Łyszczarz A, Kaczoruk M, Kolarzyk E. Relationship between periodontal diseases and non-specific inflammatory bowel diseases – an overview. Part I. Ann Agric Environ Med. 2024;31(1):1–7. doi: 10.26444/aaem/185764

Abstract

Introduction and Objective. An increasing number of studies indicate that the oral cavity and gastrointestinal tract are interconnected and that there is a potential causal link between non-specific inflammatory bowel diseases (IBD) and oral diseases. Therefore, following the example of the brain-gut axis, the concept of the gum-gut axis has now been put forward. The aim of the review is to assess the literature confirming the existence of the recently proposed gum-gut axis and the resulting relationships between non-specific inflammatory bowel diseases and oral diseases, especially periodontal diseases.
Review Methods. The review sums-up information concerning the relationship between periodontal diseases and non-specific bowel diseases. A literature review was carried out by searching databases PubMed, Google Scholar, and Web of Science.
Brief description of the state of knowledge. Previously, it was presumed that oral microflora and intestinal microflora remain separate. because it was considered that salivary microbes are killed by stomach and bile acids during translocation through the gastrointestinal tract. Presently, it has been confirmed that oral microorganisms have been found in the faeces of even healthy people. The comparison of oral and intestinal microbiomes of adults does not show full convergence; but pathogenic bacteria such as Klebsiella, Porphyromonas gingivalis and Fusobacterium nucleatum may act as the microbial bridge between periodontitis and IBD.
Summary. Dysbiosis of oral microflora may disrupt the normal functioning of the immune system, in this way increasing the development of periodontitis which, in turn, increases the risk of IBD and other complex systemic pathological processes. The gum-gut axis plays a crucial role in these associations. Additional studies are necessary to specify the role of nutritional intervention concerning oral and intestinal microbiome for precise health management.

Key words

gum-gut axis, inflammatory bowel diseases (IBD), periodontal diseases, gut microbiome

INTRODUCTION

Human health, to a great extent is determined by complex internal mechanisms, ensuring the maintenance of physiological homeostasis at the cellular and organ levels. Some organs are very closely interconnected, creating a two-way feedback axis. The most well-known are the hypothalamic-pituitary adrenal axis [1, 2, 3], and the gut-brain axis [4, 5, 6, 7]. Less known is the recently distinguished gum-gut axis [8, 9].

The hypothalamic-pituitary-adrenal axis (HPA) ensures body homeostasis at the neuroendocrine level. This is a self-controlled system adjustable by long-term and short-term feedback loops. The hypothalamus plays a primary role which, via corticotropin (CRH), stimulates the anterior pituitary gland to produce the adrenocorticotropic hormone (ACTH). Subsequently, ACTH, by precisely influencing the adrenal cortex, stimulates it to produce corticosteroids, such as cortisol and corticosterone. Corticosteroids circulating in the blood modulate a wide range of physiological processes, especially immunity, fertility and, above all, the body's reaction to stress [3].

Abnormal development of the HPA axis in the embryonic period may result in long-term changes in the synthesis of neuropeptides and neurotransmitters in the central nervous system which, in consequence, leads to neuroendocrine, behavioural, autonomic, and metabolic functions disorders in adulthood [1]. In turn, the proper functioning of the HPA axis is crucial for maintaining mental and physical health, and the hormone level is then precisely adjusted to the body's needs [2]. This is especially important in the situation of acute or chronic stress. Stress is the factor which also activates the gut-brain axis.

The gut-brain axis involves two-way communication (with multiple feedback loops), between the brain, gut, and gut microbiome. Neural communication between the gut and the brain takes place through the enteric nervous system (ENS). ENS controls intestinal motility, affects epithelial proliferation and modulates the intestinal immune system – GALT [10]. An important line of communication in the

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Received: 17.01.2024; accepted: 04.03.2024; first published: 21.03.2024

gut-brain axis is the vagus nerve, the afferent fibres of which transmit information from gastrointestinal enterocytes to the brain, whereas the efferent fibres provide feedback. An important link in the neural communication pathway is performed by neurotransmitters (acetylcholine, gamma-aminobutyric acid – GABA and serotonin), produced by microorganisms colonizing the digestive tract. Commensal intestinal microflora play an important role in brain physiology [4]. In turn, intestinal dysbiosis, leading to disorders in the bidirectional relationship between intestinal microflora and the nervous system, has been associated with the pathogenesis of psychiatric and neurological disorders, such as: multiple sclerosis, Parkinson's disease, depression and autism spectrum disorders [4]. Recent research indicates that the brain-gut axis also includes a relationship between certain mental disorders and inflammatory bowel disease (IBD), especially with ulcerative colitis, allowing for targeted prevention, treatment and investigation of the pathomechanisms of these diseases [5]. Stress is a factor inducing the development of IBD and activates the brain-gut axis, resulting in the activation of the mast cells of the mucous membrane. It also increases the production of pro-inflammatory cytokines and other endocrine and humoral mediators. Intestinal permeability also increases, which enables translocation of bacteria to the intestinal wall and partially weakens immune reactivity, resulting in the development of inflammatory bowel disease (IBD) [6].

The aim of this study is to review the literature confirming the existence of the recently proposed gum-gut axis, and the resulting relationships between non-specific inflammatory bowel diseases (IBD) and oral diseases, especially periodontal diseases.

REVIEW METHODS

The review sums-up information concerning the relationship between periodontal diseases and non-specific inflammatory bowel diseases. A literature review was carried out by searching databases PubMed, Google Scholar, and Web of Science. After preliminary evaluation, articles, meta-analyses and reviews were selected which contained information simultaneously concerning periodontal diseases and non-specific inflammatory bowel diseases. Publications were analyzed using a non-systematic review method, with the aim of compiling a brief synthesis of the collected information.

DESCRIPTION OF THE STATE OF KNOWLEDGE

An increasing number of studies indicate that inflammations in the oral cavity, especially periodontitis, play an important role in the etiology of non-specific bowel diseases. As a basis for investigating interrelationships between the periodontium and gastrointestinal system, the concept of a gum-gut axis has been introduced [7, 8]. This concept assumes that the oral cavity and gastrointestinal tract are interconnected and can influence each other, especially from the immunological and microbiological point of view [9]. Previously, it was presumed that the oral microflora and intestinal microflora remain separate, because it was assumed that salivary microbes are killed by stomach and bile acids during translocation through the gastrointestinal tract. It has now been proven that oral microorganisms are found in the faeces of even healthy individuals, and studies conducted by Schmidt et al. on 470 people, showed that approximately one-third of the gut bacteria strains came from the oral cavity, or were specialized intestinal subtypes of the same oral species [11]. It has also been found that in patients with IBD the transmission of microorganisms from the oral cavity is higher than in healthy people from the control group, and periodontitis exerts a special effect on the pathophysiology of the intestinal system [12].

Periodontitis is caused by the complex effect of epigenetic, environmental, and microbiological factors. It is an inflammatory disease of the tissues that hold the tooth in its socket. The structure of the periodontium is diverse and includes: the gums, root cementum, periodontal fibre, and dental alveolar bone. The etiology of periodontitis is of a multifactorial character; however, dysbiosis in terms of bacterial commensals which contributes to changes in the immune-inflammatory response from adequate to excessive and non-controlling the biofilm on periodontal pocket, is considered as a basic etiologic factor in the case of chronic periodontitis [13]. Biofilm bacteria cause activation of neutrophils, which secrete chemokines CCL_2 and $CCL_{20,}$ which leads to attraction of Th17 lymphocytes to the focus of inflammation. They secrete IL-17, IL-21, IL-22, Il-26, as well as Il-6, TNF-α and RANKL, and intensify the secretion of MMP and PGE_2 being a strong osteoclastic and pro-inflammatory stimulus [14]. This chronic condition may lead to the breakdown of periodontal tissues and ultimately to the loss of teeth [15]. According to the classification introduced in 2017 by the American Academy of Periodontology and the European Federation of Periodontology, periodontal diseases may be divided into 4 groups: 1) healthy periodontium, and diseases and changes in the gums; 2) periodontitis; 3) other disease states that may predispose to periodontal disease; 4) diseases and changes in the tissues around implants [16]. Periodontitis is closely related with several systemic diseases, including: atherosclerosis [17], diabetes [18], rheumatoid arthritis [19], and Alzheimer's disease [20].

In 2021, due to the efforts of various professional organizations and based on clinical trials, gold standards in periodontology were published [21]. Some of the established gold standards cover: periodontal examination, measurement of clinical loss of alveolar attachment, bone loss, cone beam computed tomography, quantitative polymerase chain reaction tests, biopsies and mouth rinsing with chlorhexidine as treatment options. Recent studies focus on confirmation of a close relationship between periodontitis and inflammatory bowel diseases (IBD) [22, 23, 24, 25].

Into non-specific bowel diseases are classified Crohn's disease (CD) and ulcerative colitis – UC (*colitis ulcerosa* – CU, or in the Polish abbreviation – WZJG). Crohn's disease is a chronic autoimmune disease in which an inflammatory state may involve each section of the gastrointestinal tract, from the mouth to the anus. The most characteristic feature of the disease are segmental inflammatory changes in the small or large intestine, separated by healthy fragments. In about half of the patients (40–50%), inflammation affects the final section of the ileum (*ileitis terminalis*), in 30–40% – inflammatory changes affect the small and large intestine (*ileocolitis*), while in 20% – only the large intestine. Considerably more rarely an inflammatory state involves the proximal part of the small intestine, and exceptionally,

the upper gastrointestinal tract or appendix [26]. The inflammatory process begins in the intestinal mucosa. The response to inflammation is characterized by changes in the innate immune barrier of the intestinal mucosa, along with the remodelling of the extracellular matrix, through the expression of metalloproteins and increased expression of adhesion molecules, such as MACCAM 1 [27]. When the inflammatory process affects all layers of the gastrointestinal tract wall, it leads to its destruction and fibrosis, resulting in the formation of fistulas and strictures, often requiring surgical treatment.

Changes in microbial composition and reduction in species diversity are considered key characteristics of the dynamic of the disease [28]. Turpin W. et al., based on prospective observation of 50 persons who developed CD within 8-year observation period, concluded that an increased intestinal permeability may serve as a biomarker of the risk of occurrence of CD [29]. In turn, a study by Kaczmarczyk O. et al. demonstrated that the determination of the level of short-chain fatty acids (SCFA) may be used to assess the degree of IBD activity. In 39 patients with active IBD, lower levels of butyric, acetic, valeric and isovaleric acids, and an increased concentration of lactic acid in stool were found, compared to 22 patients with inactive IBD [30].

In the case of ulcerative colitis, an auto-aggressive disease, inflammatory changes concern the mucous membrane of the rectum, or rectum and colon, and consequently, some patients develop ulcers. Inflammation of the rectum and sigmoid colon is diagnosed in 30–50% patients, 20–30% have the left-sided form of the disease, whereas in 20–30% of patients the pathological process covers the whole large intestine. Bacterial dysbiosis plays an important role in which gram-negative anaerobes predominate: *Enterobacteriaceae, Clostridium*, *Salmonella*, *Pseudomonas* or *Shigella*. The existing dysbiosis contributes to the production of endotoxins with pro-inflammatory properties, and to a reduced immune response. In the course of the disease, alternating states of exacerbation and remission are observed. Episodes of exacerbations may take a mild, moderate, severe, or even life threatening course [31]. If ulcerative colitis begins in childhood or during the period of puberty it is often characterized by rapid progression and frequent comorbidities [32]. A personalized approach to the treatment of ulcerative colitis is recommended. At present, the applicable recommendations of the Polish Society of Gastroenterology include 49 detailed recommendations concerning diagnostics and treatment of ulcerative colitis in adults, both pharmacological and surgical [33].

The main common clinical symptoms of CD and UC are abdominal pain, diarrhea, bloody stools, and loss in body weight [34, 35]. The presence of extraintestinal symptoms is also important, to which often belong pathological changes in the oral cavity, including periodontitis [34, 36]. Meta-analysis carried out by She Y. [34], including 6 studies of 599 patients with IBD and 448 persons from the control group, demonstrated a statistically significant relationship between periodontitis and IBD (joint OR – 3.17 (95% CI: 2.09–4.8). Clinical studies indicate that in patients with Crohn's disease the risk of development of periodontal diseases is clearly higher than in persons without this disease [37]. It was also confirmed that in persons with periodontitis, the risk of development of Crohn's disease and ulcerative colitis is higher than in persons without oral inflammatory diseases [38, 39]. Some studies indicate the effect of treatment of periodontal diseases on the course of IBD and *vice versa*. Treatment of periodontitis reduces systemic immune activation, and treatment of IBD is associated with the resolution of periodontitis. This is of great importance for the diagnosis and treatment of both diseases [40, 41, 42].

The etiology of both periodontal diseases and IBD is multifactorial; however, intestinal microbiota, modified by environmental factors, e.g. diet, cigarette smoking, oral hygiene, and genetic susceptibility of the host, play an important role in their development and progression [43, 44, 45, 46]. The comparison of oral and intestinal microbiomes of adults does not show full convergence; nevertheless, they have several taxa in common, including *Streptococcus*, *Bacteroides* and *Prevotella*, as well as such invasive microorganisms as: *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Klebsiella* spp., *Campylobacter* spp., which indicates the coexistence of periodontal diseases and IBD [47].

The human oral cavity is colonized by more than 1,000 bacterial species in the amount of 10^8 cfu/g, with the domination of bacteria of the genus *Streptococcus*, *Peptococcus*, *Bifidobacterium*, *Staphylococcus*, *Lactobacillus* and *Fusobacterium*. In the etiology of periodontitis there occurs dysfunction of the ecological environment of the oral cavity, and an increase in the concentration of gram-negative bacteria in the subgingival flora [48]. A specialized gram-negative anaerobic bacterium *Porphyromonas gingivalis* (*P. gingivalis*) is especially considered the main pathogen participating in the development and progression of chronic periodontitis [49]. Metabolites secreted by this bacterium (proteases, acidic lipopolysaccharides and alkaline phosphatases, organic acids) lead to the degradation of periodontal proteins and reduction of immune defence [50].

In patients with periodontitis, compared to healthy adults, there occur significant differences in the composition of microbial metabolites in saliva. In these patients, higher levels were detected of serine, isoleucine, serotonin, 4-hydroxy cinnamic acid and hydro cinnamic acid [51]. In turn, the amount of bacteria in the intestines is estimated at 10^5 cfu/g in the jejunum, and 10^8 cfu/g in the ileum, 99% of which originate from *Firmicutes*, *Bacteroidetes*, *Proteobacteria* and *Actinobacteria*. These microorganisms contain approximately 100 times more genes than those found in the human genome. Dysbiosis plays an important role in the etiopathogenesis of IBD, consisting of reduced bacterial diversity, which concerns mainly a decrease in *Firmicutes* and an increase in *Proteobacteria* [52, 53].

Detailed clinical studies have shown that, e.g. in the presence of Mycobacterium avium subsp. in patients with Crohn's disease, an increase is observed in the paratuberculosis count and adherent invasive *Escherichia coli*; while the presence of *Clostridium difficile* is increased both in patients with Crohn's disease and those with ulcerative colitis in the states of relapse and remission [54, 55]. In patients with Crohn's disease an increased number of mucous membrane bacteria is also found, and reduced numbers of anti-inflammatory commensal bacteria *Faecalibacterium prausnitizii* [53]. Intestinal dysbiosis is reflected in the stool metabolic profile in patients with ulcerative colitis and Crohn's disease. Metabolomic analyses of stool samples of patients diagnosed with IBD demonstrated a higher concentration of amino acids, and a lower concentration of short chain fatty acids, compared to healthy individuals. However, the non-specific

inflammatory process of the intestines has a significant effect on the profile of lipids and amino acids in the blood serum of the patients with IBD during the period of exacerbation: the concentration of phenylalanine in plasma increases, whereas the concentration of low-density lipoproteins (LDL) and very-low-density-lipoproteins in plasma decreases, compared to the group of patients during the period of remission. In turn, in the urine samples of patients with exacerbation of the inflammatory process, higher concentrations of glycine and lower concentrations of acetoacetate were found than in the group of patients in the inactive phase of the disease [56].

Periodontitis and inflammatory bowel disease – gum-gut axis. There are both direct and indirect connections between periodontitis and inflammatory bowel disease. Direct connections include translocation of pro-inflammatory microorganisms from the oral cavity to the intestines. It has been demonstrated that >10% of oral species may transmit via an oral-faecal route throughout the entire gastrointestinal tract [57]. Other studies confirmed that microorganisms related with gingivitis, such as *Aggregatibacter*, *Campylobacter*, *Enterobakterie*, *Fusobacterium*, *Gemella*, *Neisseria*, *Pasteurella*, *Peptostreptococcus* and *Streptococcus,* were present in the intestines of adult patients with IBD [58]. Among all the bacteria colonizing the oral cavity, such co-pathogens as *Porphyromonas gingivalis*, *Fusobacterium fusionum*, *Klebsiella* spp. and *Campylobacter* spp, provide (as previously mentioned) the best evidence of the bi-directional relationship between periodontitis and IBD [47].

Experiments carried out by Jia et al. [59] revealed a relationship between *Porphyromonas gingivalis* and IBD based on a mouse model of IBD, induced by dextran sulfate sodium (DSS). The researchers showed that *Porphyromonas gingivalis* increases the level of a transcription factor for Th17 and RoRγt, and increases the levels of IL-17 and IL-6. However, it reduces the expression of transcription factors Treg Foxp3, TGF-β and IL-10 through the TLR4 pathway. *Porphyromonas. gingivalis* activated T CD4+ lymphocytes and exacerbated colitis by increasing the Th17/Tregm ratio through the JAK-STAT signalling pathway, and additionally impaired the function of the intestinal barrier. In the case of *Klebsiella pneumoniae* 2H7, it was confirmed that it may ectopically colonize the intestines through the oral cavity and considerably induce the response of Th1 cells, which evidences that pathogenic bacteria of the oral cavity may exacerbate bowel diseases. The subsequent pathogen which plays an important role in the formation of dental plaque and periodontitis is *Fusobacterium* spp. Huh and Roh [60] analyzed metagenomic data from an integrative project – the Human Microbiome Project (iHMP) – and discovered that *Fusobacterium nucleatum* may be related with early intestinal dysbiosis, and may serve as a biomarker for the detection of IBD. Gemmel MR et al. [61] also indicated the role of periodontopathogens in gastrointestinal diseases. The research showed similarity of the genes *Campylobacter concisus* isolated from the environment of the intestines and oral cavity of the same patients, which is evidence of the translocation of microorganisms from the oral cavity into the intestines.

Experiments carried out on mice by Kitamoto S. et al. [62] contribute to explaining in what way periodontitis can cause and exacerbate enteritis. Pathobionts from the oral cavity cause periodontitis, especially *Enterobacteriaceae*, such as *Klebsiella* and *Enterobacter* spp. After penetration into the gastrointestinal tract, they activate inflammasome in mononuclear phagocytes of the colon, causing its inflammation. Simultaneously, periodontitis induces the formation of Th17 cells in the oral cavity (subpopulation of CD4+ helper T lymphocytes). Th17 cells, after reaction with pathobionts specific for periodontitis, show intestinal tropism and migrate to the inflamed intestine. In the intestines, Th17 cells from the oral cavity may be activated by pathobionts originating from the oral cavity, causing aggravation of colitis. It is important that oral Th17 cells may be activated in the intestines only by pathogens originating from the oral cavity, and are not activated by microorganisms colonizing the intestines. Thus, exacerbation of enteritis is caused by periodontitis, which becomes the source of both colitogenic pathobionts and pathogenic T lymphocytes [62]. This is only one of the mechanisms evidencing the role of periodontium in the development of IBD.

There are many ways of activation of the immune system on the systemic level, with possible non-specific effect on the intestines [35]. Systemic inflammation caused by periodontitis may result in a local increase in oxidative stress, change in defence functions, decreased immunity and disruption of intestinal barrier function.

The intestinal barrier is a structure formed collectively by the microflora, a single layer of epithelial cells, and circulatory, lymphatic, intestinal and nervous systems located in the lamina propria associated with the intestinal mucosa (intestinal lymphoid tissue, GALT). As a result of disruption of intestinal barrier function, there occurs an increase in the permeability of the intestinal barrier, and translocation of microbial metabolites and inflammatory mediators into the circulation, which additionally exacerbates chronic systemic inflammation [35]. The whole immunological processes combining periodontitis and inflammatory bowel disease is presented below.

Oral pathogen-mediated immune responses that drive gut inflammation in IBD [63–66]. Swallowing saliva allows bacteria to enter the intestines. Impaired intestinal barrier function, characterized by reduced integrity of the mucus and epithelial barrier, facilitates the entry of oral bacteria into subepithelial areas. Neutrophils, as the main cells of the innate immune system, phagocytize oral bacteria and secrete anti-microbial molecules (degranulation).

Moreover, dendritic cells recognize foreign microorganisms in the intestines thanks to specific Toll-like receptors (TLRs). After activation, these cells produce pro-inflammatory factors: interleukins (IL-6, IL-12, IL-23, IL-1β), as well as TNF-α and chemokines. As a consequence, Th0 lymphocytes differentiate into Th1, Th2, Th17 and Treg cells [12].

Antigens of bacterial cells originating from the oral cavity are also recognized by B lymphocytes, which leads to the production and secretion of specific antibodies. The resulting antigen-antibody complexes may contribute to the intensification of the inflammatory process in the intestines

All immunological processes linking periodontitis and inflammatory bowel disease have been illustrated by graphics created by H. Tanwar [63].

Important connections between IBD and periodontitis have been confirmed in a study conducted by Gugnani S. and Gugnani N. [67] which included patients from the University Hospital of Turin, Italy, diagnosed with non-specific bowel

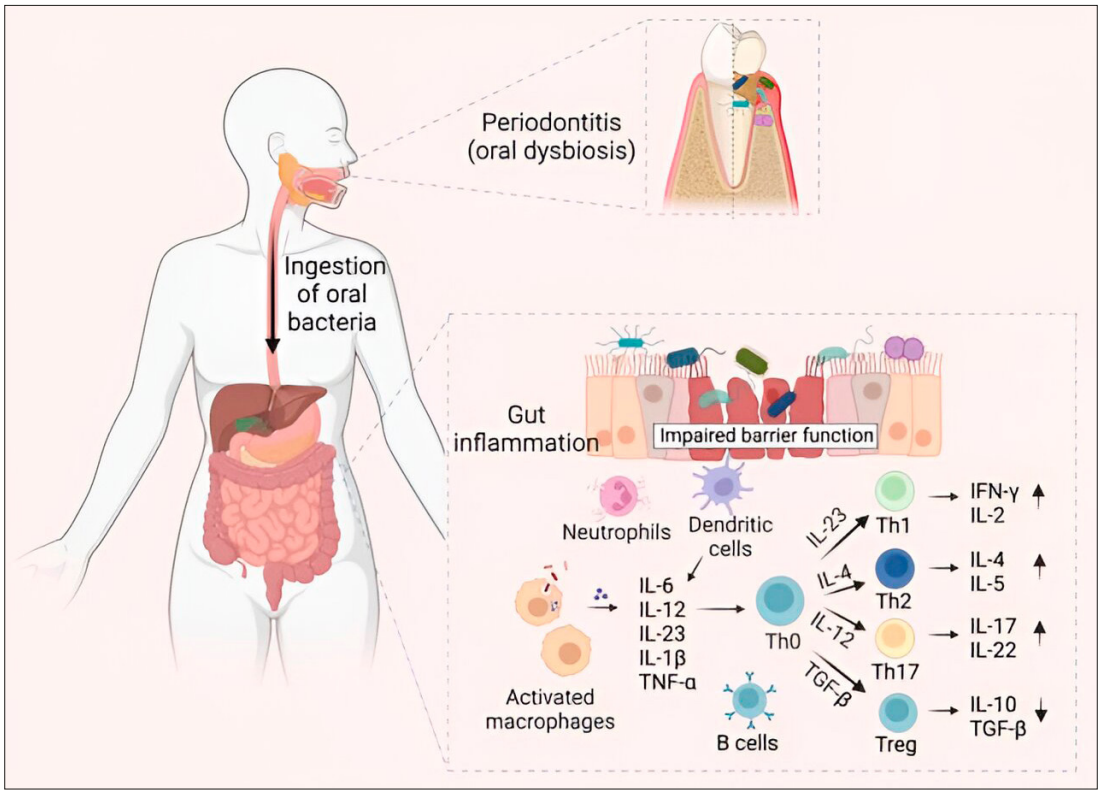

Figure 1. Immunological processes: periodontitis and inflammatory bowel disease [63]

disease (IBD), i.e. ulcerative colitis or Crohn's disease. The control group was an equal number of patients without IBD, matched in terms of age, gender and ethnicity. In all patients in the study, data on periodontal status were assessed, which included clinical loss of alveolar attachment, bleeding on probing, recession, presence and severity of periodontitis. Significant differences were observed in the frequency of occurrence of severe periodontitis between patients with IBD (85.6%) and the control group (65.6%). Using the methods of logistic regression, strong relationships were confirmed between IBD and periodontitis, and *vice versa*. This two-way connection between the oral cavity and intestines, i.e. the presence of the gum-gut axis, confirms a common immunomodulatory mechanism between periodontitis and IBD. The theoretical basis of this interdependence is becoming better understood.

Pathogenic bacteria associated with periodontitis may migrate to the intestines and disturb the functioning of the intestinal barrier, thus causing ecological dysregulation of the intestines and disruption of immunological mechanisms, and consequently cause chronic inflammation typical of Crohn's disease and ulcerative colitis. In turn, the immune response associated with IBD may contribute to inflammation in the oral cavity, primarily through Th17/Treg imbalance.

Yuan et al. [68] demonstrated that ecological intestinal dysbiosis caused by long-term use of antibiotics led to an increase in the number of pathogens related with periodontitis, and decreased the content of probiotics inn the oral microflora exerting an effect on periodontal health, whereas pro-inflammatory cytokines related with Th17 cells (IL-17A, IL-6) were increased, while the expression of cytokines related with Treg cells (Foxp3 and IL-10) was decreased on the periodontal tissues. A study by Figueredo et al. [69] also showed that indicators of inflammation in the gum tissue (IL-1β, IL-6, IL-21 and sCD40L) were significantly higher in patients with active IBD, and the levels of IL-4 were significantly lower in the gingival sulcus of patients with IBD and periodontitis.

The above-mentioned research reinforces the importance of the two-way role of the gum-gut axis. Dysbiosis of the oral microflora may disturb the normal functioning of the immune system, and in this way increases the development of periodontitis which, in turn, increases the risk of IBD and other complex systemic disease processes. It is an important fact that the above-mentioned relationship is useful information in the early diagnostics and treatment of both dysbiosis of the oral cavity and the intestines, as well as related inflammatory diseases [70].

Nutrition is an important factor in the shaping of intestinal microbiota and oral microflora. Through its pro- and anti-inflammatory properties, nutrition plays an important role in the prevention and treatment of oral and gastrointestinal inflammatory diseases. Therefore, diet plays an important, supplementary role in the process of treatment, and is also an important instrument in actions preventing the development of inflammatory states involving the gastrointestinal tract and the oral cavity.

The gum-gut connection provides new perspectives for future therapeutic and prophylactic methods. Additional studies are necessary which would specify the role of nutritional intervention concerning the oral and intestinal microbiome for precise health management. In future, the authors of this review intend analysing the results of research in the field of relationships between nutrition and periodontal diseases and intestinal inflammatory conditions.

REFERENCES

1. Sheng JA, Bales NJ, Myers SA, Bautista AI, Roueinfar M, Hale TM, Handa RJ. The hypothalamic-pituitary-adrenal axis: development, programming actions of hormones, and maternal-fetal interactions. Front Behav Neurosci. 2021;14:256.
2. Leistner C, Menke A. Hypothalamic–pituitary–adrenal axis and stress. Handbook Clin Neurol. 2020;175:55–64.
3. DeMorrow S. Role of the Hypothalamic-Pituitary-Adrenal Axis in Health and Disease. Int J Mol Sci. 2018 Mar 26;19(4):986. doi:10.3390/ijms19040986. PMID: 29587417; PMCID: PMC5979578
4. Dinan TG, Gryan JD The mictrobiote Gut-Brain-Axix in health and disease Gastrenterol. 2017;46:77–89.
5. Mayer EA, Nance K, Chen S. The Gut–Brain Axis. Annual Rev Med. 2022;73:439–453.
6. Brzozowski B, Mazur-Bialy A, Pajdo R, Kwiecien S, Bilski J, Zwolinska-Wcislo M, Brzozowski T. Mechanisms by which stress affects the experimental and clinical inflammatory bowel disease (IBD): role of brain-gut axis. Curr Neuropharmacol. 2016;14(8):892–900.
7. Xu Y, Luo J, Gao Y, Tao Y, Xu J, Yao T, Chen Y. Causal effects between inflammatory bowel disease and oral diseases based on Oral-GUT Axis: a Mendelian randomization study. Nutrients 2023;15(20):4445 https://doi.org/10.3390/nu15204445
8. Byrd KM, Gulati AS. The "Gum-Gut" Axis in Inflammatory Bowel Diseases: A Hypothesis-Driven Review of Associations and Advances. Front Immunol. 2021 Feb 19;12:620124. doi:10.3389/fimmu.2021.620124. PMID: 33679761; PMCID: PMC7933581
9. Baima G, Ribaldone DG, Romano F, Aimetti M, Romandini M. The Gum–Gut Axis: Periodontitis and the Risk of Gastrointestinal Cancers. Cancers 2023;15(18):4594.
10. Schneider S, WrightCM, Heuckeroth RO. Unexpected Roles for the Second Brain: Enteric Nervous System as Master Regulator of Bowel Function. Annual Rev Physiol. 2019;81:235–259.
11. Schmidt TS, Hayward MR, Coelho LP, Li SS, Costea PI, Voigt AY, et al. Extensive Transmission of Microbes along the Gastrointestinal Tract. ELife 2019;8:e42693.
12. Nagao J-I, Kishikawa S, Tanaka H, Toyonaga K, Narita Y, Negoro-Yasumatsu K, et al. Pathobiont-Responsive Th17 cells in gut-mouth axis provoke inflammatory oral disease and are modulated by intestinal microbiome. Cell Rep. 2022;40:111314.
13. Frank DN, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proc Natl Acad Sci USA. 2007;104(34):13780–5. doi:10.1073/pnas.0706625104. Epub 2007 Aug 15. PMID: 17699621; PMCID: PMC1959459
14. Meyle J, Chapple I. Molecular aspects of the pathogenesis of periodontitis. Periodontol 2000. 2015 Oct;69(1):7–17. doi:10.1111/prd.12104. PMID: 26252398
15. Kinane DF, Stathopoulou PG, Papapanou PN. Periodontal diseases. Nat Rev Dis Primers 2017;3:17038. doi:10.1038/nrdp.2017.38
16. Chapple ILC, Mealey BL, Van Dyke TE, Bartold PM, Dommisch H, Eickholz P, et al. Periodontal health and gingival diseases and conditions on an intact and a reduced periodontium: Consensus report of workgroup 1 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Periodontol. 2018 Jun;89 Suppl 1:S74-S84. doi:10.1002/JPER.17-0719. PMID: 29926944
17. Isola G, Santonocito S, Distefano A, Polizzi A, Vaccaro M, Raciti G, et al. Impact of periodontitis on gingival crevicular fluid miRNAs profiles associated with cardiovascular disease risk. J Periodontal Res. 2022;58(1):165–174.
18. Genco RJ, Sanz M. Clinical and public health implications of periodontal and systemic diseases: An overview. Periodontol 2000. 2020;83:7–13. doi:10.1111/prd.12344
19. Möller B, Kollert F, Sculean A, Villiger PM. Infectious triggers in periodontitis and the gut in rheumatoid arthritis (RA): A complex story about association and causality. Front Immunol. 2020;11. doi:10.3389/fimmu.2020.01108
20. Torrealba-García D, Garcia-Morales P, Torrealba E, Cejudo JC, Silvestre-Rangil J. Is there a relationship between periodontitis and alzheimer's disease? systematic review and comparative analysis. Alzheimers Dement. 2021;17:e051470. doi:10.1002/alz.051470
21. Koirala PK, Pradhan S. Gold Standards in Periodontics: A Review. J Nepalese Soc Periodontol Oral Implantol. 2021;5(1):49–53.
22. Zhou T, Xu W, Wang Q, Jiang C, Li H, Chao Y, Sun Y, A L. The effect of the "Oral-Gut" axis on periodontitis in inflammatory bowel disease: A review of microbe and immune mechanism associations. Front Cell Infect Microbiol. 2023;13:1132420. doi:10.3389/fcimb.2023.1132420. PMID: 36923589; PMCID: PMC10008960
23. Baima G, Muwalla M, Testa G, Mazza F, Bebars A, Perotto S, et al. Periodontitis prevalence and severity in inflammatory bowel disease: A case–control study. J Periodontol. 2022:1–10. doi:10.1002/jper.22-0322
24. Imai J, Ichikawa H, Kitamoto S, Golob JL, Kaneko M, Nagata J, et al. A potential pathogenic association between periodontal disease and crohn's disease. JCI Insight 2021;6:e148543. doi:10.1172/jci.insight.148543
25. Zhang Y, Qiao D, Chen R, Zhu F, Gong J, Yan F. The association between periodontitis and inflammatory bowel disease: A systematic review and meta-analysis. BioMed Res Int. 2021:1–8. doi:10.1155/2021/6692420
26. https://www.mp.pl/pacjent/gastrologia/choroby/jelitogrube/65252,choroba-lesniowskiego-i-crohna
27. Petagna L, Antonelli A, Ganini C, Bellato V, Campanelli M, Divizia A, et al. Pathophysiology of Crohn's disease inflammation and recurrence. Biol Direct. 2020;15(1):1–10.
28. Caparrós E, Wiest R, Scharl M, Rogler G, Gutiérrez Casbas A, Yilmaz B, et al. Dysbiotic microbiota interactions in Crohn's disease. Gut Microbes 2021;13(1):1949096
29. Turpin W, Lee SH, Garay JAR, Madsen KL, Meddings JB, Bedrani L, et al. Increased intestinal permeability is associated with later development of Crohn's disease. Gastroenterol. 2020;159(6):2092–2100.
30. Kaczmarczyk O, Dąbek-Drobny A, Woźniakiewicz M, Paśko P, Dobrowolska-Iwanek J, Woźniakiewicz A, et al. Association between fecal levels of short-chain fatty acids and serum pro-and anti-Inflammatory cytokines in patients with inflammatory bowel disease. Folia Medica Cracoviensia. 2022:43–54.
31. Segal JP, LeBlanc JF, Hart AL. Ulcerative colitis: an update. Clin Med. 2021;21(2):135.
32. Raine T, Bonovas S, Burisch J. ECCO guidelines on the therapeutics in ulcerative colitis: medical treatment. J Crohns Colitis. 2022;16:2–17.
33. Eder P, Łodyga M, Gawron-Kiszka M, et al. Guidelines for the management of ulcerative colitis. Recommendations of the Polish Society of Gastroenterology and the Polish National Consultant in Gastroenterology. Gastroenterol Rev. 2023;18:1–42.
34. She Y, Kong X, Ge Y, Liu Z, Chen J, Jiang J, et al. Periodontitis and inflammatory bowel disease: a meta-analysis. BMC Oral. Health. 2020;20:67. doi:10.1186/s12903-020-1053-5
35. Jairath V, Feagan BG. Global burden of inflammatory bowel disease. Lancet Gastroenterol Hepatol. 2020;5(1):2–3.
36. Marotto D, Atzeni F, Ardizzone S, Monteleone G, Giorgi V, Sarzi-Puttini P. Extra-intestinal manifestations of inflammatory bowel diseases. Pharmacol Res. 2020;161:105206. doi:10.1016/j.phrs.2020.105206
37. Chi YC, Chen JL, Wang LH, Chang K, Wu CL, Lin SY, et al. Increased risk of periodontitis among patients with Crohn's disease: a population-based matched-cohort study. Int J Colorectal Dis. 2018;33:1437 44. doi:10.1007/s00384-018-3117-4
38. Lin CY, Tseng KS, Liu JM, Chuang HC, Lien CH, Chen YC, et al. Increased risk of ulcerative colitis in patients with periodontal disease: a nationwide population-based cohort study. Int J Environ Res Public Health. 2018;15:602. doi:10.3390/ijerph15112602
39. Kang EA, Chun J, Kim JH, Han K, Soh H, Park S, et al. Periodontitis combined with smoking increases risk of the ulcerative colitis: a national cohort study. World J Gastroenterol. 2020;26:5661–72. doi:10.3748/wjg.v26.i37.5661
40. Machado V, Lobo S, Proença L, Mendes JJ, Botelho J. Vitamin d and periodontitis: A systematic review and meta-analysis. Nutrients. 2020;12:2177. doi:10.3390/nu12082177
41. Liu H, Hong XL, Sun TT, Huang XW, Wang JL, Xiong H. Fusobacterium nucleatum exacerbates colitis by damaging epithelial barriers and inducing aberrant inflammation. J Dig Dis. 2020;21:385–398. doi:10.1111/1751-2980.12909
42. Zhang Y, Chen J, Fu H, Kuang S, He F, Zhang M, et al. Exosomes derived from 3D-cultured MSCs improve therapeutic effects in periodontitis and experimental colitis and restore the Th17 cell/Treg balance in inflamed periodontium. Int J Oral Sci. 2021;13:43. doi:10.1038/s41368-021-00150-4
43. Ni J, Wu GD, Albenberg L, Tomov VT. Gut microbiota and IBD: causation or correlation? Nat Rev Gastroenterol Hepatol. 2017;14:573 84. doi:10.1038/nrgastro.2017.88
44. Franzosa EA, Sirota-Madi A, Avila-Pacheco J, Fornelos N, Haiser HJ, Reinker S, et al. Gut microbiome structure and metabolic activity in inflammatory bowel disease. Nat Microbiol. 2019;4:293–305. doi:10.1038/s41564-018-0306-4
45. Lavelle A, Sokol H. Gut microbiota-derived metabolites as key actors in inflammatory bowel disease. Nat Rev Gastroenterol Hepatol. 2020;17:223–237. doi:10.1038/s41575-019-0258

46. Lee Y-C, Liu C-Y, Lee C-L, Zhang R-H, Huang C-J, Yen T-L. The periodontopathic pathogen, porphyromonas gingivalis, involves a gut inflammatory response and exacerbates inflammatory bowel disease. Pathogens 2022;11:84. doi:10.3390/pathogens11010084
47. Cai Z, Zhu T, Liu F, Zhuang Z, Zhao L. Co-pathogens in Periodontitis and Inflammatory Bowel Disease. Front Med. 2021;8:723719. doi:10.3389/fmed.2021.723719
48. Curtis MA, Diaz PI, Van Dyke TE. The role of the microbiota in periodontal disease. Periodontology. 2020;83(1):14–25. doi:10.1111/prd.12296
49. Reyes L. Porphyromonas gingivalis. Trends Microbiol. 2021;29:376–377. doi: 10.1016/j.tim.2021.01.010
50. Xu W, Zhou W, Wang H, Liang S. Roles of porphyromonas gingivalis and its virulence factors in periodontitis. Adv Protein Chem Struct Biol. 2020;120:45–84. doi:10.1016/bs.apcsb.2019.12.001
51. Wei Y, Shi M, Nie Y, Wang C, Sun F, Jiang W, et al. Integrated analysis of the salivary microbiome and metabolome in chronic and aggressive periodontitis: A pilot study. Front. Microbiol. 2022;13. doi:10.3389/fmicb.2022.959416
52. Matsuoka K, Kanai T. The gut microbiota and inflammatory bowel disease. Semin Immunopathol. 2014;37:47–55. doi:10.1007/s00281-014-0454-4
53. Guan Q. A comprehensive review and update on the pathogenesis of inflammatory bowel disease. J Immunol Res. 2019:7247238. doi:10.1155/2019/7247238
54. Nishida A, Inoue R, Inatomi O, Bamba S, Naito Y, Andoh A. Gut microbiota in the pathogenesis of inflammatory bowel disease. J Clin Gastroenterol. 2018;11(1):1–10. doi:10.1007/s12328-017-0813-5
55. Dolan KT, Chang EB. Diet, gut microbes, and the pathogenesis of inflammatory bowel diseases. Molecular Nutrition Food Res. 2017;61(1) doi:10.1002/mnfr.201600129
56. Andrzejewska M, Dereziński P, Kokot ZJ, Grzymisławski M. Metabolomika i proteomika w diagnostyce nieswoistych chorób zapalnych jelit. Forum Zaburzeń Metabolicznych. 2016;7(4):145–151.
57. Schmidt TS, Hayward MR, Coelho LP, Li SS, Costea PI, Voigt AY, et al. Extensive transmission of microbes along the gastrointestinal tract. eLife 2019; 8:e42693. doi:10.7554/eLife.42693
58. Newman KL, Kamada N. Pathogenic associations between oral and gastrointestinal diseases. Trends Mol Med. 2022;28:1030–1039. doi:10.1016/j.molmed.2022.05.006
59. Jia L, Wu R, Han N, Fu J, Luo Z, Guo L, et al. Porphyromonas gingivalis and Lactobacillus rhamnosus GG regulate the Th17/Treg balance in colitis via TLR4 and TLR2. Clin Transl Immunology. 2020;9:e1213. 10.1002/cti2.1213
60. Huh JW, Roh TY. Opportunistic detection of Fusobacterium nucleatum as a marker for the early gut microbial dysbiosis. BMC Microbiol. 2020;20:208. 10.1186/s12866-020-01887-4
61. Gemmell MR, Berry S, Mukhopadhya I, Hansen R, Nielsen HL, Bajaj-Elliott M, et al. Comparative genomics of Campylobacter concisus: analysis of clinical strains reveals genome diversity and pathogenic potential. Emerg Microbes Infect. 2018;7:116. 10.1038/s41426-018-0118-x
62. Kitamoto S, Nagao-Kitamoto H, Jiao Y, Gillilland MG, Hayashi A, Imai J, et al. The intermucosal connection between the mouth and gut in commensal pathobiont-driven colitis. Cell. 2020;182:447–62. e14.10.1016/j.cell.2020.05.048
63. Tanwar H, Gnanasekaran JM, Allison D, Chuang LS, He X, Aimetti M, Baima G, et al. Unraveling the Link between Periodontitis and Inflammatory Bowel Disease: Challenges and Outlook. ArXiv 2023 Aug 19:arXiv:2308.10907v1. PMID: 37645044; PMCID: PMC10462160
64. Jaeger N, Gamini R, Cella M, Schettini JL, Bugatti M, Zhao S, et al. Single-cell analyses of Crohn's disease tissues reveal intestinal intraepithelial T cells heterogeneity and altered subset distributions. Nat Commun. 2021;12:1921. doi:10.1038/s41467-021-22164-6
65. Read E, Curtis MA, Neveres JF. Oral pathogen-mediated immune responses that drive gut inflammation in IBD. Nature Rev Gastroenterol Hepatol. 2021;18:731–742.
66. Yang B, Pang X, Li Z, Chen Z, Wang Y. Immunomodulation in the treatment of periodontitis: Progress and perspectives. Front Immunol. 2021;12. doi:10.3389/fimmu.2021.781378
67. Gugnani S, Gugnani N. Is there any link between periodontitis and inflammatory bowel diseases? Evid Based Dent. 2023 Sep;24(3):127–129. doi:10.1038/s41432-023-00917-0. Epub 2023 Jul 20. PMID: 37474731
68. Yuan X, Zhou F, Wang H, Xu X, Xu S, Zhang C, et al. Systemic antibiotics increase microbiota pathogenicity and oral bone loss. Int J Oral Sci. 2023;15:4. doi:10.1038/s41368-022-00212-1
69. Figueredo CM, Martins AP, Lira-Junior R, Menegat JB, Carvalho AT, Fischer RG, et al. Activity of inflammatory bowel disease influences the expression of cytokines in gingival tissue. Cytokine. 2017;95:1–6. doi:10.1016/j.cyto.2017.01.016/ijms24119577
70. Lauritano D, Boccalari E, Di Stasio D, Della Vella F, Carinci F, Lucchese A, et al. Prevalence of oral lesions and correlation with intestinal symptoms of inflammatory bowel disease: a systematic review. Diagnostics (Basel). 2019;9:77. doi:10.3390/diagnostics9030077