Journal of Dental Sciences 18 (2023) 972–975

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jds.com

Review article

The role of microbiome in the pathogenesis of oral-gut-liver axis between periodontitis and nonalcoholic fatty liver disease

Tsung-Po Chen [a,b], Hui-Chieh Yu [c], Wen-Yuan Lin [a,b], Yu-Chao Chang [c,d*]

[a] *Department of Family Medicine, China Medical University Hospital, Taichung, Taiwan*
[b] *School of Medicine, China Medical University, Taichung, Taiwan*
[c] *School of Dentistry, Chung Shan Medical University, Taichung, Taiwan*
[d] *Department of Dentistry, Chung Shan Medical University Hospital, Taichung, Taiwan*

Received 2 March 2023; Final revision received 14 March 2023
Available online 25 March 2023

KEYWORDS
Nonalcoholic fatty liver disease;
Periodontitis;
Gut microbiotas;
Oral-gut-liver axis

Abstract Periodontitis and nonalcoholic fatty liver disease (NAFLD) are two prevalent non-communicable diseases affecting people worldwide. The delicate interplay between oral microbiome, intestinal barrier, immune system, and liver is susceptible to disruption by environmental and genetic factors which could result in the onset of systemic diseases. The oral-liver and liver-gut axes have been proposed as the possible mechanisms to explain the links among these factors. Many evidences are mounting to support the role of imbalanced interactions between microbiota and immune system in the development of immune-mediated diseases. The emerging concept of the oral-gut-liver axis is gaining recognition as a means to explore the interconnections among NAFLD, periodontitis, and gut dysbiosis. There is substantial evidence indicating that oral and gut dysbiosis are the significant risk factors for liver disease. Therefore, the role of inflammatory mediators in linking these organs cannot be overlooked. Understanding these complex relationships is crucial in the development of effective strategies for the prevention and management of liver diseases.

* Corresponding author. School of Dentistry, Chung Shan Medical University, 110, Sec.1, Chien-Kuo N. Rd., Taichung, 40201, Taiwan.
E-mail address: cyc@csmu.edu.tw (Y.-C. Chang).

https://doi.org/10.1016/j.jds.2023.03.012

Introduction

In addition to caries, periodontitis is the most prevalent oral diseases with a gradually increasing prevalence worldwide.[1] The prevalence of periodontitis has significantly increased in Taiwan over the past 17 years.[2] Periodontitis is a chronic inflammatory disease that destroy the supporting tissues of teeth such as gingiva, cementum, alveolar bone, and periodontal ligament. It occurs as a result of a complex interaction between the subgingival biofilm and the host's immune-inflammatory response. In addition, many studies have indicated that periodontitis could cause systemic inflammatory diseases.[3] Oral cavity is the upper part of digestive system. From our previous studies by Taiwan's National Health Insurance Research Database, periodontitis could be positive associated with digestive system diseases such as peptic ulcer disease,[4] inflammatory bowel disease,[5] and pyogenic liver abscess.[6]

Nonalcoholic fatty liver disease (NAFLD) is a growing problem and also the most prevalent liver disease worldwide with an estimated global prevalence of 25%.[7] NAFLD manifests as a spectrum of liver phenotypes, ranging from simple steatosis to nonalcoholic steatohepatitis, liver fibrosis, and even hepatocellular carcinoma (HCC).[8] As the global campaign to eliminate hepatitis B and C virus infections continues, NAFLD is expected to become the leading cause of HCC. The increasing prevalence of obesity and type 2 diabetes is further fueling the disease burden of nonalcoholic steatohepatitis.[9] According to the report from Estes et al.,[10] about 27% of NAFLD cases will be classified as nonalcoholic steatohepatitis in 2030 compared to 20% in 2015. As a result, NAFLD-related liver disease and mortality will increase worldwide.[10,11]

NAFLD and periodontitis are two of the most widespread non-communicable diseases globally. The relationship between these two conditions and their link to other bodily systems are the focus of ongoing research. The oral-liver and liver-gut axes have been proposed. There is growing evidence to suggest that imbalances in the interactions between the microbiota and immunity may play a role in the development of a range of immune-mediated diseases. Recently, the idea of an interconnecting oral-gut-liver axis has been gaining traction and this concept is the subject of current research studies.[12–14] In this review, we briefly summarized the current state of knowledge on the oral-gut-liver axis.

Oral-liver axis

The oral cavity is home to a diverse community of bacteria primarily belonging to the phyla *Firmicutes, Fusobacteria, Proteobacteria, and Actinobacteria*.[15] These bacteria create complex ecosystems that are adapted to their unique environment, with certain commensal oral bacteria serving as the first line of defense against the colonization of exogenous pathogens. Imbalances in the interactions between the microbiota and immunity can contribute to the onset of immune-mediated diseases. Some oral bacteria, such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, have been linked to disorders beyond the oral cavity.[16] *Porphyromonas gingivalis, Treponema denticola*, and *Tannerella forsythia* are considered the key pathogens in the development of periodontitis.[12] Dysbiosis, or imbalances in the microbial community, can exacerbate the normally ecologically balanced biofilm that is associated with the maintenance of periodontal tissue homeostasis.[17]

Periodontitis has been identified as a potential risk factor for pyogenic liver abscess.[6] The oral microbiota is a complex ecosystem that contains over 500 different bacterial species. Previous reports have shown that periodontal pathogens commonly found inside the oral cavity *Fusobacterium necrophorum*[18] and *Prevotella* species[19] were detected in the liver abscess. The presence of periodontitis may increase the likelihood of liver abscess through bacteremia, which occurs when bacteria from the oral cavity enter the bloodstream and spread to distant organs, such as the liver.

There is also a potential link between periodontitis and NAFLD through the hematogenous spread of immunogenic factors and oral pathogenic bacteria from the periodontal tissues.[20,21] Individuals with periodontal disease exhibit an increase in circulating bacteria and lipopolysaccharides (LPS), derived from oral infections, compared to those with healthy periodontal tissue. Moreover, the host cells in the periodontium, triggered by immune responses to biofilm bacteria, escalate the emission of reactive oxygen species and pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α.[22] This potential liver damage caused by periodontitis may be transmitted to the liver via the bloodstream and contribute to the progression of nonalcoholic steatohepatitis and NAFLD.

Gut-liver axis

The gut microbiome plays a crucial role in the development and progression of NAFLD.[23] Disruption of the gut barrier, which is often caused by tight junction impairment, is prevalent in adults with NAFLD and leads to increased translocation of microbial products such as LPS into the portal circulation, resulting in endotoxemia and inducing hepatic inflammation.[24] The gut microbiome can also impact NAFLD through the regulation of bile acid metabolism and the production of short-chain fatty acids, ethanol, and choline.[25] Preclinical studies have shown evidence of the gut microbiome's causal role in the progression of liver disease in NAFLD.[26] The gut microbiomes of NAFLD patients are often dominated by members of the *Firmicutes* and *Bacteroides* phyla, with *Bacteroides* being associated with nonalcoholic steatohepatitis and *Ruminococcus* being linked to significant fibrosis.[25,27] As such, the gut microbiome may serve as a biomarker for NAFLD disease severity and provide new insights into the pathogenesis of NAFLD in the future.[28]

Possible mechanism linking oral-gut-liver axis

The relationship between the liver and the oral cavity can be complex and multi-faceted. One possible avenue of connection is through the gut, as a result of impaired intestinal permeability. This permeability issue can allow for the direct transfer of bacteria and their products, as well as

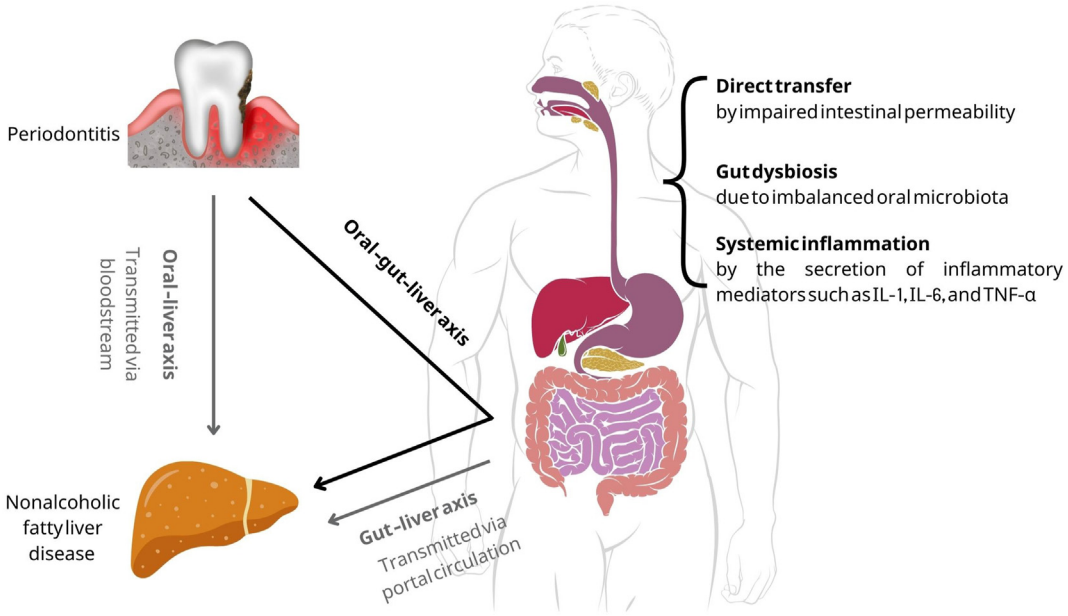

Figure 1 The proposed mechanism of oral-gut-liver axis could occur through the following pathways: (1) direct transfer of bacteria and their products. (2) gut dysbiosis due to imbalanced oral microbiota. (3) systemic inflammation by the secretion of inflammatory mediators.

inflammatory mediators, from the oral cavity to the bloodstream.[14] An imbalanced oral microbiota, which is enriched in virulence factors and thrives in an inflammatory environment, can further exacerbate the situation.[16] The decrease in gastric acid secretion can cause oral bacteria to translocate to the gut, leading to dysbiosis and disruption of bile acid regulation. Bile acids are essential for digestion and maintaining the health of both the gut microbiome and intestinal epithelial cells.[14] Different types of gut bacteria can affect the production of short chain fatty acids, which can have a significant impact on the risk of NAFLD. *Bacteroides* increases acetate and propionate production, and propionate trigger hepatic gluconeogenesis. *Firmicutes* increases butyrate production. All these metabolites are short chain fatty acids, which furtherly increase reaction of G-protein-couple receptor and glucagon-like peptide-1 (GLP-1).[25] GLP-1 increases expression of fatty acid β-oxidation. Taken together, this pathway may increase the risk of NAFLD.

Another possible mechanism is systemic inflammation, which can be triggered by the secretion of inflammatory mediators such as IL-1, IL-6, and TNF-α by oral bacteria. Furthermore, gut dysbiosis increased ethanol and its metabolite acetaldehyde in the intestinal lumen mediate.[26] These mediators can weaken the tight junctions of the intestine, leading to an increased translocation of microbial-associated molecular patterns and gut metabolites, such as trimethylamine.[12] These metabolites elicits intestinal and hepatic inflammatory responses, leading to progressive liver damage.[29]

The overproduction of pro-inflammatory cytokines by neutrophils and monocytes, in response to circulating LPS, can also contribute to chronic inflammation and oxidative stress. LPS furtherly triggers toll-like receptors (TLRs) family, such as TLR-4, which causes chronic inflammation and increases oxidative stress.[30] This increased production of reactive oxygen species by these immune cells can further deteriorate liver parenchymal tissue.[12]

Taken together, as illustrated in Fig. 1, the connection between the liver and the oral cavity can occur through multiple pathways, including gut dysbiosis, systemic inflammation, and the direct transfer of bacteria and their products. Understanding these complex relationships is important in developing strategies to prevent and manage liver diseases.

Conclusion

The oral-gut-liver axis is a concept that aims to understand the potential relationships between different organs, particularly the oral cavity, gut, and liver. Oral and gut dysbiosis have been identified as important risk factors for liver disease, and the role of inflammatory mediators in the connection between these organs cannot be ignored. It is believed that the link between the oral cavity and the liver is not just a result of shared risk factors but is also driven, to a large extent, by oral infections leading to liver injury. The role of periodontal treatment as a potential method for improving NAFLD through the reduction of endotoxin levels has been proposed,[31] but more research is needed to confirm these findings.

In conclusion, the oral-gut-liver axis is a complex and evolving area of study, and there are still many questions that remain unanswered. Further investigation is needed to better understand the mechanisms driving this connection and to develop more effective strategies for the prevention and management of liver disease.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

References

1. Petersen PE, Ogawa H. The global burden of periodontal disease: towards integration with chronic disease prevention and control. *Periodontol 2000* 2012;60:15—39.
2. Yu HC, Su NY, Huang JY, Lee SS, Chang YC. Trends in the prevalence of periodontitis in Taiwan from 1997 to 2013: a nationwide population-based retrospective study. *Medicine* 2017;96:8585.
3. Yang LC, Yu HC, Chang YC. The recent new findings of periodontal-systemic connection from Taiwan's National Health Insurance Research Database. *J Dent Sci* 2021;16:789—90.
4. Yu HC, Chen TP, Wei CY, Chang YC. Association between peptic ulcer disease and periodontitis: a nationwide population-based case-control study in Taiwan. *Int J Environ Res Publ Health* 2018;15:912.
5. Yu HC, Chen TP, Chang YC. Inflammatory bowel disease as a risk factor for periodontitis under Taiwanese national health insurance research Database. *J Dent Sci* 2018;13:241—7.
6. Yeh YT, Wang BY, Lin CW, et al. Periodontitis and dental scaling associated with pyogenic liver abscess: a population-based case-control study. *J Periodontal Res* 2018;53:785—92.
7. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016;64:73—84.
8. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. *JAMA* 2015;313:2263—73.
9. Kanwal F, Shubrook JH, Younossi Z, et al. Preparing for the NASH epidemic: a call to action. *Metabolism* 2021;122:154822.
10. Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. *Hepatology* 2018;67:123—33.
11. Estes C, Anstee QM, Arias-Loste MT, et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. *J Hepatol* 2018;69:896—904.
12. Albuquerque-Souza E, Sahingur SE. Periodontitis, chronic liver diseases, and the emerging oral-gut-liver axis. *Periodontol 2000* 2022;89:125—41.
13. Wang T, Ishikawa T, Sasaki M, Chiba T. Oral and gut microbial dysbiosis and non-alcoholic fatty liver disease: the central role of *Porphyromonas gingivalis*. *Front Med* 2022;9:822190.
14. Acharya C, Sahingur SE, Bajaj JS. Microbiota, cirrhosis, and the emerging oral-gut-liver axis. *JCI Insight* 2017;2:e94416.
15. Costalonga M, Herzberg MC. The oral microbiome and the immunobiology of periodontal disease and caries. *Immunol Lett* 2014;162:22—38.
16. Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. *Nat Rev Immunol* 2015;15:30—44.
17. Hajishengallis G, Lamont RJ. Beyond the red complex and into more complexity: the polymicrobial synergy and dysbiosis (PSD) model of periodontal disease etiology. *Mol Oral Microbiol* 2012;27:409—19.
18. Lei WY, Chang WH, Shih SC, Liu CJ, Shih CH. Pyogenic liver abscess with *Prevotella* species and *Fusobacterium necrophorum* as causative pathogens in an immunocompetent patient. *J Formos Med Assoc* 2009;108:253—7.
19. Yoneda M, Kato S, Mawatari H, et al. Liver abscess caused by periodontal bacterial infection with *Fusobacterium necrophorum*. *Hepatol Res* 2011;41:194-6.
20. Konkel JE, O'Boyle C, Krishnan S. Distal consequences of oral inflammation. *Front Immunol* 2019;10:1403.
21. Kuraji R, Sekino S, Kapila Y, Numabe Y. Periodontal disease-related nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: an emerging concept of oral-liver axis. *Periodontol 2000* 2021;87:204—40.
22. Cekici A, Kantarci A, Hasturk H, Van Dyke TE. Inflammatory and immune pathways in the pathogenesis of periodontal disease. *Periodontol 2000* 2014;64:57—80.
23. Leung C, Rivera L, Furness JB, Angus PW. The role of the gut microbiota in NAFLD. *Nat Rev Gastroenterol Hepatol* 2016;13:412—25.
24. Aron-Wisnewsky J, Vigliotti C, Witjes J, et al. Gut microbiota and human NAFLD: disentangling microbial signatures from metabolic disorders. *Nat Rev Gastroenterol Hepatol* 2020;17:279—97.
25. Sharpton SR, Ajmera V, Loomba R. Emerging role of the gut microbiome in nonalcoholic fatty liver disease: from composition to function. *Clin Gastroenterol Hepatol* 2019;17:296—306.
26. Loomba R, Seguritan V, Li W, et al. Gut microbiome-based metagenomic signature for non-invasive detection of advanced fibrosis in human nonalcoholic fatty liver disease. *Cell Metabol* 2017;25:1054—62.
27. Boursier J, Mueller O, Barret M, et al. The severity of nonalcoholic fatty liver disease is associated with gut dysbiosis and shift in the metabolic function of the gut microbiota. *Hepatology* 2016;63:764—75.
28. Sharpton SR, Schnabl B, Knight R, Loomba R. Current concepts, opportunities, and challenges of gut microbiome-based personalized medicine in nonalcoholic fatty liver disease. *Cell Metabol* 2021;33:21—32.
29. Tripathi A, Debelius J, Brenner DA, et al. The gut-liver axis and the intersection with the microbiome. *Nat Rev Gastroenterol Hepatol* 2018;15:397—411.
30. Martin-Mateos R, Albillos A. The role of the gut-liver axis in metabolic dysfunction-associated fatty liver disease. *Front Immunol* 2021;12:660179.
31. Kamata Y, Kessoku T, Shimizu T, et al. Efficacy and safety of PERIOdontal treatment versus usual care for Nonalcoholic liver disease: protocol of the PERION multicenter, two-arm, open-label, randomized trial. *Trials* 2020;21:291.