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Relationship Between Gastrointestinal Microbiome and Periodontitis: A Systematic Review

Kamran Lahoorpoor[1], Abdollah Ebrahimi[2], Masume mohammadi[3], Donya Alaei[4], Reza Sardari[5]*

1. Assistant professor at Department of Periodontology, School of Dentistry, Kurdistan University of Medical Sciences, Iran. Email: drkamranor2@gmail.com
2. Student Research Committee, School of Dentistry, Semnan University of Medical Sciences, Semnan, Iran. *Corresponding author. Email: ebrahimi56666@gmail.com
3. Student Research Committee, School of Dentistry, Semnan University of Medical Sciences, Semnan, Iran. Email: masoumehmohammadi926@yahoo.com
4. Doctor of dental surgery , Member of student research committee, School of Dentistry, Semnan University of Medical Science, Semnan, Iran. Email: donyaalaei1997@gmail.com
5. Dentistry Student, School of Dentistry, Kurdistan University of Medical Sciences, Iran. Email: ***Corresponding author**. Email: drsardari123@gmmail.com

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Abstract:
Periodontitis, which is a type of inflammatory disease, mostly affects the tooth surrounding tissues and causes a series of symptoms as well as systemic diseases, which are significant in turn.
Digestive dysbiosis can be mentioned among these diseases. New evidence suggests that there is a complex and actually two-way relationship between the gut microbiome and periodontitis.
Dysbiosis in the intestine is related to changes in the microbial composition, especially the increase in the ratio of Firmicutes to Bacteroidetes. It is also evident that this may associate with systemic inflammation so that it aggravates periodontal disease. It should be noted that a series of oral pathogens such as Porphyromonas gingivalis, Fusobacterium nucleatum, etc. can also be transferred to the intestine and lead not only to intestinal inflammation but also to diseases such as inflammatory bowel disease (IBD). The intestinal dysbiosis in turn can make periodontal disease worse through systemic inflammation and immune dysregulation.
On the other hand, pro-inflammatory cytokines such as IL-6, TNF and IL-17, which can be mentioned as very important mediators in both conditions, create a cycle of inflammation that can affect both the oral cavity and it also affects the digestive system. A better ability to understand the interaction that these microbiomes have with each other can create new ways for therapeutic interventions, including the use of probiotics and prebiotics, etc., which are aimed at restoring the microbial balance as well as anti-inflammatory treatments.
There is an undeniable need for more and deeper research in this regard in order to better understand the above-mentioned connections and also to improve the management of periodontitis and digestive diseases.

Keywords: Periodontitis, microbiome, dysbiosis, inflammation, intestinal.

Introduction

The relationship between the microbiome of the gastrointestinal tract and periodontitis is considered to be complex, so that in recent years, this issue has received a lot of attention from researchers. Periodontitis, which is actually an inflammatory condition of the gingiva, is common among the population, so that about 20-50% of the global population suffer from it. The distinctive feature of this disease is the destruction of the periodontal ligament as well as the alveolar bone, after which the teeth are lost[1,2,3]. On the other hand, the microbiome of the gastrointestinal tract, which has millions of types of microorganisms, including bacteria, viruses and fungi, plays a significant role in regulating immune responses and maintaining the overall health of the body[4]. Recent studies have shown that there is a significant relationship between the microbiome of the digestive system and periodontitis. Therefore, dysbiosis in the intestine can be illustrated, which is more than 30% of patients with periodontitis. Therefore, it can be claimed that there is a potential two-way relationship between these two diseases[5].

Until now, researchers have come to the conclusion that those patients who suffer from periodontitis are usually associated with a decrease in microbial diversity in the oral and intestinal microbiomes. Also, in a study that investigated the effect of microbes that cause gum disease on the function of the intestinal barrier, it was concluded that these microbes can be transferred to the intestine through different routes and disturb its homeostasis. Researches show that periodontal microbes reduce intestinal microbial diversity and increase the ratio of Firmicutes to Bacteroidetes, and these disorders can lead to the destruction of the physical and immune barrier of the intestine and ultimately increase the risk of inflammatory bowel diseases and metabolic disorders. On the other hand, the changes that occur in the intestinal microbiome increase the systemic inflammation, and as a result of this, it can lead to the development of periodontitis and digestive diseases[6,7,8]. New research has shown that there is a relationship between the severity of the disease and the imbalance of oral microbiota. Oral conditions such as fissures at the corners of the mouth and periodontitis are also recognized as extraintestinal manifestations of IBD and are associated with the severity of intestinal inflammation. During a research that examined the evidence and future trends in the relationship between oral microbiota and IBD, it was concluded that changes in oral microbiota can serve as markers for early diagnosis and predicting the progression of the disease. Bacteria in the oral cavity, which are often found in high concentrations in the subgingival plaque of periodontitis patients, are also detected in the gut microbiota of IBD patients, highlighting the microbial connection between the mouth and the gut[9,10,11].

On the other hand, chronic inflammatory processes in the oral mucosa and periodontitis can also be caused by microflora and microbial biofilms that activate innate and acquired immune systems and produce pro-inflammatory cytokines. These cytokines,

including IL-1beta, TNF, IL-6, IL-17 and IL-23, play an important role in the pathogenesis of gingivitis and periodontitis and can cause local inflammation and damage to periodontal ligaments, gingiva and alveolar bone. In experimental models, TNF and the IL-23/IL-17 axis are effective in disease, and inactivation of these pathways using neutralizing antibodies or IL-10 can reduce disease activity[12].

However, the relationship between the gastrointestinal microbiome and periodontitis is complex and bidirectional, and numerous studies consistently show that addressing the oral and intestinal microbiome through targeted therapeutic interventions may be a more comprehensive strategy for the management of periodontitis and its associated systemic complications[13,14].

Background

The microbiome of the digestive system of the human body has a large number of different types of microorganisms, including bacteria, fungi, viruses, etc. These microbes are very useful and efficient in maintaining the health of the body, so that they even affect the regulation of the immune system and keep it healthy[6]. On the other hand, periodontitis, which is actually a chronic inflammatory disease, causes a person to lose his teeth over time by affecting the gums, periodontal ligaments and alveolar bone. It should be noted that around 20 to 50 percent of people worldwide suffer from periodontitis[11]. During the conducted research, researchers have noticed the relationship between the two, i.e. gut microbiome and periodontitis, so that there is convincing evidence between dysbiosis in the gut microbiome and the development or development of periodontitis[4,15]

Periodontitis is caused by bacterial infections in the oral cavity and then causes damage to the gum tissues. This can subsequently lead to chronic inflammation. It cannot be denied that the activity of local bacteria is a main cause of periodontitis, but researchers have also found that the health of the digestive system's microbiome also plays an important and serious role in this case. Research shows that a large number of patients with periodontitis experience significant changes in the gut microbiota, suggesting a potential bidirectional relationship between the two systems. It should be mentioned that in addition, a strong relationship between periodontitis and diseases such as diabetes, metabolic syndromes, etc. has been found[11,15]. It has been observed that patients who suffer from intestinal dysbiosis have a drastic decrease in microbial diversity, which is actually a common trend in patients with periodontitis. Therefore, it

can be claimed that keeping the gut healthy probably helps to reduce inflammation in the oral cavity and vice versa[10,16].

It should be noted that the transf”r of pathogens from the mouth to the intestine is also a proven fact, so that they may even play a key role in modulating systemic inflammation and, in addition, they can aggravate intestinal and oral diseases[6,14,16]. It can even be stated that periodontitis-related pathogens, including Porphyromonas gingivalis, Fusobacterium nucleatum and Klebsiella spp have not only been found in the intestinal microbiota of patients with inflammatory bowel diseases (IBD), but research has shown that there is a significant relationship between oral infections and the disease. But in any case, it can be claimed that the change that occurs in the balance of the intestinal microbiota, especially the increase in the ratio of Firmicutes to Bacteroidetes, and on the other hand, are related to inflammatory diseases such as Crohn's disease and ulcerative colitis, is a very important indicator in this field. Also it can be stated that the mentioned increased ratio can disrupt the integrity of the intestinal barrier which may create an immune response that aggravates the inflammation of the oral cavity tissues[10,14,17].

It has also been proved that systemic inflammation resulting from gut dysbiosis can heighten the risk of periodontal diseases. Another fact in this regard is that the systemic inflammation that originates from intestinal dysbiosis increases the risk of periodontal diseases and at the same time that the inflammation spreads in the body, the response of the immune system also becomes more aggressive. This can subsequently lead to more imbalance in the oral microbiota. Therefore, these events create a cycle of continuous inflammation that will exist in the oral cavity and digestive system. During the research, inflammatory markers including IL-6, IL-17, and TNF are mentioned as factors for the continuity and in fact the dynamics of these Inflammations. In other words, these indicators increase both in periodontal diseases and in digestive disorders, and this is an indication of their main role in immune disorders, which is true in both conditions.[6,12,18,19].

Microbial transfer from the mouth to the intestine can also be done, which is actually through saliva or other biological fluids. This also strengthens the link between these two diseases. In the intestinal microbiota of patients with IBD, a high concentration of periodontitis-related bacteria was found in their sub-gingival plaque, which indicates that periodontal pathogens can be transferred to new environments in the body and form a colony. The results of these findings clearly indicate that the microbial interactions between the oral cavity and the digestive system are more extensive than what was thought until now[9,20,21].

Recent research in this field has also pointed to the role of oral microbiota as biomarkers that are useful for early diagnosis of gastrointestinal diseases, especially IBD. Changes in the oral environment, including the formation of ulcers, are now considered as manifestations of intestinal inflammation. When the severity of IBD increases, the oral symptoms increase accordingly, which can be considered as an early warning system for therapists[14,22,23].

A sufficient knowledge of scientific transparency and clarity between the gastrointestinal microbiome and periodontal health can lead to a deeper vision and understanding for future treatment strategies for therapists. Treatments whose primary goal is around the intestinal microbiota, especially in cases where probiotics or prebiotics are used, can not only be useful in reducing systemic inflammation, but can also play a key role in improving oral and dental health. On the other hand, dealing with periodontal infections can also help reduce some gastrointestinal disorders. Therefore, in the meantime, there is a need for an integrated approach to manage these diseases that are related and continuous[15,24,25,26].

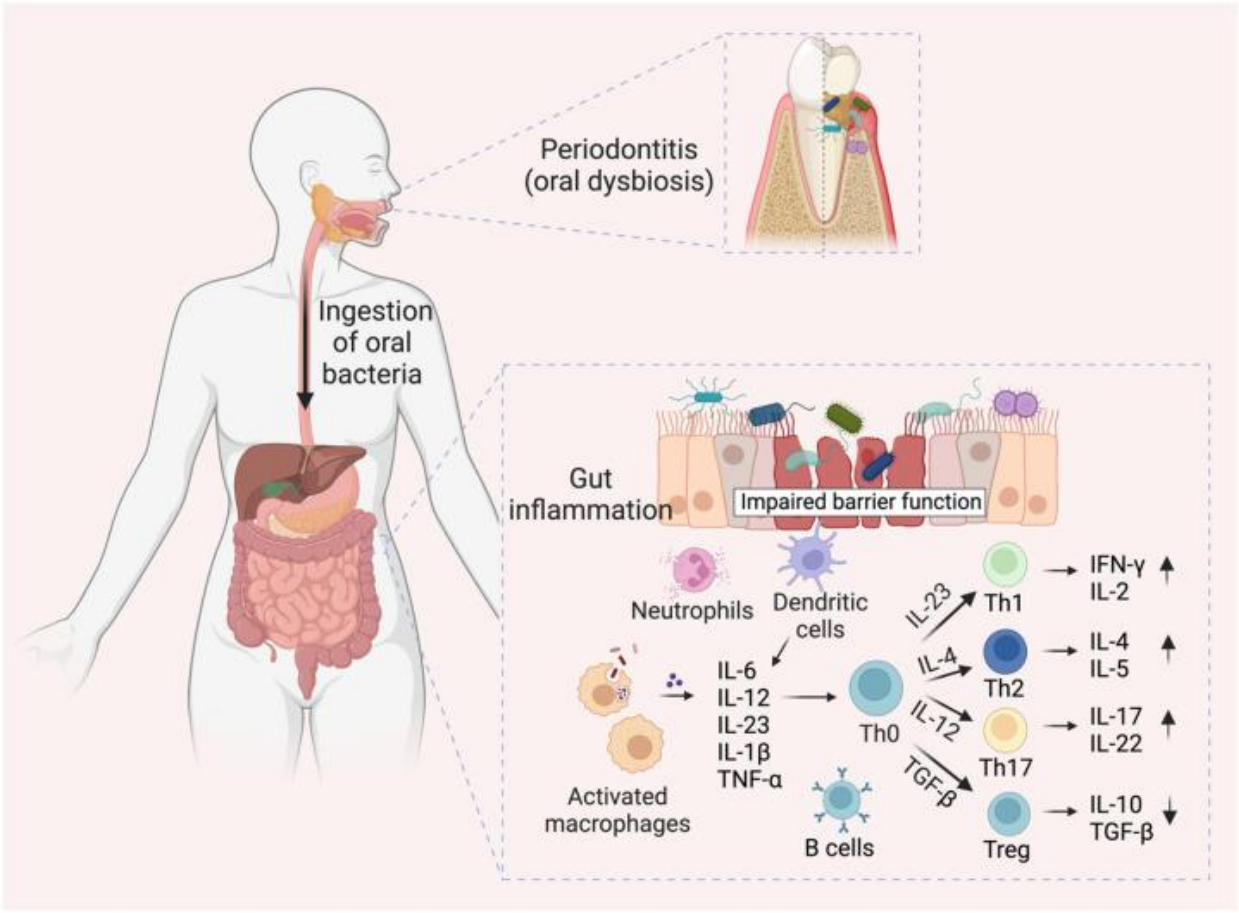

Figure 1: Oral pathogen-mediated immune responses that drive gut inflammation in IBD[29].

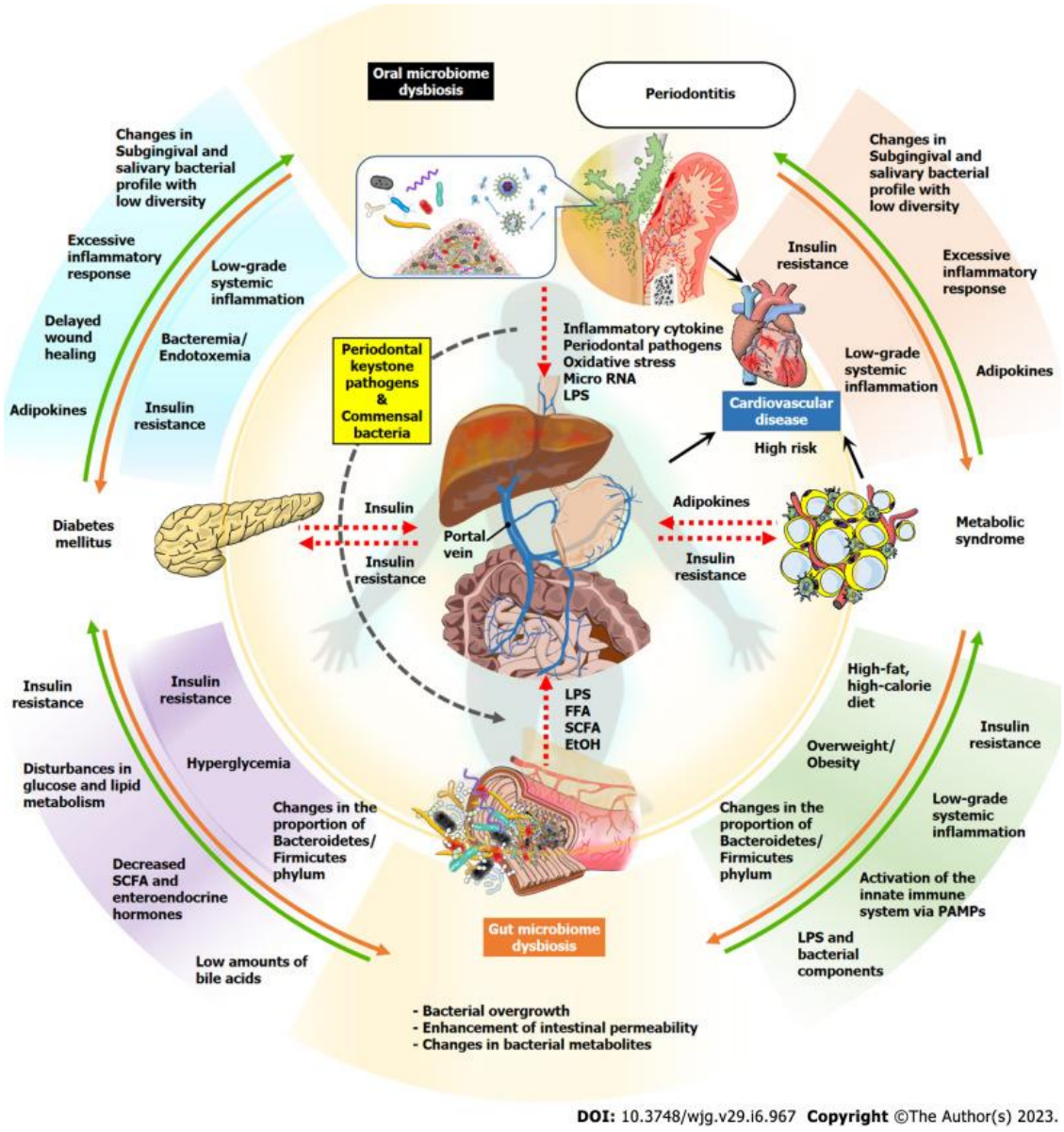

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Figure 2: Circular model of crosstalk between periodontal disease, gut microbiota, diabetes mellitus, and metabolic syndrome in the pathogenesis of nonalcoholic fatty liver disease[28].

Future research directions

According to the above-mentioned cases, it can be concluded that the relationship between the microbiome of the digestive system and periodontitis is not only complex but also bilateral. It is obvious that in the human body, dysbiosis in one system can aggravate another system, and by understanding more and more of this interaction, we

can have deeper and more complete strategies for managing periodontal diseases and digestive diseases[27,28].

Materials and methods

In this systematic study, the relationship between gastrointestinal (GI) microbiome and periodontitis was discussed. This research was conducted with a structured method with the aim of identifying related studies and combining data to draw conclusions about this complex and two-way interaction.

1. Literature search:

A comprehensive and detailed search was performed in the PubMed database, and the search terms used included periodontitis, gastrointestinal microbiome, dysbiosis, oral microbiome, systemic inflammation, and the ratio of Firmicutes to Bacteroidetes. Published articles were selected to focus on the relationship between gut dysbiosis and periodontitis.

2. Inclusion and exclusion criteria:

In order to make a decision for the definitive selection of the inclusion criteria, studies that specifically focused on the relationship between dysbiosis of the digestive tract microbiome and periodontal diseases and especially periodontitis in human subjects were selected. Also, in order to decide on the exclusion criteria, studies that were only based on animal models without human application, articles that did not investigate a clear connection between both microbiomes (oral and GI), and in addition all studies related to periodontal diseases that did not have any analysis at all.

3. Study selection and quality assessment:

Two reviewers were selected from all the authors and screened the titles and abstracts of the studies that were identified. Also, the quality of studies were evaluated for randomized and controlled trials.

In this way, we tried to create a comprehensive understanding of the current evidence on the relationship between gastrointestinal microbiome dysbiosis and periodontitis, and

we were also able to more efficiently gain insights into potential therapeutic interventions.

Results and discussion

As a result of various researches there is a significant relationship between dysbiosis in the gastrointestinal microbiome and the development of periodontitis[30]. Studies clearly say that many patients who are suffering from periodontitis actually have some type or it is better to say some types of basic changes in their gut microbiome. These changes are simultaneously accompanied by a decrease in microbial diversity and an increase in the ratio of Firmicutes to Bacteroidetes bacteria. This difference actually means that there are severe microbial disorders in patients with periodontitis[18,24,28].

It has been proven that dysbiosis in the gut microbiome can increase systemic inflammation and exacerbate periodontitis by increasing the production of pro-inflammatory cytokines such as IL-6, TNF and IL-17[31]. In this regard, researchers have been able to achieve the fact based on blood samples obtained from patients that the level of C-reactive protein (CRP), which is an indicator of systemic inflammation, has increased significantly, which indicates a direct relationship[32,33].

Another important result obtained in this systematic review is the direct transfer of oral bacteria such as Porphyromonas gingivalis, Fusobacterium nucleatum and Klebsiella spp to the intestine, which are actually present in the subgingival plaque of periodontitis patients. Also, these microorganisms have been observed in the intestinal microbiota of patients with inflammatory bowel diseases. The findings of this research clearly indicate that these bacteria are able to be transferred through saliva or even through the path where other liquids pass into the intestine. In addition, they can not only play a role in causing and aggravating intestinal inflammation, but they can also cause the same symptoms in the oral cavity[8,17,34,35]

Therefore, it is obvious that there is a two-way relationship, which is even considered complex, between periodontitis and intestinal dysbiosis. When microbial diversity is formed in both the oral and intestinal systems, it causes the systemic inflammation to intensify and eventually lead to more severe diseases related to these two systems in the body[11,36]. On the other hand, changes in the intestinal microbiome, especially when the ratio of Firmicutes to Bacteroidetes increases, can be recognized as an important indicator of dysbiosis[37]. This actually leads to the destruction of the physical and immune barriers of the intestine and the increase of systemic inflammation[38].

There are many other studies that indicate the possibility of transferring periodontitis-related bacteria to the intestine, causing the destruction of the intestinal barrier and increasing the risk of inflammatory bowel diseases[39].

It Is obvious that by making changes in the oral microbiome, it is an early marker for the diagnosis and prediction of digestive diseases including inflammatory bowel disease[8]. With the increase of pro-inflammatory cytokines such as IL-6 and TNF, etc., in both periodontitis and intestinal dysbiosis, it is concluded that systemic inflammation plays a significant role in the connection of both of these diseases[19,29].

In general, it can be stated that these findings, in turn emphasize that in case of a decision on targeted treatments the modification of the intestinal and oral microbiome will lead to help in reducing systemic inflammation as well as it can improve the condition of periodontitis and digestive diseases[14,40]. The application and use of probiotics as well as prebiotics can also be useful as a new treatment approach in the management of these diseases[11,41].

Findings	Details
Significant link between dysbiosis in the gut microbiome and periodontitis.	Changes in the gut microbiome are often found in patients with periodontitis.
Decrease in microbial diversity and increase in Firmicutes to Bacteroidetes ratio.	Indicator of severe microbial imbalance in periodontitis patients.
Dysbiosis exacerbates periodontitis through systemic inflammation.	Pro-inflammatory cytokines (IL-6, TNF, IL-17) are elevated, worsening the condition.
Elevated C-reactive protein (CRP) in periodontitis patients.	CRP levels indicate a direct link between systemic inflammation and dysbiosis.
Oral bacteria transferred to the gut contribute to inflammation.	Oral bacteria like Porphyromonas gingivalis aggravate both gut and oral inflammation.
Two-way relationship between gut and oral dysbiosis.	Inflammation in one system can worsen the condition in the other.
Increased Firmicutes/Bacteroidetes ratio as a marker of dysbiosis.	This change leads to greater intestinal inflammation and damage.
Transfer of periodontitis-related bacteria to the intestine increases risk of bowel disease.	This transfer weakens the intestinal barrier, raising the risk of inflammatory bowel diseases.

Modifying gut and oral microbiome can reduce inflammation and improve outcomes	Treatment approaches include targeting microbiome adjustments to reduce systemic inflammation.

Table 1: Based on the article results and discussion

Preventive and Management Instructions

Periodontitis and gastrointestinal (GI) microbiome dysbiosis are related to each other, and a two-pronged approach is needed for both their prevention and management regarding the occurrence of diseases, so then in this way, oral and intestinal health can be made possible in the best possible way. In fact, it can be said that a two-way management, as explained below, both reduces inflammation and makes the treatment results more satisfactory for both mentioned diseases[29,30].

1. Oral hygiene and regular dental care:

a. Maintaining dental hygiene is the basis for preventing periodontitis. Thus, if the teeth are brushed twice a day with toothpaste containing fluoride, floss is used regularly, and antibacterial mouthwashes are used, the growth of periodontal pathogens can be controlled and actually limited[42].

b. Professional cleaning of the teeth by a dentist and regular dental examinations that take place every 6 months can help early diagnosis and better management of gum disease[43].

2. Optimizing the gut microbiome:

a. By using a healthy diet that includes foods rich in fiber, grains, fruits, vegetables, etc., you can improve the healthy microbial diversity of the intestine[44].

b. Using a diet that is both anti-inflammatory and rich in omega-3 fatty acids such as fish oil and flax seeds, as well as using antioxidants including berries and leafy vegetables can not only reduce systemic inflammation but also It will also play a useful role in reducing oral inflammation. In this way, it is actually possible to reduce the level of cytokines including IL-6 and TNF, which are involved in periodontitis and intestinal dysbiosis[45,46,47].

c. The principled use of probiotics and prebiotics is not only useful for restoring but also for maintaining the balance of the intestinal microbiome, so that probiotics that are rich in Lactobacillus and Bifidobacterium species have the ability to modulate the immune responses of the intestinal and oral health[48,49].

3. Management of systemic inflammation:

a. Obviously, both periodontitis and intestinal dysbiosis are associated with increased systemic inflammation. Therefore, anti-inflammatory treatments, i.e. the use of non-steroidal drugs or cytokine inhibitors including IL-1 and TNF blockers for use in severe cases, can reduce the inflammatory response in the gums and intestines[50,51].

4. Management and treatment of digestive diseases:

a. If the patients with periodontitis are evaluated in relation to having or not having inflammatory bowel disease, it is better to identify their oral problems and take action regarding their management. This is because oral symptoms can be an early sign of inflammation of the digestive tract[29,52].

5. Lifestyle modifications:

a. Stress management can also reduce inflammation and promote overall health, which can subsequently improve gut and oral health. This can be done through activities such as yoga, meditation, exercise, etc[53].

b. Measures such as quitting smoking and reducing alcohol consumption can significantly improve problems related to periodontal and digestive health[54,55].

Conclusion

The findings of this systematic review reveal a complex and definitely two-way relationship between the digestive microbiome and periodontitis. Thus, this review clearly states that gut dysbiosis can exacerbate periodontal inflammation and vice versa, microbial translocation and systemic inflammation on the other hand are factors that act as key mechanisms. Oral microbiome including Porphyromonas gingivalis, etc., have been identified in the gut microbiota of patients with IBD. This puts a seal of approval on the microbial association between the oral cavity and the gut, and also the changed microbial ratio in the gut, one of the most important of which is the Firmicutes-to-Bacteroidetes ratio which is a very important indicator of this dysbiosis. If therapists

address the health of the oral and intestinal microbiomes through comprehensive treatment strategies and for an example try to manage these patients by prescribing probiotics as well as anti-inflammatory treatments, it can potentially reduce both systemic inflammation and other outcomes specially for periodontitis and digestive diseases. It should be noted that all the aforementioned claims emphasize the need for integrated treatment approaches.

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Conflict of Interest

The authors declare no conflict of interest.

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Ethics Statement

No human or animal subjects were involved in this study, and no ethical approval was required.

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