

Chronic Periodontitis and Non-Alcoholic Fatty Liver Disease: Recent Advances in Mechanisms of Association

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Background: Chronic periodontitis (CP) and non-alcoholic fatty liver disease (NAFLD) are increasingly prevalent worldwide. Although mechanisms remain incompletely defined, recent studies suggest a close association between these two diseases. This review systematically outlines potential links between periodontitis and NAFLD, emphasizing their pathological mechanisms and interactions within an oral–gut–liver framework.

Methods: We reviewed observational, interventional, and mechanistic studies evaluating associations between periodontal status/treatment and NAFLD-related outcomes, integrating evidence on dysbiosis, inflammatory mediators, microbial metabolites, oxidative stress, microRNA regulation, and gut barrier function.

Results: Across epidemiological studies, periodontitis is associated with higher risk and greater severity of NAFLD. Mechanistically, oral dysbiosis, especially enrichment of oral pathobionts, is linked to hepatic steatosis and fibrosis. Translocation of microbial products and the resulting cytokine release drive systemic inflammation, impair gut barrier integrity, and induce hepatocellular injury. Microbial metabolites (such as short-chain fatty acids (SCFAs) and trimethylamine N-oxide (TMAO)) and oxidative stress contribute to metabolic dysregulation. Emerging evidence suggests that microRNAs (miRNAs) function as epigenetic regulators linking periodontal inflammation and bone remodeling to immune-metabolic pathways relevant to non-alcoholic fatty liver disease (NAFLD). However, direct evidence on whether treating periodontitis can improve NAFLD outcomes remains limited. Despite heterogeneity in study designs and diagnostic criteria, cumulative evidence supports periodontitis as a modifiable risk factor for the progression of NAFLD.

Conclusion: CP and NAFLD appear to be linked through systemic inflammation, dysbiosis, and metabolic disturbances. Future research should prioritize microbiome modulation, advance interdisciplinary care models, and develop personalized prevention and treatment strategies. Integrating oral and liver health within comprehensive management may provide new options for preventing and treating these frequently coexisting diseases.

Keywords: periodontitis, non-alcoholic fatty liver disease, NAFLD, oral-gut-liver axis, dysbiosis, inflammatory mediators

Introduction

Chronic periodontitis (CP) and non-alcoholic fatty liver disease (NAFLD) are prevalent chronic conditions that significantly impact global public health. CP is characterized by chronic gingival and periodontal tissue inflammation, primarily driven by pathogenic microorganisms such as *Porphyromonas gingivalis*. Approximately 50% of adults worldwide—particularly those in middle-aged and older populations—are affected by CP. Beyond oral health, this condition contributes to systemic diseases, including cardiovascular disease, diabetes, and Alzheimer's disease, via inflammatory pathways.¹

NAFLD, a metabolic disorder defined by abnormal fat accumulation in the liver, can progress from simple fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH), potentially leading to liver fibrosis, cirrhosis, or hepatocellular

carcinoma.² As obesity, diabetes, and metabolic syndrome become increasingly common, NAFLD has emerged as the most prevalent chronic liver disease globally.³

Recent studies suggest a potential link between chronic periodontitis and NAFLD, with chronic inflammation serving as a bridge between these two diseases. The interplay between oral and liver health can be understood through the “oral-gut-liver axis” and microbial metabolic pathways. Dysbiosis of the oral microbiome due to periodontitis may exacerbate NAFLD by inducing systemic inflammation and intestinal barrier dysfunction.^{4,5} Moreover, microbial metabolites, such as short-chain fatty acids and endotoxins, play crucial roles in this process.⁴

Emerging research indicates that microRNAs (miRNAs) are key regulators of periodontal inflammation and bone remodeling. Clinical trials demonstrate that gingival crevicular fluid miRNAs, including miR-21-5p, miR-7a, and miR-100-5p, exhibit predictive changes during orthodontic movement, suggesting their potential as biomarkers and upstream regulators that link immune, metabolic, and redox pathways within the oral-gut-liver axis.⁶ Periodontal disease management also influences systemic inflammation; for example, chlorhexidine adjunctive therapy has been shown to significantly reduce peri-implantitis bleeding and pathogenic bacteria,⁷ potentially offering downstream benefits for gut barrier integrity and hepatic inflammation throughout the oral-gut-liver axis.

However, comprehensive analyses of the multiple mechanisms—such as microbial metabolites, cytokine cascades, oxidative stress, and interactions within the oral-gut-liver axis—driving NAFLD development and progression remain limited. Further research is essential to elucidate the relationships between systemic inflammation and metabolic dysregulation. This review aims to: (1) assess the epidemiological and clinical evidence linking chronic periodontitis with NAFLD; (2) explain the mechanisms underlying this link, focusing on inflammatory mediators, microbial metabolites, oxidative stress, and communication along the oral-gut-liver axis; and (3) identify knowledge gaps and propose testable hypotheses for future research targeting these mediators.

Methods

Literature Search and Study Selection

A comprehensive literature search was conducted using PubMed/MEDLINE and Web of Science databases, covering publications from 2000 to 2025. The search strategy utilized both controlled vocabulary and free-text terms related to the following topics: periodontitis, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), and the oral-gut-liver axis. Specific terms included inflammation, dysbiosis, microbial metabolites, oxidative stress, and gut barrier function.

Eligibility Criteria

We included human observational and interventional studies while also incorporating animal and in vitro studies as supportive mechanistic evidence when relevant. These studies indicate a close relationship between periodontal disease assessment in adults and non-alcoholic fatty liver disease (NAFLD) as well as non-alcoholic steatohepatitis (NASH), with NAFLD/NASH diagnosis relying on imaging, histology, or validated non-invasive scoring systems. The exposures or interventions we focused on primarily involved periodontal status, severity, and therapy, compared to periodontal health, lesser disease severity, and standard or alternative care. The primary outcomes concentrated on the incidence and severity of NAFLD/NASH and related biomarkers. Additionally, the mechanistic endpoints encompassed inflammatory responses, microbiome dysbiosis, endotoxemia, gut barrier integrity, metabolites, oxidative stress, and microRNAs.

The Correlation Study Between Periodontitis and Non-Alcoholic Fatty Liver Disease

Periodontitis as a Risk Factor for NAFLD

Recent research has increasingly focused on the relationship between periodontitis and non-alcoholic fatty liver disease (NAFLD), revealing a significant association between the two conditions.^{8–17} Evidence suggests that periodontitis may serve as a potential risk factor for the development of NAFLD.

For instance, in a retrospective cohort study involving 129,087 participants, Joo et al identified a significant correlation between NAFLD scores and the incidence of chronic periodontitis. They reported that when the fatty liver index (FLI) was at uncertain and high levels, the Hazard Ratios (HR) for developing chronic periodontitis were 1.19 and 1.32, respectively.⁸ Additionally, Weintraub et al highlighted a significant association between NAFLD and moderate to severe periodontitis, along with untreated caries. Their findings indicated that the odds ratio (OR) for moderate to severe periodontitis was 1.54, while the OR for untreated caries was 1.51.⁹ In a prospective study, Akinkugbe et al observed that after 7.7 years of follow-up, patients with periodontitis demonstrated a significantly higher incidence of NAFLD compared to those without periodontitis, further supporting the notion of periodontitis as a risk factor for NAFLD.¹⁰ Moreover, Alazawi et al found that the relationship between periodontitis and NAFLD was particularly pronounced in patients with hepatic fibrosis. Their study revealed that the incidence of periodontitis among patients with non-alcoholic steatohepatitis (NASH) was significantly higher than that in non-NASH patients.¹¹

The Impact of Oral Microbiota on NAFLD

Periodontitis is recognized as a clinical manifestation of oral microbial dysbiosis, characterized by an imbalance in the oral microbiome. Recent studies have demonstrated that both specific periodontal pathogens and the resulting periodontal tissue destruction contribute to the development of non-alcoholic fatty liver disease (NAFLD) through interconnected pathways.^{12–16}

For instance, Tonomura et al conducted a pioneering study revealing a critical association between oral pathogens and non-alcoholic steatohepatitis (NASH). Their findings indicated that Cnm-positive *Streptococcus mutans* (*S. mutans*, Cnm+) was significantly enriched in patients with NASH, correlating positively with liver fibrosis severity. Additionally, NASH patients were found to have fewer remaining teeth than healthy individuals, shedding light on the oral microbiome's impact on liver pathology.¹²

Experimental studies investigating these mechanisms further substantiate this link. For example, research using the TW871 strain of *Streptococcus mutans* in high-fat diet mouse models demonstrated that intravenous injection of this strain significantly accelerated NASH progression.^{13,14} Infected mice exhibited increased liver weight, inflammatory cell infiltration, and fibrosis. Notably, the severity of NASH worsened progressively with prolonged infection duration. Epidemiological studies reinforce the complex relationship between oral health and liver metabolism. Ahmad et al found that periodontal health status was significantly correlated with liver function abnormalities, especially among male populations.¹⁵ Specifically, deep periodontal pockets were linked to elevated liver enzyme levels (ALT) and a higher incidence of metabolic syndrome. Additionally, Iwasaki et al confirmed that deep periodontal pockets (PPD \geq 4 mm) were significantly more prevalent in NAFLD patients than in non-NAFLD individuals (86.7% vs 72.9%, $p < 0.05$). After adjusting for confounding factors, deep periodontal pockets were independently associated with NAFLD (adjusted odds ratio = 1.881, 95% CI: 1.184–2.987, $p < 0.01$), indicating that they may serve as an independent risk factor for NAFLD.¹⁶

The Relationship and Controversy Between Periodontitis and NAFLD

Research has shown that there may be an association between periodontitis and non-alcoholic fatty liver disease (NAFLD), but there remains significant controversy in this field, particularly regarding the strength and consistency of these associations.¹⁷ On one hand, Alazawi et al pointed out that there is a significant relationship between periodontitis and NASH (non-alcoholic steatohepatitis) as well as hepatic fibrosis, especially in patients confirmed through biopsy, where the incidence of periodontitis is notably higher than in those without NASH. However, after considering the factors of metabolic syndrome, the significance of this association diminishes. This finding highlights the potential confounding or mediating role of metabolic factors in the relationship between periodontitis and NAFLD.¹¹

On the other hand, a meta-analysis conducted by Xu and Tang, which integrated data from seven studies involving 192,815 participants, indicated that there is no significant overall association between periodontitis and NAFLD (OR=1.04, 95% CI: 0.97–1.12). However, the study also revealed a moderate degree of heterogeneity among the studies ($I^2=58\%$), noting that only cohort studies demonstrated a non-significant risk trend, while cross-sectional and case-control studies failed to find this association.¹⁸ This heterogeneity may stem from methodological differences such as the inclusion criteria for participants and study design.

Further research by Akinkugbe et al explored the impact of racial differences on the association between periodontitis and NAFLD. The study found that the incidence of NAFLD is higher among Hispanic/Latino populations; however, the relationship between periodontitis and NAFLD exhibits inconsistent patterns across different ethnic groups, suggesting that genetic, cultural, and environmental factors may significantly influence this association.¹⁹

Overall, while there is some evidence for an association between periodontitis and NAFLD, this relationship is affected by environmental and biological factors. This complexity necessitates future studies to establish consistent definitions and methodologies, and to emphasize longitudinal and experimental research to clarify the causal links and mechanisms between periodontitis and NAFLD.

The Oral–Gut–Liver Axis: Mechanistic Pathways Linking Periodontitis and NAFLD

Table 1 provides an overview of the molecular landscape linking oral and hepatic pathology, summarizing key biomarkers, their specific roles, interactions mediated by the axis, and their clinical significance. The following sections will further detail these relationships, explaining how changes in oral microbiota influence hepatic pathophysiology through both direct and indirect mechanisms.

Dual Mechanisms of the Oral–Gut–Liver Axis

Oral microbiota dysbiosis plays a critical role in the onset and progression of non-alcoholic fatty liver disease (NAFLD) through two distinct yet interconnected pathways: a direct bacterial translocation pathway and an indirect gut-mediated pathway.

In the direct translocation pathway, oral pathogenic microorganisms, such as *Porphyromonas gingivalis*, disrupt the oral mucosal barrier and enter systemic circulation, reaching the liver directly. Upon arrival, these bacteria alter hepatic metabolism and inflammatory responses. Animal studies have demonstrated that *P. gingivalis* can translocate to the liver and modulate hepatic glycogen synthesis via the Akt/GSK-3 β pathway, providing a mechanistic basis for the direct crosstalk between oral infections and liver pathology.²⁰

The indirect pathway involves shifts in gut microbiota composition due to oral dysbiosis, which weakens intestinal barrier integrity. This alteration increases the influx of bacterial toxins and metabolites (particularly lipopolysaccharide, LPS) into the liver. Given that the liver is the first organ to receive nutrient-rich blood from the intestines via the portal venous system, it is especially vulnerable to gut-derived toxins. This vulnerability explains why increased intestinal permeability can preferentially trigger hepatic inflammation and metabolic disturbances.⁴⁰

Evidence from animal models demonstrates the complete oral–gut–liver pathway: transplantation of salivary microbiota from periodontitis patients into mice fed a high-fat diet exacerbates gut dysbiosis and barrier impairment, promotes the translocation of bacterial products—including LPS—along the gut–blood–liver axis, and worsens NAFLD phenotypes.²³ At the molecular level, circulating LPS mediates hepatic inflammation primarily through the activation of TLR4 signaling across multiple hepatic cell types. In Kupffer cells, LPS stimulation induces the release of pro-inflammatory cytokines (eg, IL-6, IL-1 β) and chemokines. In hepatic stellate cells, it promotes α -SMA expression and cellular activation, accelerating fibrogenesis; these mechanisms have been validated in models of alcoholic steatohepatitis.²⁴ The increase in IL-6 is associated with LPS, which promotes the upregulation of IL-6 through TLR4 activation, enhancing systemic inflammation. This indicates that controlling LPS levels in the oral cavity may help reduce IL-6 and potentially offer protective effects against NAFLD (see Table 1). Furthermore, TLR4 signaling in hepatocytes contributes to obesity-related inflammation and insulin resistance; LPS and saturated fatty acids can synergistically activate this pathway, exacerbating hepatic lipid accumulation and inflammatory responses.^{25,26}

From a therapeutic perspective, modulating periodontal microecology may reduce local and systemic LPS burden along with inflammatory mediators in animal models.²⁸ However, translating these findings into improvements in hepatic outcomes requires further validation through cross-organ clinical endpoints. Overall, TLR4 signaling serves as a central hub in both pathways and represents a promising therapeutic target.

Table 1 Key Biomarkers and Mechanistic Factors Linking Periodontitis and NAFLD

Marker/Factor	Manifestations in Periodontitis	Manifestations in NAFLD	Mechanistic Interplay and Axis Links	Clinical Significance
Porphyromonas gingivalis ^{20–22}	Oral pathogen; may escape via mucosal breaches/bacteremia; antimicrobial peptide-targeted inhibition reduces bone loss and inflammation (animal)	Affects hepatic glycogen synthesis and Akt/GSK-3 β signaling; associated with lipid accumulation, insulin resistance, and aggravated fibrosis	Two pathways: hematogenous/hepatic translocation (direct evidence); swallowing→gut dysbiosis→metabolic endotoxemia. Time sequence: microbiota changes precede inflammation, establishing causality	Key pathogenic factor and intervention target; keystone pathogen concept: low colonization but high impact; suggests oral antimicrobial strategies
Lipopolysaccharide (LPS) ^{21,23,24}	Oral/gut-derived gram-negative bacteria produce LPS; barrier disruption and bacterial swallowing increase endotoxin entry	Activates hepatic TLR4→pro-inflammatory and pro-fibrogenic; exacerbates steatosis in obesity/NAFLD	Axis: LPS via portal vein to liver; triggers TLR4 on Kupffer cells and HSCs. Metabolic endotoxemia: similar effects to high-fat diet	Supports “metabolic endotoxemia” concept; oral source control and anti-endotoxin strategies
TLR4 ^{24–26}	Indirectly upregulated by LPS and PAMPs from periodontal pathogens	Hepatic TLR4 mRNA upregulated in NASH vs NAFL; drives insulin resistance, steatosis, and HSC-mediated fibrosis; plasma LPS and free fatty acids elevated	Axis core: oral/gut-derived LPS→liver; hepatocyte TLR4 promotes metabolic dysfunction; Kupffer cell and HSC TLR4 promotes inflammation/fibrosis	Disease stratification: TLR4 upregulation distinguishes NAFL from NASH; therapeutic target for hepatocyte-specific inhibition
IL-6 ^{21,24,27}	Systemic inflammatory factor elevated; significantly decreased after periodontal intervention (human trial)	Released by hepatic macrophages; pro-inflammatory; promotes insulin resistance	LPS→TLR4→IL-6 upregulation; systemic inflammation amplification. Tissue-specific: IL-6 elevated in small intestine following oral pathogen exposure	Systemic inflammation biomarker; periodontal intervention-mediated IL-6 reduction potentially beneficial for NAFLD
IL-1β ^{24,28}	Upregulated in periodontitis; targeted P. gingivalis clearance reduces IL-1 β and TNF- α (animal)	Key mediator of hepatic inflammation and tissue injury	LPS→TLR4→IL-1 β ; inflammasome-mediated activation. Intestinal response: upregulation tendency following oral pathogen exposure	Pro-inflammatory driver; intervention target for both oral and hepatic inflammation
Chemokines (CCL2, CXCL1) ²⁴	Promote inflammatory cell infiltration in periodontal tissues	Recruit monocytes/macrophages and neutrophils to liver	LPS-activated Kupffer cells secrete CCL2/CXCL1→inflammatory cell recruitment	Facilitate hepatic inflammatory infiltration; potential anti-inflammatory targets
Tjp1/ZO-1 (tight junctions) ^{21,22}	Oral pathogens induce tight junction protein downregulation	Barrier dysfunction; intestinal permeability increase; endotoxin translocation	P. gingivalis→gut dysbiosis→tight junction disruption→enhanced LPS translocation. Molecular: tjp-1 and occludin mRNA downregulation at 48h	Barrier integrity biomarker; restoration may reduce metabolic endotoxemia; causality established
Akp3 (IAP) ²⁹	Intestinal IAP dephosphorylates LPS for detoxification; maintains microbiota homeostasis	IAP deficiency→reduced LPS detoxification→enhanced endotoxemia	IAP-LPS detoxification axis: reduced IAP activity→increased inflammatory burden	Barrier protective factor; IAP supplementation as therapeutic intervention
Gut microbiota ^{21–23}	Oral P. gingivalis administration→gut dysbiosis; Bacteroidetes expansion, Firmicutes reduction; enhanced endotoxemia and barrier dysfunction (animal)	Dysbiosis associated with NAFLD; gram-negative bacteria increase→endotoxin elevation	Keystone pathogen mechanism: P. gingivalis triggers dysbiosis→Bacteroidetes \uparrow , Firmicutes \downarrow →barrier dysfunction→LPS translocation→TLR4 activation	Rationale for microbiota-targeted interventions; keystone concept supports targeted oral therapy despite low bacterial burden
Th17/IL-23R+ cells ^{30,31}	Total Th17 cell proportions unchanged in chronic periodontitis, but Th17IL-23R+ cells significantly increased in peripheral blood	IL-17RA upregulated in NASH patients; participates in hepatic inflammation and fibrogenesis through hepatic stellate cell activation	Chronic periodontitis→IL-23R+ Th17 cell activation→enhanced pro-inflammatory phenotype; systemic circulation enables cross-tissue immune effects. Total Th17 levels unaffected, but functional subset altered	IL-23R+ Th17 subset elevation indicates enhanced pro-inflammatory potential; selective targeting of IL-23 pathway may modulate systemic inflammation
TMAO ^{32,33}	Periodontal-gut microbiota interaction may influence TMA/TMAO metabolism (limited evidence)	Via FXR suppression→ \uparrow lipogenesis + \uparrow inflammation; promotes oxidative stress and inflammation with limited structural liver damage	Proposed pathway: Altered gut microbiota→modified TMA production→FMO3→TMAO→bile acid dysregulation→FXR inhibition	Potential pro-inflammatory metabolite biomarker; mechanistic links require further investigation
SCFAs (acetate/propionate/butyrate) ^{34–39}	Context-dependent: At physiologic gut concentrations, SCFAs are anti-inflammatory and barrier-protective; millimolar butyrate reported cytotoxic to gingival epithelial cells in vitro	At physiological concentrations: anti-inflammatory via HDAC inhibition; barrier-protective; improves glucose metabolism and insulin sensitivity	Dose-dependent effects: physiological levels promote anti-inflammatory and barrier functions via GPR41/43/109A and HDAC inhibition. Microbiota source: Clostridiales reduction decreases beneficial SCFA production	Site and dose-dependent: Beneficial in gut at physiological levels; potentially detrimental at high oral concentrations; therapeutic target for microbiota restoration

Abbreviations: Akp3 (IAP), Alkaline Phosphatase 3 (Intestinal Alkaline Phosphatase); CCL2, C-C Motif Chemokine Ligand 2; CXCL1, C-X-C Motif Chemokine Ligand 1; FXR, Farnesoid X Receptor; FMO3, Flavin-containing Monooxygenase 3; GPR, G Protein-Coupled Receptor; HSCs, Hepatic Stellate Cells; IL, Interleukin; IL-1 β , Interleukin 1 beta; IL-6, Interleukin 6; LPS, Lipopolysaccharide; NAFL, Non-Alcoholic Fatty Liver; NAFLD, Non-Alcoholic Fatty Liver Disease; NASH, Non-Alcoholic Steatohepatitis; PAMPs, Pathogen-Associated Molecular Patterns; SCFAs, Short-Chain Fatty Acids; Th17, T Helper 17 cells; TMA, Trimethylamine; TMAO, Trimethylamine N-oxide; TLR4, Toll-Like Receptor 4; TNF- α , Tumor Necrosis Factor alpha; ZO-1, Zonula Occludens-1.

Intestinal Permeability: Critical Mediator of the Indirect Pathway

Swallowed oral pathogens such as *Porphyromonas gingivalis* reshape ileal microbiota while simultaneously down-regulating epithelial tight junction proteins (e.g., ZO-1/Tjp1 and occludin) and intestinal alkaline phosphatase (Akp3). This process compromises barrier function and elevates serum endotoxin levels. In the single-gavage mouse model, *P. gingivalis* DNA is undetectable in blood, indicating that endotoxemia originates predominantly from dysbiotic gut microbiota rather than direct bacteremia.²¹ The resulting portal LPS flux activates hepatic TLR4 signaling in Kupffer cells, hepatocytes, and hepatic stellate cells, promoting pro-inflammatory cytokine release, insulin resistance, and fibrogenesis.^{24–26} Meanwhile, patients with chronic periodontitis exhibit an increased IL-23R+ Th17 subset in peripheral blood, while the total Th17 cell proportions remain unchanged.³⁰ This observation suggests a systemic immune skew that may synergize with gut-derived lipopolysaccharides (LPS) to amplify hepatic inflammation and metabolic dysfunction. Table 1 shows how the downregulation of tight junction proteins Tjp1 and ZO-1 in periodontitis influences NAFLD by enhancing endotoxin translocation, underscoring the importance of maintaining intestinal barrier integrity.

Recent analyses underscore the bidirectional nature of the gut–liver inflammatory axis, with barrier dysfunction serving as a key mechanism for oral–systemic signal propagation.⁴¹ Thus, abnormal intestinal permeability is not merely a conduit for endotoxin translocation but a central mediator that amplifies inflammatory and metabolic crosstalk between periodontitis and NAFLD. This interplay may potentially establish a self-perpetuating cycle of dysbiosis, permeability, and inflammation. Figure 1 provides a comprehensive network view of these molecular interactions, illustrating how key biomarkers from Table 1 functionally connect periodontitis and NAFLD through the oral-gut-liver axis, with emphasis on the temporal sequence and multicellular targets involved in disease progression.

Epigenetic Regulation: MicroRNAs as Mechanosensitive Mediators

Mechanically induced miRNA reprogramming represents a distinct pathway linking periodontal inflammation to NAFLD, separate from microbial translocation and barrier dysfunction.^{6,42,43} In a randomized orthodontic trial, researchers observed increased levels of gingival miR-21-5p, miR-7a-2-3p, and miR-100-5p, which correlated with clinical indicators such as bleeding and bone remodeling. This finding indicates that these mechanosensitive periodontal

Oral-Gut-Liver Axis Network Molecular markers connecting periodontitis, gut dysbiosis, and NAFLD

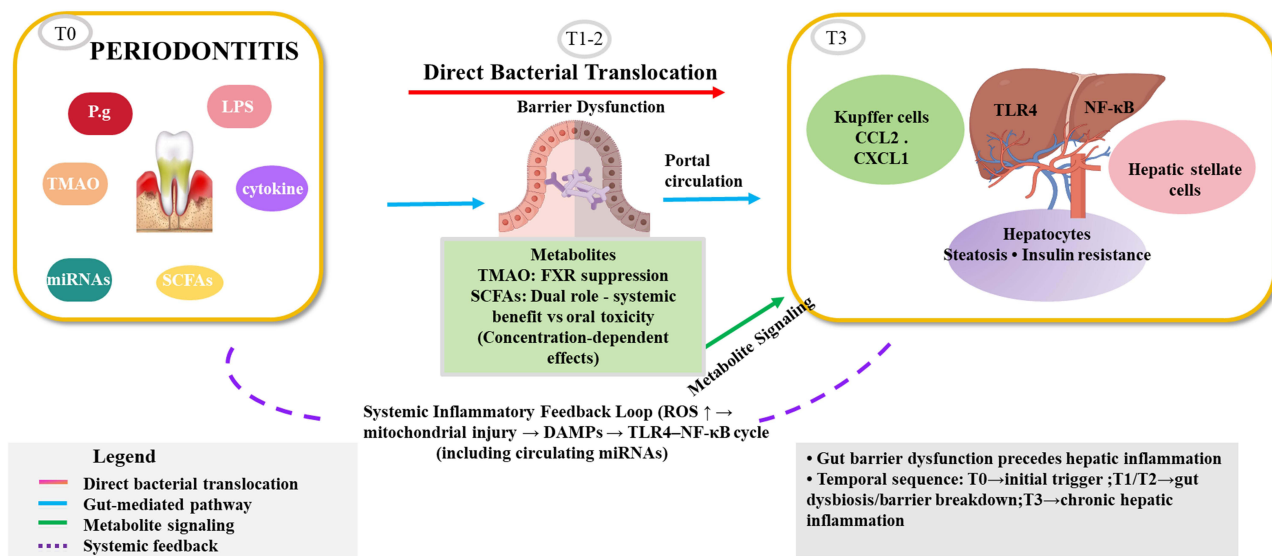


Figure 1 Oral–Gut–Liver axis linking periodontitis to NAFLD.

Abbreviations: Pathogens: P.g., *Porphyromonas gingivalis*; LPS, Lipopolysaccharide; Receptors: TLR4, Toll-like Receptor 4; FXR, Farnesoid X Receptor; Metabolites: SCFAs, Short-Chain Fatty Acids; TMAO, Trimethylamine N-oxide; Cytokines: CCL2, Chemokine (C-C Motif) Ligand 2; CXCL1, Chemokine (C-X-C Motif) Ligand 1; Disease: NASH, Non-Alcoholic Steatohepatitis; NAFLD, Non-Alcoholic Fatty Liver Disease; Signaling: ROS, Reactive Oxygen Species; DAMPs, Damage-Associated Molecular Patterns; NF-κB, Nuclear Factor Kappa B.

miRNAs may have systemic implications for liver health.⁶ In rat models, ligature-induced periodontitis resulted in elevated serum levels of miR-3591, miR-181a-2-3p, and miR-6321, all of which target hepatic endoplasmic reticulum (ER) stress genes such as *Hyo1*, *Chac1*, and *Bloc1s3*. This interaction induces hepatocyte apoptosis, providing support for the existence of an oral-liver miRNA axis that operates independently of microbial translocation.⁴²

Moreover, miR-155 acts as a central inflammatory regulator, amplifying Toll-like receptor (TLR)-mediated responses by suppressing the negative regulators SOCS1 and SHIP1. This amplification may also increase the liver's sensitivity to gut-derived endotoxins, contributing to the progression of metabolic dysfunctions.⁴³ While this “mechanical–inflammatory–miRNA–liver” axis presents a coherent narrative, it necessitates prospective and interventional validation to ensure cross-cohort consistency, establish temporality, and quantify effect sizes. Future studies are needed to elucidate the role of these miRNAs and their mechanosensitive properties in liver pathology, especially in the context of periodontal disease.

The Role of Microbial Metabolites: A Bridge Between Periodontitis and NAFLD

Microbial Metabolites as a Key Link Between Periodontitis and NAFLD

Microbial metabolites serve as critical mediators linking periodontitis and non-alcoholic fatty liver disease (NAFLD) through two opposing pathways. Pro-inflammatory metabolites—including lipopolysaccharide (LPS), trimethylamine N-oxide (TMAO), and dysregulated secondary bile acids—amplify hepatic inflammation, oxidative stress, and fibrogenesis via multi-receptor mechanisms.

Conversely, protective metabolites, particularly short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate, maintain hepatic homeostasis through immune-modulatory and barrier-protective effects.^{32,34–36,44–46} Gut-derived SCFAs, generated from the fermentation of dietary fiber, activate G-protein-coupled receptors (GPR41/43/109A) and inhibit histone deacetylases. This action, in turn, attenuates inflammatory signaling and supports hepatic insulin sensitivity.^{34–36,44} In contrast, LPS triggers TLR4-mediated hepatic inflammation.⁴⁵ TMAO—produced by hepatic FMO3 from gut-derived trimethylamine—disrupts lipid metabolism and suppresses farnesoid X receptor (FXR) activity.³² Similarly, dysbiotic secondary bile acids impair FXR and TGR5 signaling, undermining metabolic homeostasis.⁴⁶

Importantly, the effects of these metabolites are context-dependent. Swallowed oral pathogens can reshape gut microbiota and compromise mucosal barriers by downregulating tight junction proteins. This disruption amplifies intestinal inflammation and systemic endotoxemia. Notably, these microbiota changes can precede systemic inflammatory responses by 24 hours, establishing causality within the oral-gut-liver axis and supporting the keystone pathogen concept, whereby low-abundance oral bacteria trigger disproportionate systemic effects.²²

While SCFAs generally exert anti-inflammatory effects at physiological concentrations,³⁷ the oral pathogen-induced reduction in SCFA-producing *Clostridiales* may compromise this protective mechanism in the gut.²² Furthermore, locally elevated butyrate within inflamed periodontal tissues can become pro-inflammatory and cytotoxic to gingival cells.⁴⁷ This highlights the importance of concentration, microenvironment, and cellular context in determining metabolic directionality within the oral-gut-liver axis.

Pro-Inflammatory Metabolite Cluster Induces Hepatic Inflammation and Fibrosis via Receptor Pathways

Within the oral–gut–liver axis, a pro-inflammatory metabolite cluster forms around LPS (lipopolysaccharide) as its central component. This cluster is synergistically amplified by TMAO (trimethylamine N-oxide) and abnormalities in secondary bile acids. Together, these metabolites create an interwoven network among Kupffer cells, hepatic stellate cells (HSCs), and hepatocytes through TLR4 and FXR/TGR5 pathways. Consequently, this network intensifies inflammation and oxidative stress, driving the progression of NAFLD along the pathological continuum toward fibrosis.⁴⁵

Portal LPS activates TLR4 signaling across these hepatic cell populations.⁴⁵ This activation induces the release of cytokines and chemokines while promoting HSC activation, characterized by increased α -SMA expression and collagen

deposition. Additionally, it disrupts insulin signaling and lipid metabolism.²⁵ Under metabolic stress conditions—such as obesity or a high-fat diet—saturated fatty acids synergize with LPS to enhance TLR4 activation.²⁶ This synergistic effect accounts for the increased susceptibility to and exacerbation of NAFLD.^{25,26}

Beyond gut-derived endotoxin, oral sources also serve as upstream amplifiers in this inflammatory cascade. Oral pathobionts remodel intestinal microbiota and compromise mucosal barriers by downregulating tight junction proteins. This process augments LPS flux and systemic inflammation. *Porphyromonas gingivalis* exemplifies the keystone pathogen principle, achieving disproportionate systemic effects despite minimal gut colonization (<0.003%). This organism can directly translocate to modulate hepatic signaling pathways.^{20–22}

TMAO further amplifies this inflammatory network through various mechanisms. Animal and mechanistic studies have demonstrated that chronic TMAO exposure elevates intrahepatic oxidative stress, inflammation, steatosis, and fibrosis, particularly under high-fat dietary conditions.^{32,33} Mechanistically, TMAO reshapes bile acid metabolism while inhibiting FXR signaling. This suppression promotes lipogenesis and inflammatory gene expression within hepatocytes.

Bile acid dysregulation represents the third component of this pro-inflammatory cluster. Increases in secondary bile acids inhibit FXR and disrupt TGR5 pathways. This disruption fosters inflammation, insulin resistance, and lipid accumulation, thereby reinforcing NAFLD progression.⁴⁶ The interaction between these pathways creates a self-perpetuating cycle where each component amplifies the others.

Collectively, this LPS-centered metabolite cluster—synergistically amplified by TMAO and bile acid abnormalities—drives hepatic injury through a multi-receptor, multi-cellular inflammatory and fibrogenic network. This coordinated response facilitates pathological progression from simple steatosis to advanced fibrosis, representing a critical therapeutic target for intervention strategies aimed at disrupting the oral–gut–liver inflammatory axis.

Short-Chain Fatty Acids Maintain Hepatic Homeostasis via Immune–Barrier–Metabolic Triadic Pathways

Short-chain fatty acids (SCFAs), as core metabolic products of the gut microbiota, maintain hepatic homeostasis through an immune-barrier-metabolic triadic regulatory network that effectively counterbalances the deleterious effects of pro-inflammatory metabolites. However, this protective SCFA network can be compromised when oral pathogens reduce beneficial *Clostridiales* populations, which are primary SCFA producers and regulators of T cell differentiation.²²

SCFAs exhibit precise dual immunomodulatory capacity. Under physiological homeostatic conditions, SCFAs promote regulatory T cell (Treg) differentiation through histone deacetylase (HDAC) inhibition, which upregulates Foxp3 expression and establishes intestinal immune tolerance.³⁸ When confronted with pathogenic challenges, SCFAs activate metabolic sensors GPR41, GPR43, and GPR109A on intestinal epithelial cells, initiating protective immune responses.^{37,48} Specifically, GPR43 activation triggers potassium efflux and cellular membrane hyperpolarization, subsequently activating the NLRP3 inflammasome. This action maintains epithelial integrity while mediating measured pro-inflammatory responses through MAPK signaling pathways, achieving pathogen clearance without compromising barrier function.^{37,48}

At the intestinal barrier maintenance level, SCFAs function synergistically with intestinal alkaline phosphatase (IAP). IAP selectively regulates microbial growth, maintaining the dominance of commensal flora while suppressing pathogenic expansion. This synergy reinforces intestinal barrier defense systems and ensures gut-liver axis stability.²⁹ Importantly, when oral pathogens disrupt this balance by promoting inflammatory bacterial overgrowth and reducing protective species, the IAP-SCFA synergy becomes compromised, leading to enhanced translocation of pathogen-associated molecular patterns (PAMPs) and hepatic inflammation.²²

SCFAs also play a central role in metabolic regulation through intestinal gluconeogenesis (IGN), establishing a dual activation mechanism.³⁹ Butyrate functions as a signaling molecule, directly inducing IGN-related gene expression through cAMP-dependent signaling pathways. Meanwhile, propionate serves a dual function, acting both as a direct gluconeogenic substrate and activating the IGN process via FFAR3/GPR41 receptors in the gut-brain neural circuit. This complementary metabolic regulatory mechanism effectively maintains glucose homeostasis and overall energy balance, providing upstream regulatory support for hepatic metabolic homeostasis.

The immune-barrier-metabolic triadic regulatory pathways achieve hepatic homeostasis maintenance through precise coordination: immune tolerance mechanisms reduce the transmission of inflammatory mediators to the liver,³⁸ barrier integrity blocks pathogenic factor translocation,²⁹ while metabolic regulation directly supports hepatic glucose metabolic homeostasis through the IGN pathway.³⁹ This multidimensional regulatory network positions SCFAs as principal homeostatic regulators of the oral-gut-liver axis. However, the disruption of the oral-gut axis by keystone pathogens like *P. gingivalis* can fundamentally compromise this protective network, creating a cascade from reduced SCFA production to enhanced hepatic inflammation.²²

SCFA regulation exhibits significant context-dependent characteristics. In the intestinal environment, micromolar concentrations of SCFAs exert mucosal protective effects and maintain homeostasis through GPR-dependent pathways.³⁷ In contrast, in inflammatory periodontal tissues, millimolar concentrations of butyrate can induce apoptosis and autophagic cell death in gingival epithelial cells, demonstrating cytotoxic effects.⁴⁷ This seemingly paradoxical phenomenon actually reflects the fundamental biological principle that metabolite bioactivity is strictly dependent on local concentration, tissue microenvironment, and specific signaling networks.^{37,47} This further confirms the important role of SCFAs as precision regulatory molecules in maintaining systemic homeostasis.

Role of Inflammatory Biomarkers: Links Between Systemic Inflammation and Liver Injury

Systemic Inflammatory Phenotype Induced by Periodontitis

Chronic periodontitis is not confined to the oral cavity; it can also provoke a systemic inflammatory state. C-reactive protein (CRP) is one of the most rigorously validated systemic inflammatory biomarkers. A systematic review and meta-analysis by Paraskevas et al reported significantly higher systemic CRP levels in patients with chronic periodontitis compared to healthy controls, suggesting that periodontitis may be an important source of systemic inflammatory burden.⁴⁹ As an acute-phase reactant, elevated CRP is closely associated with the degree of periodontal inflammation, bacterial load, and host immune responses.

Beyond CRP, an increasing number of studies suggest that pro-inflammatory cytokines in plasma—such as IL-6, IL-1 β , and TNF- α —are elevated in patients with chronic periodontitis. This reflects an upregulated systemic inflammatory burden and immune activation.^{27,50,51}

Inflammatory Linkages Along the Oral–Gut–Liver Axis and Intrahepatic Inflammation

Systemic inflammation and endotoxin flux associated with periodontitis drive intrahepatic immune activation via the oral–gut–liver axis. Gut-derived LPS activates hepatic TLR4 signaling, promoting Kupffer cell release of pro-inflammatory mediators (IL-6, IL-1 β , TNF- α) and contributing to hepatic inflammation and metabolic disruption. Notably, oral pathogen-induced microbiota changes precede systemic inflammatory responses by 24 hours, establishing causality and supporting the keystone pathogen principle, where minimal oral bacteria trigger disproportionate effects.^{21,22}

Concurrently, the downregulation of intestinal barrier molecules, such as ZO-1/Tjp1 and alkaline phosphatase, indicates barrier impairment and increased endotoxin translocation. This impairment is mechanistically linked to the oral pathogen-induced reduction of protective *Clostridiales* species that normally maintain tight junction integrity. At the adaptive immunity level, the Th17/Treg immune balance becomes dysregulated in patients with periodontitis, resulting in tissue-specific effects, including gut Th17 suppression and compensatory Treg responses. This dysregulation contributes to altered intrahepatic immune patterns.^{31,52,53}

Modulation of the Inflammatory Biomarker Profile by Metabolic Mediators

Oral pathobionts can reshape the gut microbiota and barrier homeostasis, thereby modulating the inflammatory biomarker profile and the hepatic inflammatory microenvironment.^{21,23} At the metabolic level, short-chain fatty acids (SCFAs), at physiological concentrations, generally exhibit anti-inflammatory and barrier-protective tendencies. Specifically, SCFAs downregulate pro-inflammatory cytokine expression and improve epithelial tight junctions and

mucosal barrier conditions, consistent with improved hepatic metabolic/inflammatory phenotypes.^{36,39} In contrast, trimethylamine N-oxide (TMAO) couples with disordered hepatic lipid metabolism and promotes the upregulation of pro-inflammatory signaling. This suggests that TMAO may exacerbate hepatic vulnerability by influencing lipid metabolism, oxidative stress, and immune regulation.³² However, evidence remains insufficient to demonstrate, within the same experimental model, direct interactions between specific cytokines (e.g., IL-6/TNF- α) and SCFAs that reproducibly worsen liver injury.

Oxidative Stress: A Key Mediator Linking Periodontitis and NAFLD

Oxidative stress, characterized by reactive oxygen species and lipid peroxidation products such as MDA and 4-HNE, along with inflammatory mediators (IL-6, TNF- α , and CRP), mutually amplify each other, forming a self-sustaining inflammatory-oxidative stress circuit. In the oral cavity, periodontal pathogens trigger neutrophils to generate ROS via the NADPH oxidase pathway. While bactericidal, this process also induces local oxidative damage and exacerbates inflammation. Clinical and histological studies show that sustained oxidative stress leads to lipid peroxidation, protein oxidation, and DNA damage, with markers such as MDA and 8-OHdG being elevated in periodontitis cases and correlating with disease severity.^{54–56} Inflammatory mediators (e.g., cytokines and chemokines) further enhance ROS generation. The activation of TLR4-NF- κ B and increased NOX activity sensitize each other, amplifying both inflammation and oxidative injury.^{54,55}

On the hepatic side, comprehensive reviews and mechanistic studies indicate that oxidative stress in NAFLD induces mitochondrial dysfunction, promotes lipid peroxidation, and activates hepatic stellate cells. This drives progression from simple steatosis to inflammation and fibrosis.⁴⁵ This supports a stepwise, mechanism-linked evidence chain: periodontitis is associated with elevated systemic and salivary oxidative stress markers;^{54,56} hepatic oxidative stress aligns with inflammatory and fibrotic phenotypes in NAFLD;⁴⁵ and an inter-organ amplification loop occurs through inflammatory amplification of ROS, ROS-induced mitochondrial injury, and DAMP release, plus positive feedback between TLR4-NF- κ B and NADPH oxidase.^{54,55}

From a translational perspective, standard periodontal therapy may reduce systemic inflammation and endotoxin exposure, thereby indirectly lowering systemic ROS levels.⁵⁵ Antioxidant and mitochondria-targeted strategies, such as inhibiting NOX, attenuating TLR4-NF- κ B amplification, and improving mitochondrial function, have shown anti-inflammatory and anti-fibrotic effects in both animal and early human studies. However, high-quality prospective trials are needed to confirm these benefits in humans.^{57,58}

Perspectives, Research Gaps, and Recommendations

Although there is growing evidence for the connection between the mouth, gut, and liver, many important pathways and relationships are still not clearly understood.

1. **Molecular and Immunological Insights:** Future studies should look into how oral bacteria spread through the bloodstream and affect the liver. It's also important to understand how intestinal problems lead to increased toxins in the blood and how imbalances in bile acids and short-chain fatty acids might lead to fat buildup in the liver. Researchers should also investigate how the balance of Th17 and Treg cells, along with pathways like TLR4/NF- κ B and the NLRP3 inflammasome, links gum disease to non-alcoholic fatty liver disease (NAFLD).^{59,60}
2. **Study Design Considerations:** Most current research is either cross-sectional or case-control, meaning it does not track changes over time. There is a need for more long-term studies and high-quality randomized controlled trials (RCTs). Multicenter studies using consistent methods will help ensure reliable results.
3. **Translational Strategies:** It's important to evaluate how standardized periodontal treatments affect liver health, including liver function, fat levels, and scarring. Combining gum disease treatments with changes in lifestyle, adjustments to gut bacteria, and medication can also be helpful. Developing tools to assess risk can aid in early detection and targeted treatment.
4. **Population Management:** Given the strong link between metabolic issues and gum disease, especially in patients with metabolic syndrome, these individuals should be a focus for management. Regular oral health checks should be part of care in relevant healthcare settings, and teamwork among different health professionals will be key to achieving better results.^{60,61}

Conclusion

Chronic periodontitis and non-alcoholic fatty liver disease (NAFLD) exhibit a complex bidirectional relationship that significantly affects both oral and systemic health. Clear evidence links periodontal diseases to NAFLD-related conditions through key mechanisms such as systemic inflammation, oral-gut microbiological dysbiosis, and oxidative stress. This creates a self-reinforcing cycle where periodontal pathogens worsen systemic inflammation and trigger hepatic metabolic issues.

A comprehensive management strategy is essential to simultaneously address both conditions. This should involve integrating periodontal care with lifestyle modifications and metabolic therapies, including dietary improvements, increased physical activity, and monitoring metabolic indices. Such an approach may help slow NAFLD progression and enhance overall patient health.

Future research must focus on standardized longitudinal studies to assess long-term changes in periodontal and liver health. Additionally, combined intervention trials should investigate the effects of periodontal treatment, microbiome modulation, and antioxidant therapies. Early identification of high-risk populations and integrated management of both health domains are vital for improving patient prognosis.

In conclusion, while evidence supports a potential link between chronic periodontitis and NAFLD, the field is limited by a lack of longitudinal studies and significant heterogeneity. Therefore, large-scale, long-term prospective cohort studies including diverse ethnic groups are needed.

Data Sharing Statement

All information obtained by the authors in this manuscript can be found in the literature.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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