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Oral–Gut–Liver axis: A Novel Link in the Pathogenesis of Metabolic Dysfunction–Associated Steatotic Liver Disease

REVIEW
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ABSTRACT

Metabolic dysfunction–associated steatotic liver disease (MASLD) is a common chronic liver disease worldwide. It has become one of the leading reasons for liver transplants, and it is strongly linked to metabolic syndrome, obesity, insulin resistance, and type 2 diabetes. Despite growing awareness of its clinical impact, the mechanisms that drive MASLD progression to steatohepatitis and cirrhosis are not fully understood, and there is currently no approved medication to stop disease progression. Recent studies indicate that oral health issues, especially periodontal disease, may influence the progression and severity of MASLD. Periodontal disease, especially periodontitis, is a chronic inflammatory condition affecting the supporting structures of the teeth and is increasingly recognized as a potential contributor to systemic diseases. Recent research shows a notable link between MASLD and periodontal disease, driven by shared metabolic risk factors, chronic systemic inflammation, and microbial imbalance. The oral–gut–liver axis has emerged as a potential biological mechanism linking periodontal pathogens to liver inflammation and metabolic disorders. This narrative review summarizes current epidemiological evidence, explores the biological mechanisms behind the link between MASLD and periodontal disease, and discusses potential clinical implications for integrated patient care.

Keywords: Hepatic steatosis, patient care, periodontitis

Introduction

Metabolic dysfunction–associated steatotic liver disease (MASLD) is a common chronic disease characterized by excess fat in the liver, leading to liver dysfunction and systemic health problems. MASLD has become the leading cause of chronic liver disease worldwide, affecting about 25-30% of the global population. In a healthy person, liver fat comes from dietary free fatty acids and cholesterol, free fatty acids released from adipocytes through lipolysis, and fatty acids synthesized from glucose via de novo lipogenesis. In the liver, these fats are initially stored in lipid droplets; some are broken down by β-oxidation in mitochondrial membranes, while others are packaged into low-density lipoproteins and released into the bloodstream, helping to remove fat from the liver. During fat detoxification, the fat content in a healthy liver remains below 5% of its weight.[1-4]

An increase in dietary fat intake, elevated fatty acid production from adipocytes due to enhanced lipolysis in the context of insulin resistance, and increased de novo lipogenesis from fructose consumption all contribute to liver fat buildup. If detoxification functions in hepatocytes are impaired or insufficient, free fatty acids and/or cholesterol can accumulate in these cells. This accumulation causes metabolic stress in hepatocytes, leading to endoplasmic reticulum and mitochondrial stress, as well as the release of reactive oxygen species, inflammatory cytokines, and hepatokines. Besides hepatocytes, the liver comprises liver sinusoidal endothelial cells, Kupffer cells, immune cells (T and B cells), and hepatic stellate cells. Communication among these liver cells during abnormal glycolipid metabolism and hepatocyte stress, combined with gut dysbiosis, contributes to the pathophysiology of MASLD. These processes can activate Kupffer cells, a response further intensified by intestinal dysbiosis. Consequently, liver inflammation is triggered, which can progress to steatohepatitis. Meanwhile, stellate cells become activated and produce collagen, leading to fibrotic tissue formation. In later stages, the loss of hepatocytes due to necrosis and apoptosis, together with existing fibrosis, advances to cirrhosis.[5-12]

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In summary, MASLD spans a disease spectrum from simple hepatic steatosis to metabolic dysfunction-associated steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. The condition is strongly associated with metabolic disorders, including obesity, type 2 diabetes mellitus, dyslipidemia, and insulin resistance.

Periodontal disease is another highly prevalent chronic inflammatory condition, characterized by the progressive destruction of the periodontal ligament and alveolar bone supporting the teeth.[13] Severe periodontitis affects nearly 10-15% of the global population and has been associated with various systemic diseases, including obesity, cardiovascular disease, diabetes mellitus, adverse pregnancy outcomes, and respiratory diseases.[14-16]

Increasing evidence suggests a possible bidirectional relationship between periodontal disease and metabolic disorders. Chronic periodontal inflammation can contribute to the systemic inflammatory burden, while metabolic disorders may exacerbate periodontal tissue destruction.[17-19] More recently, attention has focused on the potential association between periodontal disease and MASLD. Shared risk factors such as obesity, insulin resistance, and chronic inflammation suggest that these 2 conditions may be interconnected. [20-25] Understanding the possible bidirectional relationship between periodontal disease and MASLD is important for both hepatologists and dental professionals, as integrated management strategies may help reduce systemic inflammatory burden and improve patient outcomes.

Early cross-sectional studies in the past decade investigating nonalcoholic fatty liver disease (NAFLD), the former term for MASLD, showed a higher prevalence and severity of periodontitis among individuals with hepatic steatosis. Interestingly, a large population-based study found that individuals with severe periodontitis had significantly higher odds of developing NAFLD compared to those without periodontal disease, even after adjusting for confounding variables such as age, smoking, and metabolic risk factors.[20] This investigation by Akinkugbe and colleagues in 2017 was the first to identify periodontitis as an independent risk factor for NAFLD incidence in a population-based sample. Another study analyzing data from an epidemiological survey and a clinical study found that NAFLD is associated with periodontitis and that this association is stronger in patients with significant liver fibrosis.[21]

MAIN POINTS

- Metabolic dysfunction-associated steatotic liver disease (MASLD) is closely associated with obesity, insulin resistance, and type 2 diabetes and represents a growing global health challenge.
- Emerging evidence suggests that periodontitis may contribute to MASLD through shared metabolic risk factors and chronic systemic inflammation.
- The oral–gut–liver axis provides a potential mechanistic framework linking periodontal dysbiosis to hepatic inflammation and metabolic dysfunction.
- Recognition of periodontal health may contribute to a more comprehensive, multidisciplinary approach to the management of patients with MASLD.
- Future studies are needed to determine whether periodontal assessment and treatment can improve outcomes in patients with MASLD.

More recent studies focusing specifically on MASLD have demonstrated comparable findings. Patients with MASLD often exhibit poorer oral health, including increased probing pocket depth, greater clinical attachment loss, and fewer functional teeth.[22-25] In addition, several cohort studies suggest that periodontal disease may be associated with increased liver fibrosis and disease severity in individuals with MASLD.[19,21,26] Moreover, in a recent randomized controlled study, periodontal treatment induced a short-term reduction in liver enzyme levels in patients with MASLD, further suggesting an association.[27]

Although most studies demonstrate an association rather than causality, the consistency of epidemiological findings suggests a meaningful relationship between these 2 conditions. The link between periodontal disease and MASLD is thought to involve several biological pathways. The key mechanisms include systemic inflammation, microbial translocation, metabolic dysregulation, and changes in the oral and gut microbiomes.

Periodontitis is characterized by a chronic inflammatory response driven by pathogenic bacterial biofilms. Chronic marginal periodontitis is the most common microbial disease in humans.[14,28] Periodontal inflammation often results in superficial ulcers on the gingival sulcus, where blood capillaries are exposed to microbial films. Infection with *Porphyromonas gingivalis* (*P. gingivalis*) is the primary cause of periodontitis.[29] Infected periodontal tissues release pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), which can enter the systemic circulation. Infection with high-virulence strains of *P. gingivalis* may produce large amounts of lipopolysaccharide and TNF-α, leading to inflammation not only of the local gingiva but also of other systemic organs.[30,31] Additionally, *P. gingivalis* can readily enter the bloodstream from the gingiva following procedures such as tooth brushing, chewing, subgingival irrigation, and dental extractions.[32-35] Such bacteremia may stimulate Kupffer cells and induce steatohepatitis. These inflammatory mediators can also increase systemic insulin resistance, thereby worsening hepatic steatosis and fibrosis. In this context, treating periodontitis may help slow the progression of MASLD. Few interventional studies suggest that periodontal treatment can improve systemic inflammatory markers and metabolic parameters. Improving periodontal health has been associated with lower levels of systemic inflammatory cytokines and better glycemic control.[36] A recent animal study using nisin, a lantibiotic, to target periodontopathogens mitigated bacterial exposure, lipid accumulation, and malondialdehyde accumulation in the liver.[37]

Both periodontitis and MASLD are associated with endothelial dysfunction and inflammation and share a common etiologic background, including unhealthy nutrition, dysbiosis, and metabolic dysfunction.[38] Metabolic syndrome or type 2 diabetes are core criteria for MASLD diagnosis and are tightly linked to periodontal disease through insulin resistance and chronic subclinical inflammation. This shared inflammatory and metabolic dysfunction profile explains the interplay between periodontal and liver health.[38] The association between MASLD and periodontitis may be bidirectional. In this regard, the role of MASLD in the development and progression of periodontitis is also important. Elevated systemic

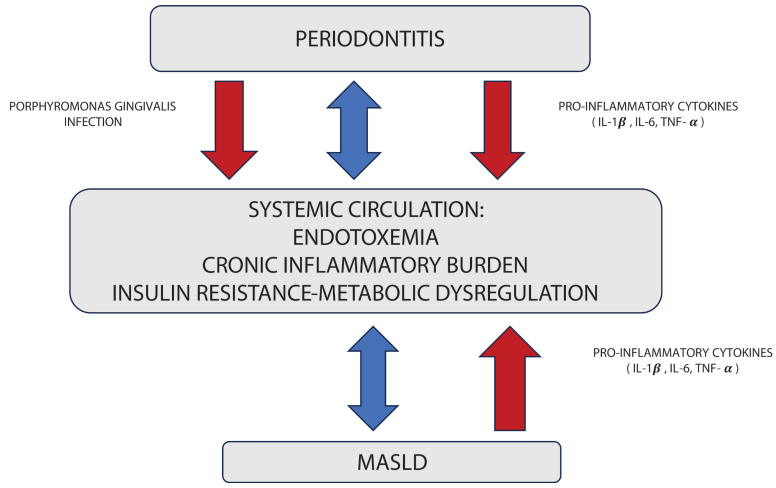

Figure 1. The link between periodontitis and MASLD.

cytokines in patients with MASLD, especially in those with steatohepatitis and beyond, can contribute to tissue destruction by increasing inflammatory cytokine levels, collagenase activity, and matrix metalloprotease activity, leading to immune dysfunction and potentially increasing the risk of periodontitis. Conversely, advanced periodontitis can worsen liver health by causing systemic inflammation. Thus, there is a 2-way negative connection between periodontal disease and liver disease due to their inflammatory nature.[39,40]

Growing evidence linking MASLD to oral health underscores the need for a multidisciplinary approach that involves dental and medical professionals. Dentists should recognize that periodontal disease can contribute to systemic inflammatory conditions, including liver disease. Similarly, physicians managing MASLD should consider oral health assessments as part of comprehensive patient care. Early detection and treatment of periodontal disease may help reduce systemic inflammation and improve overall health in patients with MASLD.[28,38-43]

Although disease-specific periodontal surveillance intervals for MASLD patients have not been standardized, current periodontal maintenance guidelines support individualized recall intervals based on risk stratification rather than fixed surveillance schedules. According to ERP S3-level clinical practice guideline recommendations, supportive periodontal care intervals should range from 3 to 12 months, depending on periodontal and systemic risk profiles. In MASLD patients with concomitant periodontitis and metabolic comorbidities such as diabetes or obesity, supportive periodontal care every 3-4 months may be reasonable, whereas clinically stable individuals may be followed at 6-12 month intervals.[44,45]

Conclusion

In conclusion, the link between MASLD and oral health is increasingly recognized in scientific research. Chronic inflammation, microbial translocation, and metabolic dysregulation appear to be the primary mechanisms linking periodontal disease to MASLD progression (Figure 1). Although current evidence shows a strong correlation, more longitudinal and interventional studies are needed to establish causality and determine whether periodontal treatment can influence MASLD outcomes.

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