

PERIODONTITIS AND METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE: AN UPDATE ON THE ORAL–GUT–LIVER AXIS

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Abstract

Metabolic dysfunction–associated steatotic liver disease (MASLD) and metabolic dysfunction–associated steatohepatitis (MASH) are now defined by clear metabolic criteria, with current approaches emphasizing fibrosis risk due to its impact on liver-related outcomes. Periodontitis is a common chronic inflammatory disease caused by dysbiotic subgingival biofilms and sustained by an exaggerated host response. This narrative review consolidates clinical and experimental evidence connecting periodontitis to MASLD/MASH through the oral–gut–liver axis.

Epidemiologic studies frequently observe the co-occurrence of periodontitis and steatotic liver disease, and several cohorts indicate dose–response patterns when periodontal severity correlates with fibrosis-related liver outcomes like elastography or validated non-invasive fibrosis scores. However, these associations are inconsistent and tend to diminish when adjusting for strongly related factors such as obesity, diabetes, smoking intensity, diet, socioeconomic status, and healthcare utilization. Interpretation is also constrained by differing case definitions, various liver outcomes (such as imaging-detected steatosis, aminotransferases, fibrosis scores, elastography, biopsy), and possible reverse causality.

Mechanistic plausibility is supported by several converging pathways: intermittent systemic spread of bacteria and microbial products (including LPS) from periodontal pockets; oral-to-gut microbial transmission causing ecological changes in the intestinal microbiome; intestinal barrier dysfunction leading to increased portal delivery of endotoxin and metabolites; and activation of hepatic innate immunity that enhances lipotoxic stress, oxidative injury, inflammasome signaling, and stellate-cell-mediated fibrogenesis. In obesity-prone models, induced periodontitis worsens steatotic liver phenotypes and highlights manageable targets such as TLR pathways and microbiota-dependent tryptophan–AHR signaling.

Clinically, the most justified implication is integrated risk recognition rather than definitive causal claims. Dental teams can start metabolic evaluation and fibrosis risk assessment for high-risk patients, while hepatology and metabolic clinics can include brief oral screenings and periodontal referrals. Future priorities include standardizing phenotyping, conducting repeated-measure cohort studies, and running periodontal intervention trials with fibrosis-related endpoints. Using multi-omics and causal frameworks will be crucial for translating research into clinical practice.

Keywords: *Periodontitis; MASLD; MASH; Oral–gut–liver axis; Gut microbiome*

1. Introduction

Metabolic dysfunction–associated steatotic liver disease (MASLD) has quickly become a key focus in hepatology and cardiometabolic medicine, due to its high impact on populations and its redefinition of fatty liver disease around metabolic risk instead of using exclusionary

alcohol-based terminology. The transition from NAFLD/NASH to the broader concept of steatotic liver disease (SLD), with MASLD and metabolic dysfunction–associated steatohepatitis (MASH) as main subcategories, was established through multisociety consensus and is now included in major society communications and

clinical guidelines. This change in terminology is more than just words; it aligns diagnostic thinking with the grouping of obesity, insulin resistance, dyslipidemia, and hypertension, and promotes greater collaboration across specialties that regularly treat cardiometabolic risk [1]. Recent reviews also highlight that MASLD is biologically diverse—spanning lipid processing, inflammation, and fibrosis susceptibility—which directly affects risk assessment and the success of metabolism-focused treatments [2, 3].

Meanwhile, periodontitis remains one of the most common chronic inflammatory diseases worldwide. It starts and persists due to dysbiotic oral biofilms in susceptible hosts, with tissue damage caused by an exaggerated and poorly resolving host response. Periodontitis is increasingly recognized as a contributor to systemic inflammation and cardiometabolic conditions through episodes of bacteremia, spread of microbial products, and immune–metabolic interactions [4]. This systemic perspective is especially important now, as medicine shifts toward integrated models of chronic disease where local inflammatory environments can impact distant organs, particularly when combined with metabolic dysfunction.

The connection between periodontitis and MASLD/MASH is therefore more than just coincidental. These conditions share many key upstream factors—dietary patterns, adiposity and adipose inflammation, insulin resistance, and socioeconomic factors—making confounding variables and reverse causality important concerns in observational studies. However, the biological plausibility of a link has grown stronger as mechanistic studies have started to show how oral dysbiosis could influence gut ecosystem changes and liver inflammatory signaling. Recent reviews describe the oral–gut–liver axis as a two-way system in

which oral microbial communities, intestinal barrier health, and liver immune–metabolic functions interact, and in which disruption at any point can lead to dysfunction throughout the system [2, 5]. In this context, periodontitis is not just a sign of unhealthy behaviors but may also be a modifiable source of inflammatory and microbial factors that can worsen liver metabolic injury in at-risk individuals.

Several pathways may link periodontal inflammation to hepatic steatosis and fibrogenic progression. First, periodontitis can increase the frequency and severity of transient bacteremia and systemic exposure to pathogen-associated molecular patterns, thereby exacerbating the low-grade inflammation already present in metabolic syndrome. Second, swallowed oral bacteria and inflammatory mediators may affect the gut microbiota and intestinal permeability, promoting endotoxemia and the portal delivery of microbial metabolites to the liver. Third, immune training and cytokine networks activated in periodontal tissues can modify hepatic innate immune responses and lipid metabolism, especially under obesogenic conditions where baseline immunometabolic balance is already disrupted [4, 6]. Importantly, new experimental data support causally oriented models: in the context of obesity, periodontitis has been shown to worsen MASLD phenotypes through gut microbiota–dependent mechanisms and downstream metabolic–immune signaling pathways [6].

Against this backdrop, the clinical and research communities face a practical question: how should periodontal disease be integrated into MASLD risk assessment and management, and what level of evidence is required before bidirectional screening or co-management becomes standard? Guidance documents and consensus recommendations increasingly emphasize multidisciplinary approaches to MASLD because of its close association with diabetes and cardiovascular disease,

and because effective therapy often requires coordinated metabolic risk reduction [3]. Oral health is rarely included in these pathways, despite growing literature suggesting that the oral cavity may serve as an accessible—and potentially actionable—component of the broader inflammatory network.

This narrative review summarizes and critically examines recent evidence linking periodontitis with MASLD/MASH, with a focus on the oral–gut–liver axis. We emphasize: (i) the rationale for including periodontal inflammation in MASLD research; (ii) the most consistent clinical findings from epidemiologic studies, while noting key sources of bias; and (iii) mechanistic insights from microbiome, barrier function, and immunometabolic research that may explain observed associations. Our goal is to clarify what is currently supported, what remains speculative, and which research paths are most likely to lead to clinically meaningful prevention or co-management strategies.

2. Definitions and clinical framing

2.1. MASLD/MASH: diagnostic criteria, clinical spectrum, and key outcomes

The terminology for steatotic liver disease has recently changed, with metabolic dysfunction–associated steatotic liver disease (MASLD) replacing NAFLD through a multisociety consensus process that adopted positive (not exclusionary) diagnostic criteria [1]. MASLD describes hepatic steatosis—confirmed by imaging or histology—that occurs alongside at least one cardiometabolic risk factor; the condition ranges from isolated steatosis to steatohepatitis, progressive fibrosis, cirrhosis, and hepatocellular carcinoma [7].

Within this framework, metabolic dysfunction–associated steatohepatitis (MASH) refers to the inflammatory phenotype (steatohepatitis) within

MASLD, often requiring histologic confirmation in research settings and remaining a clinically relevant concept for prognosis and treatment targeting [1, 7]. In clinical practice, diagnosis and staging increasingly depend on non-invasive tests (e.g., FIB-4 and elastography) in a stepwise approach to identify clinically significant or advanced fibrosis, because fibrosis stage is the main factor affecting liver-related outcomes and long-term prognosis [1].

2.2. Periodontitis: contemporary case definitions and severity staging/grading

The current periodontal nosology originates from the 2017 World Workshop, which redefined periodontitis as a chronic inflammatory disease characterized by dysbiotic biofilm and a susceptible host response, leading to clinical attachment loss, radiographic bone loss, and (in severe cases) tooth loss [8]. The classification highlights an integrated staging and grading system that reflects both the disease's severity and complexity, as well as its biological risk of progression [9].

Staging (I–IV) primarily indicates the extent of periodontal damage and the complexity of treatment, taking into account probing depths, patterns of bone loss, furcation involvement, and tooth loss due to periodontitis [9]. Grading (A–C) assesses the risk of disease progression using direct or indirect evidence (e.g., bone loss relative to age) and clearly includes risk factors—most notably smoking and glycemic control—within routine clinical assessment [9]. This approach is especially useful when evaluating periodontitis alongside systemic conditions because it helps distinguish “current disease burden” from “future progression risk,” which may relate differently to systemic pathways.

2.3. Shared risk factors

MASLD/MASH and periodontitis cluster within a shared cardiometabolic and behavioral risk environment. Obesity,

insulin resistance/type 2 diabetes, dyslipidemia, and smoking are core exposures for MASLD and are also consistently linked to periodontitis severity and progression [7, 10]. These exposures are also related to dietary habits, physical activity, healthcare engagement, and socioeconomic status, forming closely interconnected “risk constellations” rather than independent factors [7, 11].

From an epidemiologic standpoint, this presents several recurring challenges. First, many shared determinants are difficult to measure accurately (diet quality, long-term smoking intensity, medication adherence, access to preventive dental care), leading to residual confounding even in well-adjusted models [11]. Second, reverse causation and bidirectionality are plausible: cardiometabolic dysregulation can worsen periodontal inflammation, while severe periodontal inflammation may contribute to systemic inflammatory responses that correlate with metabolic risk—yet observational studies often cannot clearly determine the direction of these relationships [10, 11]. Third, treatment-related factors can distort inferences: cardiometabolic pharmacotherapy and comorbidity burden influence dental attendance, antibiotic exposure, salivary function, and gingival phenotypes (including drug-induced gingival overgrowth with certain agents), each of which may alter periodontal measurements without directly indicating changes in the core host–microbiome disease process [12].

In the context of the oral–gut–liver axis literature, these issues imply that “association” should not be over-interpreted as “causation” without careful consideration of temporality, clinical phenotyping (including fibrosis risk in MASLD and staging/grading in periodontitis), and analytical strategies that minimize confounding (such as well-defined covariates, sensitivity analyses,

negative controls, and—where possible—genetic methods like Mendelian randomization) [9, 11].

3. Epidemiologic evidence linking periodontitis and MASLD/MASH

Most epidemiologic research was conducted under the NAFLD/NASH terminology; however, the underlying phenotype in these datasets largely overlaps with what is now classified as MASLD/MASH once alcohol intake and secondary causes are properly considered. As a result, this body of literature is often seen as the evidence base for the spectrum of metabolic steatotic liver disease, while recognizing that reclassification can significantly alter denominators and comparability across studies [13].

3.1 Cross-sectional evidence: signals are common, but adjustment matters

Across population surveys and clinic-based groups, periodontitis and NAFLD often occur together. In a U.S. NHANES study, NAFLD was associated with moderate or severe periodontitis and indicators of long-term oral health problems (such as tooth loss), even after adjusting for various sociodemographic and behavioral factors [13].

However, cross-sectional designs also make confounding particularly hard to resolve because metabolic risk factors are “upstream” of both conditions and are measured with varying detail. In a combined population- and patient-based study, periodontitis was associated with steatosis in NHANES after sociodemographic adjustment, but this association was significantly attenuated after accounting for metabolic syndrome features. In the patient-based part, periodontitis was more common among biopsy-confirmed NASH and among those with fibrosis, indicating that the connection

might be most clear once liver disease becomes clinically significant.

A complementary cross-sectional approach has been to concentrate on fibrosis surrogates rather than just steatosis, since fibrosis is the main prognostic factor in MASH. In patients with NAFLD, deeper periodontal pockets and increased salivary *Porphyromonas gingivalis* burden were associated with higher liver stiffness measured by MR elastography and transient elastography, as well as higher endotoxin-related measures. This approach links periodontal severity to a clinically significant liver endpoint, while remaining susceptible to reverse causality and shared exposures [14].

3.2 Longitudinal evidence: modest effect sizes, stronger when periodontal exposure is well-phenotyped

Longitudinal studies are fewer, but they help establish temporal order. In the Study of Health in Pomerania, baseline periodontitis—defined using detailed clinical measures—predicted incident NAFLD on follow-up ultrasound. Notably, a dose–response pattern was observed when periodontitis was expressed as the proportion of sites with clinical attachment loss, with more extensive disease associated with higher NAFLD incidence rates after adjustment and censoring [15].

In contrast, large administrative datasets often rely on ICD coding and utilization proxies, which increase statistical power but can reduce exposure specificity. Using a national Korean insurance sample cohort (2002–2015), periodontitis was associated with a modest increase in incident NAFLD risk, and the number of dental visits for periodontal disease showed a graded relationship with NAFLD incidence—findings that align with a weak but detectable population-level signal [16]. However, these designs are particularly vulnerable to detection bias, as individuals accessing dental care may differ systematically in their health-seeking

behaviors and in their comorbidity screening.

Emerging analyses that explicitly adopt MASLD-era framing have started to explore more severe outcomes. For instance, NHANES-based research has connected the severity of periodontitis to mortality among participants classified with MASLD, expanding the epidemiological question beyond simply detecting steatosis to understanding downstream risks [17].

3.3 Dose–response patterns: periodontal severity ↔ liver disease severity

Where periodontal exposure is measured clinically (rather than coded), dose–response signals are more often reported. In Pomerania, extensive attachment loss (compared to periodontal health) was associated with a higher incidence of NAFLD, consistent with a gradient of periodontal tissue destruction [15]. In clinical NAFLD cohorts, greater numbers of deep pockets and higher *P. gingivalis* burden correlated with increased liver stiffness, aligning periodontal severity with a fibrosis-relevant endpoint rather than steatosis alone [14].

On the liver side, Alazawi and colleagues reported that the prevalence of periodontitis was higher among those with biopsy-confirmed NASH and those with significant fibrosis [18], reinforcing the idea that the association may be stronger along the MASH–fibrosis axis rather than consistent across all steatosis.

3.4 Outcomes used: from surrogate steatosis to fibrosis-enriched endpoints

Variability in liver outcomes is a key reason the literature can seem inconsistent. Studies define liver disease in various ways, including: (i) imaging for steatosis (most commonly ultrasound in population surveys; MRI-based fat quantification in smaller clinical groups),

(ii) liver enzymes, (iii) non-invasive risk scores designed to identify advanced fibrosis, (iv) elastography-derived stiffness as a proxy for fibrosis, and (v) biopsy when available. The interpretability of any association with periodontal health depends heavily on the endpoint chosen and how alcohol use, viral hepatitis, and hepatotoxic medications are addressed [14, 15, 18].

3.5 Key limitations: residual confounding, reverse causality, and definition drift

Even in well-designed cohorts, residual confounding remains a significant concern because factors like obesity, insulin resistance/diabetes, smoking, diet, socioeconomic status, and medication use influence both periodontal health and MASLD risk—and are often measured imperfectly.

Reverse causality is also possible: metabolic liver disease (through systemic inflammation, immune dysfunction, xerostomia-inducing medications, or healthcare utilization patterns) could worsen periodontal outcomes. This aligns with newer “reverse direction” analyses showing that NAFLD-related scores are linked to incident chronic periodontitis [19].

Finally, synthesis efforts highlight how sensitive conclusions are to study selection and adjustment methods. A recent meta-analysis reported an overall estimate close to zero, underscoring that heterogeneity in periodontal and NAFLD definitions—alongside differences in covariate handling—can heavily influence pooled results [20]. Causal inference approaches using bidirectional Mendelian randomization have also yielded mixed results, with at least one study showing no genetic evidence of causality in either direction [21]. At the same time, other MR analyses indicate directional signals depending on the instrument and phenotype choices [22].

4. The oral–gut–liver axis: biological plausibility

The proposed oral–gut–liver axis provides a mechanistic link between a chronic, ulcerated periodontal environment and liver immunometabolic injury. Instead of suggesting a single cause-and-effect pathway, current models highlight multiple biologically plausible routes through which oral dysbiosis and periodontal inflammation can influence systemic inflammation, intestinal ecology, and barrier function—and, through portal delivery, activate hepatic innate immunity that contributes to steatosis progression toward MASH and fibrosis.

4.1 Oral dysbiosis and systemic dissemination

Periodontitis involves a dysbiotic, proteolytic biofilm next to an inflamed, ulcerated pocket epithelium. This creates conditions for bacteria and microbial products to intermittently enter the circulation during routine activities and periodontal procedures [23]. Besides intact organisms, circulating pathogen-associated molecular patterns—especially lipopolysaccharides (LPS) from Gram-negative periodontal bacteria—may contribute to systemic low-grade inflammation by activating innate immune receptors and enhancing cytokine networks linked to metabolic disease [24].

A related idea is immune “priming” at the level of innate effector cells and their progenitors. Trained immunity refers to long-lasting functional changes in innate immune responses—driven by immunometabolic and epigenetic modifications—that lead to exaggerated (or, depending on the context, reduced) inflammatory responses upon secondary stimulation [25]. In chronic inflammatory conditions, trained immunity can become harmful, maintaining systemic inflammatory readiness that likely promotes clustering of cardiometabolic diseases [26]. In the context of

periodontitis, this model offers a clear explanation for why local oral inflammation may be linked to increased systemic inflammatory response, even when visible bacteremia is not detectable at a single time point.

4.2 Oral-to-gut seeding and gut dysbiosis

The oral cavity acts as a continuous reservoir of microbes for the gastrointestinal tract. Although gastric acid, bile acids, and colonization resistance limit the survival of many oral microbes, swallowed microbes and their products can still impact gut community structure—especially when ecological barriers are compromised (e.g., impaired barrier function, altered bile acid pools, medication effects, or existing dysbiosis) [27, 28].

Multiple lines of evidence across metabolic and inflammatory disease contexts indicate the enrichment of normally oral-associated taxa in fecal metagenomes, supporting the idea that oral-to-gut transmission can be biologically significant rather than just transient [28]. Importantly, “seeding” does not necessarily mean stable colonization by traditional periodontal pathogens alone. Even a low abundance of oral taxa can contribute to ecological changes by modifying redox conditions, nutrient levels, and inter-bacterial competition, which may promote the growth of pathobionts and reprogram the gut microbiome’s functions.

In models of periodontitis, disruptions in oral microbes have been associated with shifts in gut microbial composition and subsequent inflammatory signaling, offering a plausible initial step for activating the gut–liver axis in hosts prone to metabolic issues.

4.3 Intestinal barrier dysfunction and portal delivery

A key amplification step in the axis is intestinal barrier impairment, which permits luminal microbial products (e.g.,

LPS and other microbe-associated molecular patterns) and pro-inflammatory metabolites to enter the portal circulation and reach the liver. In MASLD/MASH, barrier dysfunction and “metabolic endotoxemia” are often discussed as contributors to hepatic inflammation and fibrogenic signaling, interacting with bile acid signaling and short-chain fatty acid (SCFA) pathways that influence both host metabolism and immune function [29]. Within this framework, periodontal-driven changes in gut ecology could have significant hepatic effects if they occur in individuals already primed by insulin resistance, visceral fat, or dietary patterns that compromise barrier integrity and mucosal immunity [28, 29].

Metabolic syndrome may thus function more as an “effect modifier” rather than a competing explanation: it can enhance gut permeability, modify bile acid composition, and sustain systemic inflammatory signals, thereby lowering the threshold at which oral-to-gut disruptions lead to clinically significant portal inflammation. This explains why links between periodontal severity and liver disease severity are often most pronounced in cohorts enriched with obesity, dysglycemia, or other metabolic risk factors [28].

4.4 Hepatic immunometabolic pathways

Once microbial products and inflammatory mediators reach the liver, resident macrophages (Kupffer cells) and recruited monocyte-derived macrophages can process these inputs along with lipotoxic and oxidative stress signals characteristic of MASLD/MASH. Activation of pattern-recognition receptors and inflammasome-linked cytokine pathways (notably IL-1 family signaling) can lead to hepatocellular injury, increase insulin resistance, and activate stellate cells—key steps in progressing from steatosis to steatohepatitis and fibrosis [29].

In this context, a chronically primed innate immune system—potentially influenced by repeated periodontal inflammatory stimuli—could plausibly heighten hepatic inflammatory responses to otherwise mild portal exposures [25, 26, 29].

Mechanistically, the most clinically important endpoint is fibrosis, which results from persistent inflammatory activation, hepatocyte stress and death signaling, and pro-fibrogenic interactions between macrophages and hepatic stellate cells. Therefore, the oral–gut–liver axis is best understood as a multi-hit system where periodontitis may contribute to (i) systemic inflammatory priming, (ii) disruptions in gut ecology and barrier function, and (iii) increased hepatic innate immune activation—effects most likely to appear in metabolically vulnerable individuals rather than all patient populations equally [29].

5. Mechanistic evidence from experimental models

Experimental models are essential for moving beyond association because they allow control of diet, metabolic background, microbial exposure, and timing—factors that are hard to untangle in human cohorts. In rodent studies, two main approaches have been used: (i) inducing periodontitis (usually by ligatures or repeated oral inoculation with periodontal pathogens) on a metabolic “background” (high-fat diet, diabetogenic models, or NASH diets), and (ii) transferring or manipulating oral/gut microbiota to test whether dysbiosis is sufficient—and sometimes necessary—for liver injury (Table 1).

5.1 Animal models of periodontitis with obesity/diabetes “background”

Ligature-induced periodontitis has repeatedly been associated with hepatic steatosis and injury phenotypes, even when periodontitis is the primary cause. In rats, placing one or two ligatures was reported to

be enough to cause fatty liver changes, supporting the idea that sustained periodontal inflammation can disrupt liver health without intentionally causing liver injury [30]. When a high-fat or hypercaloric diet is added, liver damage becomes more severe: steatosis scores and biochemical markers of oxidative stress and liver cell damage (e.g., ALT) increased in animals with both a high-fat diet and periodontitis compared to those with periodontitis alone [31]. These “two-hit” models (periodontal inflammation combined with metabolic overload) are clinically relevant because MASLD/MASH usually develop in the context of overnutrition and insulin resistance.

Several models have examined *P. gingivalis* (Pg) exposure as a standard trigger for periodontal disease. In mice with metabolic syndrome or NAFLD induced by high-fat feeding, Pg-induced periodontitis worsened insulin resistance and liver inflammation; inhibiting acid sphingomyelinase (ASMase) with imipramine reduced both metabolic and liver inflammatory markers, suggesting that sphingolipid–ceramide signaling is a possible link between periodontal inflammation and progression of liver steatosis [32]. Similarly, in obese diabetic db/db mice, repeated oral Pg treatment altered gut microbiota and intestinal metabolites and was associated with poorer glycemic control and alterations in liver enzymes and metabolites involved in gluconeogenesis [33]. Although this model focuses on diabetes, it supports a broader idea: exposure to periodontal pathogens can alter enterohepatic metabolism, likely increasing the risk of MASLD/MASH.

5.2 Microbiota-transfer and antibiotic intervention experiments

A major strength of recent research is the use of transfer experiments that directly test causality along the oral–gut–liver axis. In the context of high-fat diet-induced obesity, intragastric transfer of

salivary microbiota from patients with periodontitis worsened NAFLD phenotypes in recipient mice, accompanied by changes in gut microbiota, impaired intestinal barrier markers, and increased systemic LPS—supporting the idea that a gut-derived “endotoxin” contributes to liver inflammation [34]. This method is important because it examines a community derived from patients (not just a single pathogen) and suggests that dysbiotic oral communities can be enough to worsen liver disease under metabolic stress.

Fecal microbiota transplantation (FMT) and genetic pathway validation are now part of the experimental research on periodontitis–MASLD. In obese, high-fat-fed mice, periodontitis worsened MASLD features and reduced gut microbiota-derived tryptophan metabolites; experiments with FMT and aryl hydrocarbon receptor (AHR) knockout supported a causal role for the gut microbiota–tryptophan–AHR axis, and supplementation with indole-3-propionic acid (IPA) or *Limosilactobacillus reuteri* reduced intestinal barrier dysfunction, systemic inflammation, and liver injury in an AHR-dependent way [6]. These findings raise microbial metabolite signaling from a mere correlation to a testable mechanism.

Antibiotic-based interventions provide a useful “necessity” test, especially when targeting a specific oral pathogen. In a high-fat diet NASH model with Pg odontogenic infection, azithromycin-based removal of Pg decreased liver inflammatory

and fibrogenic markers (including Tnf- α /Il-1 β , galectin-3, and pSmad2) and improved histologic activity and fibrosis scores, suggesting that Pg acts as a disease-amplifying factor in this context [35]. Although antibiotics are not precise tools for manipulating the microbiome, the observed trend (elimination $\rightarrow$ improvement) supports microbial involvement and encourages the development of more targeted approaches (e.g., selective antimicrobials or ecological therapies).

5.3 Mechanistic nodes highlighted in models

TLR signaling and endotoxin-driven inflammation. Multiple models support LPS–TLR4 signaling as a key link between periodontal dysbiosis and liver inflammation. In the salivary microbiota transfer model, liver injury was suggested to occur after increased LPS delivery and activation of TLR4-related inflammatory pathways [34]. Similarly, repeated intravenous exposure to sonicated Pg (which retains endotoxin activity) worsened steatosis and insulin resistance in high-fat-fed mice and changed liver gene expression to favor inflammatory pathways. This supports the idea that episodic systemic spread of microbial products can worsen NAFLD features [36]. These results align with the broader MASLD framework, where innate immune activation increases hepatocellular stress and fibrogenic signaling.

Table 1. Experimental models supporting an oral–gut–liver axis in steatotic liver phenotypes

Study (year)	Species / metabolic background	Periodontitis induction / exposure	Liver endpoints	Mechanistic node tested	Main finding
Pessoa (2018)	Rat; standard diet	Ligature periodontitis	Histologic steatosis	Inflammation-driven hepatic changes	Periodontitis alone sufficient to induce fatty liver features
de Andrade (2019)	Rat; high-fat diet	Ligature periodontitis + HFD	Steatosis, ALT, oxidative stress markers	“Two-hit” metabolic amplification	HFD aggravates periodontal-driven liver injury

Sasaki (2018)	Mouse; HFD	Systemic exposure to <i>P. gingivalis</i> products	Steatosis, metabolic parameters, gut shifts	Endotoxin-driven inflammation	Endotoxemia aggravates NAFLD-like phenotype and alters microbiota
Nagasaki (2021)	Mouse; NASH model	Pg odontogenic infection ± antibiotic elimination	Inflammation/fibrosis markers; histology	Pathogen necessity (antibiotic “removal”)	Pg elimination attenuates inflammatory and fibrogenic signaling
Kashiwagi (2021)	db/db mouse; diabetic background	Oral Pg exposure	Enterohepatic metabolites, hepatic metabolic genes	Enterohepatic metabolic regulation	Pg alters gut metabolites and hepatic metabolic pathways
Lu (2023)	Mouse; metabolic syndrome	Periodontitis superimposed on metabolic background	Hepatic inflammation, insulin resistance	Sphingolipid/ASMase–ceramide	ASMase inhibition mitigates metabolic and hepatic effects
Wang (2023)	Mouse; HFD obesity	Intragastric transfer of periodontitis salivary microbiota	Steatosis/inflammation; barrier markers	Community-level “sufficiency”	Human periodontitis salivary microbiota worsens NAFLD phenotype
Chen (2025)	Mouse; HFD obesity	Periodontitis model with gut profiling ± FMT/AHR knockout	MASLD features; barrier/endotoxemia	Tryptophan–AHR axis	Microbiota-derived tryptophan metabolites/AHR signaling causally implicated

Tryptophan–AHR axis (including ligand-specific effects). The AHR pathway has become a particularly “tractable” target because it is both sensitive to the microbiota and amenable to experimental targeting. In the MASLD-focused model, periodontitis was linked to decreased microbiota-derived tryptophan metabolites and worsening of barrier function and endotoxin translocation; genetic Ahr deletion or supplementation with an AHR-relevant microbial metabolite or a probiotic reduced liver injury [6]. Conversely, in the salivary microbiota transfer NAFLD model, a hepatic tryptophan–kynurenine–Ahr axis was reported to be upregulated [34]. Together, these findings imply that “AHR involvement” may not be consistent; the overall effect may depend on the balance of microbial indole derivatives versus host kynurenine pathway activity, tissue compartment, and disease stage—factors

that experimental systems are well suited to examine.

Bile acids and enterohepatic metabolic regulation. Direct experimental links between periodontal disturbances and bile acid homeostasis are less developed than those involving endotoxin or tryptophan pathways, but emerging metabolomic research indicates a connection. In db/db mice treated orally with Pg, researchers observed enterohepatic metabolic disruptions, including changes in intestinal metabolites and hepatic gene expression, with signals suggesting modulation of bile acid synthesis pathways (e.g., Cyp7a1 upregulation) [33]. Given the crucial role of bile acids as metabolic and immune signals in MASLD/MASH, these findings support the need for targeted bile acid profiling and FXR/TGR5-focused experiments in future periodontitis–MASLD models.

6.2 Bidirectional screening and integrated care

6.2.1 What dentists should look for: metabolic risk profile and referral triggers

Because periodontitis and MASLD/MASH are part of the same cardiometabolic risk environment, the dental setting can be an effective point for opportunistic case-finding—not to diagnose MASLD, but to identify patients who could benefit from medical assessment for metabolic risk and, where appropriate, liver fibrosis risk. Modern liver guidelines recommend targeted case-finding for MASLD with clinically relevant fibrosis using non-invasive tests in individuals with cardiometabolic risk factors, abnormal liver enzymes, and/or imaging evidence of steatosis—especially in those with type 2 diabetes or obesity, along with additional metabolic risk factors [1].

In practice, the dentist's role is best centered on structured risk assessment and referral. A practical, justifiable approach is to record a brief metabolic risk profile for patients with moderate to severe periodontitis (or at risk of rapid progression) and to refer them to primary care, diabetology, or hepatology when any of the following are present: known type 2 diabetes or prediabetes; central obesity or BMI in the obese range (especially if accompanied by hypertension or dyslipidemia); a history of "fatty liver" from previous imaging; persistently elevated ALT/AST reported by the patient; or a clustering of metabolic syndrome features [7].

This aligns well with periodontal care pathways because the current staging and grading framework already includes major systemic risk factors, such as smoking and blood sugar levels, into routine periodontal diagnosis. This makes it natural to perform brief medical triage without over-medicalizing dental care [37]. In other words, the referral isn't because periodontitis causes MASLD, but because

the combination of periodontitis severity and metabolic risk features identifies a patient group for whom liver risk assessment aligns with guidelines and is clinically relevant.

6.2.2 What hepatology/metabolic clinics should ask about: periodontal symptoms and oral health referral

From a medical perspective, MASLD pathways increasingly focus on stratifying for advanced fibrosis through stepwise non-invasive tests (e.g., FIB-4 followed by elastography or second-line tests in selected patients), because fibrosis stage is the primary prognostic factor and the main basis for escalation decisions [7].

Within these care pathways, a brief oral health screening can be integrated with minimal burden. Clinically useful questions include: frequent gingival bleeding; persistent halitosis; gum recession or tooth mobility; history of periodontal treatment; and dental attendance patterns. A positive screening—especially in patients with obesity, diabetes, or elevated inflammatory markers—can justify referral for periodontal evaluation and supportive therapy, consistent with evidence-based periodontal management frameworks [37].

Integrated care is also important for safety and planning in advanced liver disease. Patients with cirrhosis may need pre-procedure assessment of bleeding risk (e.g., platelet count and coagulation profile) before invasive dental procedures; local hemostatic measures and coordinated management are often highlighted in clinical reviews, and anticoagulant/antiplatelet guidance generally supports proceeding with most dental procedures without routine discontinuation, using local measures when necessary [38, 39].

6.2.3 Patient-centered prevention messaging

Patient communication is most effective when it highlights shared, actionable factors rather than mechanical speculation. A practical message is that oral and liver health “share the same terrain”: excess adiposity, insulin resistance, smoking, poor diet quality, and low engagement in preventive care increase the risk for both severe periodontitis and metabolic liver disease. Therefore, lifestyle steps recommended for MASLD—such as weight reduction where needed, improving dietary quality, increasing physical activity, quitting smoking, and optimizing glycaemic control—also help maintain periodontal stability and improve treatment response [7].

For many patients, the most motivating framing is bidirectional benefit: “Treating gingival inflammation and maintaining regular supportive care helps reduce the chronic inflammatory burden and improves oral function, while metabolic risk control enhances gum healing potential.” This approach avoids overstating causality while still encouraging coordinated prevention. It also promotes shared-care workflows in which dentists reinforce metabolic risk modification messages already provided in hepatology and diabetes clinics, and medical teams normalize oral health referrals as part of comprehensive chronic disease management.

7. Methodological challenges and how to interpret the literature

7.1 Case definition heterogeneity (periodontitis and MASLD)

One major reason the evidence base seems inconsistent is that both “exposure” and “outcome” are often defined differently across studies. For periodontitis, current clinical guidelines are based on the 2017 World Workshop classification, which describes diagnosis and severity through staging and grading [9, 40]. However, epidemiologic studies often use older surveillance definitions, partial-

mouth protocols, index-teeth approaches, administrative codes, or self-report proxies—each capturing different aspects and leading to non-comparable misclassifications.

On the liver side, the ongoing transition from NAFLD/NASH to MASLD/MASH has improved conceptual clarity but has introduced additional definitional variation during the adoption phase [1, 2]. “MASLD” in observational datasets may be inferred from ultrasound reports, elevated aminotransferases, ICD codes, composite indices, elastography-derived stiffness, or biopsy. These methods differ in sensitivity, especially for mild steatosis, and in their association with prognostically meaningful endpoints, such as fibrosis [41, 42]. As a result, weak or no associations might reflect outcome misclassification rather than a true lack of effect.

7.2 Confounders and causal inference (smoking, BMI, diabetes duration, medications)

Shared determinants are significant and challenging to manage with routine covariate adjustment alone. Smoking, adiposity, glycemic burden (including diabetes duration and control), diet quality, socioeconomic status, health literacy, and access to preventive care all influence both periodontal health and MASLD risk, creating a complex confounding structure that varies across different settings and populations [40, 43]. Medication confounding is also substantial: statins, GLP-1 receptor agonists, SGLT2 inhibitors, metformin, anti-inflammatory agents, antibiotics, and proton pump inhibitors can alter metabolic profiles, inflammatory responses, and microbiome composition, and are also linked to healthcare utilization.

Interpretation improves when studies explicitly define a causal estimand (e.g., “effect of severe periodontitis on incident clinically significant fibrosis”) and

use causal diagrams to identify a minimally sufficient adjustment set rather than defaulting to "maximal adjustment" [44]. This is especially important because different covariate sets can significantly alter effect estimates and—depending on what is included—may increase bias rather than reduce it [45].

Genetic approaches can help identify causality but have their own limitations. Recent Mendelian randomization analyses examining periodontitis and fatty liver disease have found little or no evidence of a bidirectional causal effect, which might reflect a true absence of a strong genetic causal pathway, limited instrument strength for periodontitis phenotypes, phenotype heterogeneity, or gene–environment interactions not captured by MR assumptions [21]. These results are best viewed as one piece of evidence within a triangulation framework rather than as a definitive refutation.

7.3 Selection bias, collider bias, and measurement error

Selection mechanisms in oral–systemic research are rarely harmless. Limiting studies to dental attenders, insured populations, specialty clinics, or people with both dental and medical records can create collider structures that open non-causal pathways between periodontitis and systemic outcomes [46]. A practical example is conditioning on healthcare utilization (or linked claims availability), which is influenced by socioeconomic factors and comorbidity burden and can distort associations even after confounders are adjusted. Related collider bias has been empirically shown in periodontal–vascular epidemiology and should be considered plausible in the periodontitis–MASLD literature as well [47].

Measurement error is a recurring issue that affects both sides of the association. For periodontitis, partial-mouth recordings can significantly underestimate prevalence and skew risk

estimates compared to full-mouth protocols, with bias that may not be random across different levels of disease severity [48]. Statistical correction methods, such as multiple imputation, have been suggested to reduce partial-recording bias, but they require clear reporting of the recording protocol and the assumptions underlying it [49]. For MASLD, common tools such as conventional ultrasound may miss mild steatosis and depend on operator experience; noninvasive fibrosis scores and elastography are helpful but have threshold effects and age-related performance issues that can affect classification in cohort studies [41, 42].

Finally, reverse causality needs to be explicitly considered. Advanced metabolic disease can exacerbate periodontal inflammation through immune dysregulation, changes in saliva composition, medications, and health behaviors; therefore, cross-sectional associations should be interpreted with caution unless the timing of events is clearly established.

8. Knowledge gaps and future directions

8.1 Standardized phenotyping that is usable across disciplines

A persistent obstacle to synthesis is that “periodontitis” and “fatty liver disease” are often defined in ways that are not comparable across studies. Future research would benefit from adopting a minimum common dataset usable in both dental and medical research environments.

On the periodontal side, studies should align case definitions and severity reporting with the 2017 World Workshop framework, explicitly including staging and grading [40]. On the liver side, cohorts should clarify whether they use the terminology for steatotic liver disease and implement MASLD using clear metabolic criteria rather than exclusion-only rules, with transparent management of alcohol intake and other competing causes [43].

Since prognosis and clinical decisions are mainly influenced by fibrosis, MASLD phenotyping should involve a fibrosis-focused pathway (e.g., stepwise FIB-4 followed by elastography or second-line tests as appropriate), in line with current guidelines [42, 43].

Actionable recommendation: report (i) the periodontal stage, grade, and extent; (ii) the MASLD definition and metabolic criteria used; and (iii) at least one validated fibrosis assessment, such as a blood-based score or elastography, even if steatosis is the primary outcome (Table 2).

Table 3. Practical integration and minimum reporting set for periodontitis–MASLD research and care pathways

Domain	Minimum elements to report / implement	Rationale for MASLD–periodontitis literature
Periodontal phenotyping	2017-based case definition; stage, grade, extent; full-mouth protocol (or justified partial-mouth with correction); examiner calibration	Reduces exposure heterogeneity; enables severity gradients and comparability
MASLD/MASH phenotyping	Explicit MASLD criteria used; handling of alcohol/secondary causes; steatosis modality; fibrosis-oriented stratification (e.g., FIB-4 + elastography where feasible)	Aligns outcome to prognosis; supports “fibrosis-enriched” endpoints
Core confounders	Smoking (intensity/duration), BMI/waist, diabetes status and duration, HbA1c, BP, lipids; SES/education; diet proxies; dental attendance	Minimizes residual confounding; improves transportability across populations
Medications and exposures	GLP-1RA/SGLT2i/metformin; statins; antihypertensives; antibiotics; PPIs; anti-inflammatory drugs; timing relative to exams	Addresses confounding and microbiome-modifying effects
Bias safeguards	Recruitment/selection description; healthcare utilization measures; missing-data strategy; sensitivity analyses (unmeasured confounding, measurement error)	Limits selection/collider bias; increases credibility of causal interpretation
Integrated care triggers (clinical use)	Dental: metabolic risk check + referral triggers (T2D/obesity/metabolic clustering, history of fatty liver, abnormal enzymes). Medical: brief periodontal symptom screen + dental referral	Operationalizes bidirectional screening without overstating causality

8.2 Prospective cohorts with repeated oral and liver measures

Most existing evidence is cross-sectional or depends on single-timepoint measurements. What is needed are prospective cohorts that track trajectories—such as periodontal progression or remission, changes in metabolic risk, and liver fibrosis risk over time—rather than static “presence/absence” snapshots. This is particularly relevant given the heterogeneity of MASLD and the chance that oral effects, if any, will be most noticeable in metabolically vulnerable subgroups [3].

Actionable design elements include: full-mouth periodontal exams at baseline and follow-up, documentation of periodontal therapy exposure between visits, and liver phenotyping that encompasses steatosis modality plus fibrosis enrichment (e.g., elastography). Cohorts enriched for diabetes/prediabetes and obesity are especially efficient because these populations are already prioritized for fibrosis case-finding in clinical pathways [42, 43]. Repeated medication inventories (including incretin-based therapies, SGLT2 inhibitors, statins, antibiotics, and PPIs) and diet/behavior measures should be considered core variables, not optional

covariates, because they may act as confounders and effect modifiers.

8.3 Randomized periodontal intervention trials with liver endpoints

Interventional evidence remains the most direct way to determine whether periodontal therapy can significantly influence liver-related outcomes. A major advancement has been the emergence of randomized clinical trials in NAFLD populations comparing periodontal treatment to usual care, demonstrating feasibility and suggesting improvements in liver-related measures in specific settings [50]. However, current trials are generally small and often depend on enzymes or surrogate markers rather than fibrosis-focused endpoints.

Actionable next steps include pragmatic, adequately powered trials that:

- standardize periodontal therapy and supportive care using guideline-based pathways;
- utilize liver endpoints aligned with MASLD clinical risk stratification, such as non-invasive fibrosis scores, transient elastography, and—where feasible—MRI-based fat quantification;
- incorporate prespecified subgroup analyses (e.g., type 2 diabetes, high baseline fibrosis risk, severe periodontitis stage/grade); and
- monitor participants long enough to identify fibrosis-relevant changes, not just short-term transaminase shifts.

8.4 Multi-omics to connect “route” biology to measurable patient signals

Mechanistic models increasingly link oral–gut microbial exchange, barrier dysfunction, and metabolite signaling to connect periodontal inflammation and liver injury. Experimental research has identified manageable targets such as microbiota-dependent tryptophan metabolism and AHR signaling [6], while salivary microbiota transfer studies using

metagenomics and metabolomics have mapped liver effects downstream [34]. Concurrent reviews highlight that interactions between oral and gut microbiota are important for cardiometabolic health and may not be fully captured by taxonomy alone, emphasizing the need for functional and metabolite-based measurements [28].

Actionable “omics” packages for human studies should include: oral microbiome (subgingival and saliva), stool metagenomics, targeted metabolomics (tryptophan-derived indoles/kynurenines, bile acid profiles, SCFAs), and a focused inflammatory panel (e.g., CRP, IL-6, TNF-related markers). These should be collected longitudinally and linked to standardized periodontal and fibrosis phenotypes [51]. Importantly, multi-omics should be integrated into designs that can assess mediation and temporality, rather than being added as cross-sectional “associations of associations.”

8.5 Precision medicine: identifying who is most likely to benefit

It is unlikely that periodontitis has uniform effects across the MASLD spectrum. MASLD itself varies in its causes and in its response to treatment, which supports the use of phenotype-based grouping rather than one-size-fits-all approaches [3]. Periodontitis staging and grading offer a straightforward clinical framework for such grouping, reflecting both existing tissue damage and the likelihood of progression [9].

Actionable, precise directions include: identifying clinical phenotypes where the oral–gut–liver axis is most likely (e.g., obesity plus dysglycemia with high fibrosis risk, along with grade C periodontitis) [42, 43]; testing whether specific microbial or metabolite signatures predict liver risk or response to periodontal treatment [6]; and aligning endpoints with what matters clinically—fibrosis

progression and cardiometabolic risk—not just presence of steatosis [43].

9. Conclusions

Periodontitis and MASLD/MASH overlap due to shared cardiometabolic risk and plausible inter-organ biology. The MASLD framework highlights metabolic dysfunction and focuses on fibrosis risk as a key prognosis indicator, which is also the most relevant liver endpoint for periodontal-systemic research. Epidemiologic studies often show co-occurrence and, in some groups, severity gradients, but conclusions are limited by diverse definitions, residual confounding, and potential reverse causality.

Mechanistic models increasingly support an oral–gut–liver axis in which

periodontal dysbiosis and inflammation may lead to gut microbial changes, barrier dysfunction, and the transfer of inflammatory signals to the portal vein, worsening liver immunometabolic damage, especially in obesity-related cases. Currently, the most justifiable clinical takeaway is integrated risk awareness: dental teams can spot metabolic risk patterns and refer patients accordingly, while hepatology and metabolic clinics can add quick oral health screenings and referrals. Achieving clear clinical applications will require standardized phenotyping, prospective cohorts with repeated measures, and sufficiently large periodontal intervention trials that focus on fibrosis as an endpoint.

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