REVIEW ARTICLE

Periodontitis, chronic liver diseases, and the emerging oral-gut-liver axis

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1 | INTRODUCTION

Periodontitis is an oral chronic inflammatory disease which has been associated with a wide range of systemic disorders some of which include diabetes, inflammatory bowel diseases, cardiovascular diseases, cancer, neurodegeneration, rheumatoid arthritis, and chronic liver diseases.1-7 Periodontitis and these systemic conditions all share some degree of similarity in their pathophysiology which is characterized by a long-lasting deregulated inflammatory response.

Today it is recognized that genetic predisposition, exposure to acquired risk factors and epigenetic changes throughout life play a decisive role for the development of immune-based disorders by modifying the host’s susceptibility.8,9 Given that time is required for their onset, the inflammatory imbalance resulting from one disease could directly alter the pathophysiology of the other or they could simply occur in a host sharing a similarly disturbed immunological background favorable for the development of general chronic disorders. Regardless of the perspective to be taken into account, periodontitis has an important place, whether as a warning time marker for the predisposition of other chronic diseases, or as an independent factor for their development or clinical worsening with direct effects on patients’ uality of life, treatment outcome, and prognosis.

The increasing knowledge also suggests that imbalances in the microbiota-immunity interactions may contribute to the onset of a multitude of immune-mediated diseases.10 While how and when this dysbiosis develops in different organs is still unknown, oral bacteria such as Porphyromonas gingivalis and Fusobacterium nucleatum have been associated with various disorders distant from the oral cavity.11-13 In this context, interactions between oral and gut microbiomes are complex, dynamic, and context-dependent since both sites are part of the multivariate environment of the gastrointestinal tract. Under physiological conditions they can keep a fine-tuned balance across the lifespan, but failures in this crosstalk due to a host-microbe disequilibrium have the potential to activate inflammatory networks in different organs.14

The liver is among the organs that can be more affected by these biological networks and pathogenic disturbances since it maintains anatomical proximity and intense physiological interdependence with the intestine via metabolic exchange and translocation of bacteria. For this reason, interest in the so-called oral-gut-liver axis has emerged, along with the idea that the oral dysbiosis caused by unrestrained inflammation could affect the pathophysiology of chronic liver diseases via blood circulation or enteral route.1,15,16,17 The activation of a susceptible host immune system by pathogen- and damage-associated molecular patterns (PAMPs; DAMPs) in the periodontal milieu could induce the systemic overexpression of an array of pro-inflammatory cytokines and chemokines hence potentially impacting the hepatic metabolism.11 In parallel, oral bacteria in the context of periodontal dysbiosis could also invade the gut, spreading the adverse events to intestinal microbiome, and likely affecting liver functions.18 Similarly, liver dysfunction could also exacerbate the on-going pathology and clinical outcomes within the oral cavity.15 Herein, we provide an overview of the current clinical and epidemiological evidence for the association between periodontitis and chronic liver diseases, whilst we track their related mechanisms and discuss gaps to be filled by future research.

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2 | LIVER: AN ORGAN WITH MULTIPLE FUNCTIONS

The liver is the largest solid organ in the body and through the uptake, metabolism, and secretion of solutes performs an important role in the metabolism of lipids (lipogenesis), carbohydrates (glyco- genesis), proteins (synthesis of heptoglobin, albumin, and clotting factors), haemoglobin, bile salts, iron, vitamins, cupper, and drugs.\(^{19,20}\) Most of the chemical levels in the blood leaving stomach and intestine are regulated by the liver exposing it to a variety of dietary products, pathogens, endotoxin and microbial components coming from the gastrointestinal tract by the portal vein.\(^{20,21}\) Thus, liver serves as an important immunological site for cytokine signaling and acute-phase protein production thereby participating in the maintenance of the equilibrium between immune surveillance against pathogens and tolerance to innocuous antigens and commensal bacteria.\(^{22}\)

Hepatocytes are the dominant parenchymal cells in the liver constituting about 70%-85% of its volume and responsible to regulate part of its immune functions. Hepatocytes are also major producers of the liver extracellular matrix (ECM). In its physiological state, liver ECM is mainly composed of collagens, glycoproteins, proteoglycans, and hyaluronic acid.\(^{20,23}\)

Hepatic stellate cells (HSCs) are another major cell type in the liver. They are primarily located in the space of Dissé between the sinusoidal endothelial cells and hepatic epithelial cells, and account for about 5%-8% of the liver volume. Under homeostatic conditions, HSCs are non-parenchymal quiescent cells that contain numerous vitamin A lipid droplets, constituting the largest reservoir of this vitamin in the body.\(^{19,24,25}\)

On the immunological side, Kupffer cells are resident macrophages (Mφs) of the liver and form the main cell population. Their functions include the clearance of particles, immune complexes, senescent red blood cells, and endotoxins.\(^{26}\)

3 | CHRONIC LIVER DISEASES

Chronic liver disease (CLD) is an umbrella term which is used for reference to a set of pathologies characterized by a progressive deterioration of liver functions over six months or more. Recent reports suggest that CLDs account for approximately 2 million deaths per year worldwide (3.5% of all deaths), although exact statistics are not always available due to lack of a clear, well-established separation of CLD burden according to etiology and stage of disease across population-based studies.\(^{27,28}\) A broad spectrum of factors, such as viral infections, toxin exposure, alcohol abuse, autoimmune diseases, genetic and metabolic disorders, can trigger persistent inflammation with a consequent destruction of the liver parenchyma leading to the release of aspartate- and alanine- aminotransferases (AST; ALT), important markers of hepatic injuries.\(^{27-29}\) The following events include gradual replacement of the liver structures by fibrous tissues, and presence of compensatory hepatocyte hyperplasia which can culminate in end-stage liver diseases, namely cirrhosis and hepatocellular carcinoma.\(^{30,31}\) The pathological fibrosis occurs mainly as a consequence of a continuous excessive deposition of the ECM by injured mesenchymal cells. Due to persistent inflammation, ECM is subjected to qualitative changes in its composition with an accumulation of proteins, especially collagen type I and III.\(^{23,32}\) This process occurs because HSCs undergo transformation to become profibrogenic myofibroblasts, which can regulate matrix deposition and resorption whilst also have contractile properties. After activation, HSCs can enter in a perpetuation phase that comprises many functional properties including proliferation, fibrogenesis, chemotaxis, contractility, retinoid loss, and cytokine expression.\(^{21,25,33,34,35}\) These subsequent phenotypic changes eventually determine the course of the disease. The Figure 1 summarizes the CLD stages.

4 | THE ASSOCIATION BETWEEN PERIODONTITIS AND CHRONIC LIVER DISEASES

The initial studies investigating the relationship between periodontitis and CLDs date back to 50s and 60s.\(^{34,37}\) Today, the interest in evaluating the interaction between oral and hepatic diseases has grown even further as we develop a more comprehensive understanding of the onset and progression of chronic diseases. Although occurring in distant parts of the body, these pathologies share several etiological factors on their onset and portray an unbalanced inflammatory response in a susceptible host. Therefore, it is not surprising that recent epidemiological and clinical studies suggest an association between CLDs and periodontitis (Figure 2).

4.1 | Non-alcoholic fatty liver disease and Periodontitis

Non-alcoholic fatty liver disease (NAFLD) is a condition characterized by the storage of excess fat in the liver in the absence of excessive alcohol consumption, a process that in most patients occur due to metabolic risk factors, such as obesity, diabetes mellitus, and dyslipidemia.\(^{38,39}\) NAFLD encompasses a spectrum of liver diseases including simple fatty liver, also called nonalcoholic fatty liver (NAFL), and nonalcoholic steatohepatitis (NASH). NAFL is characterized by the excess accumulation of triglycerides in hepatocytes (>5% fat content in the liver; referred to as hepatic steatosis) with little or no inflammation or liver cell damage. By contrast, NASH is defined as the presence of hepatic steatosis along with lobular or portal inflammation, and ballooning degeneration of hepatocytes (a form of cell death) that entail liver injuries with or without fibrosis.\(^{38,40}\) The rate of NAFLD is estimated to be 24% worldwide and the disease incidence continues to rise likely due to an increase in the prevalence of its risk factors such as obesity and diabetes. Based on the
prevalence of biopsy-proven NASH in patients with NAFLD (6.7%–29.9%), it is assumed that approximately 1.5% to 6.5% of the general US population has NASH.28,41,42

Lipotoxicity is one of the key pathophysiological processes in NAFLD and occurs when the liver is exposed to high levels of circulating free fatty acids, as well as high levels of insulin, which is produced to compensate for systemic insulin resistance in obesity and/or diabetes, as well as other highly toxic lipid metabolites such as ceramides, diacylglycerols, and oxidized cholesterol metabolites.43 In this lipotoxic milieu, the liver itself also contributes to hepatic steatosis by synthesizing lipids from carbohydrates by de novo lipogenesis, which in a homeostatic liver is not a primary source of lipid.38,44

The demand for metabolizing excess fatty acids places strain on hepatocyte mitochondria, which over time increases the production of reactive oxygen species (ROS).45 Periodontitis and NAFLD share numerous risk factors and the progression of both diseases can be aggravated by insulin resistance and the increased systemic pro-inflammatory profile found in diabetic and obese individuals. Additionally, both diseases also appear to affect the course of other systemic disorders such as cardiovascular diseases.11,39 In fact, the overproduction of ROS is a common finding in periodontitis patients as well.46

While recent epidemiological studies and systematic reviews investigating the relationship between periodontitis and NAFLD suggest possible associations, a causal link between the two conditions is still elusive.16,47,48,49,50,51,52,53,54 Akinkugbe et al48 investigated whether periodontitis could contribute to the onset of NAFLD through evaluating data from the Pomerania-based cohort. The incidence of NAFLD and periodontal disease status was monitored in 2,623 participants for 7.7 years follow-up. After adjusting for founders such as excessive alcohol consumption, hepatitis diagnosis in past years, and use of hepatotoxic medications, the NAFLD incidence was moderately elevated with a ratio of 1.60 (1.05-2.43) in subjects who at baseline had ≥30% of periodontal sites with CAL≥3mm.48

In another cohort, Kuroe et al55 investigated whether periodontitis could affect the progression of NAFLD towards fibrotic liver injuries in a Japanese population. 341 subjects with NAFLD diagnosis without liver fibrosis at baseline were followed-up for 5-years. The results indicated that having moderate to severe periodontitis increased the risk of developing liver fibrosis with an odds ratio of 2.06 (0.89-4.76). Similarly, in a national Finnish cohort of 6,165 individuals who have been monitored for ~12-years, Helenius-Hietala and collaborators showed that the presence of advanced periodontitis and diagnosis of NAFLD at baseline increased the incidence of severe liver events including hospitalization due to liver disease, liver-related death, or a diagnosis of primary liver cancer.56

Most of these studies used hepatic ultrasound and/or measurement of serum levels of general liver injury markers, such as AST and ALT to diagnose and monitor NAFLD without making any distinction between NAFL and NASH. The inflammatory component of liver injury is present in NASH but not in NAFL and the actual diagnosis of NASH requires microscopic evaluation of liver to check for ballooning degeneration, which is an obstacle for population-based studies and identifying associations with periodontitis.27,38

To overcome this, Alazawi and colleagues conducted a longitudinal
study which monitored several parameters associated with NAFLD and periodontitis in a group of 45 NAFLD cases. The investigators performed biopsies to differentiate those with NAFL and NASH and defined NASH with minimum or no fibrosis, or NASH with significant fibrosis. The results demonstrated increased periodontitis prevalence in patients with liver biopsy-proven NASH fibrosis. Similarly, Iwasaki et al. reported increased prevalence of NAFLD which was accompanied by higher stages of periodontitis severity and elevated serum levels of CRP in a cross-sectional study. Consistently, Akinkugbe and collaborators reported positive association between presence of periodontitis, prevalence of NAFLD and elevated serum CRP levels. Together, these findings indicate an association between NAFLD and periodontitis.

Studies also assessed the association of periodontal pathogens and other oral bacteria with NAFLD/NASH. Alazawi et al. evaluated the link between periodontitis and liver fibrosis in a population-based study including 8,153 NHANES III participants and reported significant association between increased levels of *Streptococcus noxia* and *S. oralis* serum antibodies and hepatic steatosis. Komazaki et al. investigated serum antibody response against periodontal bacteria, including *Aggregatibacter actinomycetemcomitans*, *F. nucleatum*, and *P. gingivalis*, in 52 individuals diagnosed with NAFLD and reported significant correlation between anti-*A. actinomycetemcomitans* IgG antibody titers and the levels of AST. However, the results were not adjusted for confounding variables. Similarly, Nakahara et al. demonstrated a significant correlation between fibrosis progression and serum antibody titers against *P. gingivalis* fimA type 4 in biopsy-proven NAFLD patients and suggested that this pathogen could regulate the transition from NAFL to NASH. In another study, Furusho et al. detected *P. gingivalis* in 21 of 40 liver biopsy specimens.
collected from patients with NASH, corresponding to 52.5%. Further, *P gingivalis*-positive cases presented higher total fibrosis scores including perisinusoidal and periportal fibrosis. Whether this periodontal pathogen could migrate from the oral cavity to the liver and contribute to the underlying intestinal dysbiosis found in NAFLD/NASH patients is still not known and need to be further investigated.

Few recent clinical studies investigated the impact of periodontal treatment on NAFLD/NASH outcome. Yoneda et al performed an interventional study to assess whether periodontal treatment in NAFLD patients with periodontitis could regulate NAFLD biochemical parameters and reported a reduction in ALT and AST levels following periodontal therapy within 3 months. Recently, Kamata and colleagues published a protocol for a multicenter randomized clinical trial aiming to evaluate whether periodontal treatment decreases liver damage and endotoxemia in patients with NAFLD and the results of this study are expected to be available in the near future.

As the emerging evidence supports a possible link between NAFLD and periodontitis, future studies are needed to determine the power of these associations and the biological mechanisms connecting these conditions. It is also possible that the effect might be bidirectional and NAFLD can affect periodontitis outcomes as well, which again needs to be further investigated. In addition, so far populational-based cohorts have only been carried out in Europeans and Japanese, which limits the external validity of these findings and warrants investigations in other cohorts.

### 4.2 Chronic hepatitis and Periodontitis

Chronic hepatitis B (CHB) infection is characterized by the detection of HBsAg antibodies and viral genomic materials in the serum, resulting from enduring active replicative and transcriptional activities of the human hepatitis B virus (HBV). The HBV is a member of the Hepadnaviridae Family, and its long-term infection strongly depends on age at acquisition. It is estimated that worldwide 257 million (3.5%) people have CHB, and the National Health and Nutrition Examination Survey (NHANES) estimates the US prevalence as 840,000 (0.35%). This is the highest prevalence among hepatitis viruses despite existence of an effective vaccine to prevent this infection. From a public health perspective, large-scale HBV vaccination would be expected to reduce the incidence of new infections and their complications.

Chronic hepatitis C (CHC) is defined by active long-term carriage of the human hepatitis C virus (HCV), a hepatotrophic RNA flavivirus. Most of the individuals infected with HCV fail to clear the infection, which commonly leads to a stage of CHC. The global prevalence of HCV infection is estimated in 1%, with 71 million people living with CHC. Despite the availability of testing and a new generation of highly effective specific direct-acting antivirals, approximately 400,000 people still die each year due to CHC related complications.

The association between chronic hepatitis and periodontitis was initially discussed by the fact that viruses, such as HCV and HBV, can be found in saliva. Oral fluids are effectively used for large-scale HBV detection and are known routes of transmission for this virus. Oral transmission of HCV, on the other hand, is a matter of debate. This virus is transmitted mainly by the parenteral route but in 30%-40% of CHC patients the source of infection is unidentified, and, besides its hepatotrophic nature, the HCV has a strong lymphotropism. Not surprisingly, this virus can be traced in fluids that have mononuclear blood cells in their composition, including saliva and gingival crevicular fluid (GCF); some studies reported prevalence of HCV ranging from 31% to 100% in saliva and GCF samples with a great variability according to the study population and method of viral RNA extraction and detection. Its potential sources could include transmigrated leukocytes through periodontal epithelium, salivary glands, and peripheral blood mononuclear cells from bleeding tissues in the oral mucosa. Interestingly, serum viral load and periodontal status do not appear to affect the detection of HCV RNA in the saliva of patients with CHC. Given that these viruses can be traced in GCF and saliva, their potential effect on the development and/or progression of periodontal diseases in individuals affected by their respective chronic infections has also been investigated, although no definitive conclusion has been reached.

Extrahepatic manifestations are common in chronic viral hepatitis, and it is thought that they can be related to complex immunological mechanisms (de) regulated by viruses. For example, in the oral cavity, lichen planus and xerostomia have been reported in both CHC and CHB patients. A cross-sectional study assessed possible impact of HCV on periodontal diseases where individuals with chronic infection by HCV were compared to the general population by using the Community Periodontal Index Treatment Needs (CPITN) and reported no differences in clinical parameters between groups. Some of the limitations of the study included lack of calibration among clinical evaluators and collection of some of the data through a telephone interview survey. Surlin et al compared 13 systemically healthy periodontitis patients versus 11 asymptomatic CHC patients and reported similar degrees of periodontitis severity despite higher levels of IL-1α and IL-1β in the GCF of the CHC group. This study, however, did not report clinical attachment loss and relevant confounding demographic data. In another study, the degree of inflammation was reported to be higher in gingival biopsies from periodontitis patients with chronic HCV infection compared to those without HCV infection using optical coherence tomography. Intriguingly, Marrone and collaborators followed a cohort of patients with implants of at least 5 years of function for the frequency of mucositis and peri-implantitis and reported that those with a history of hepatitis were more susceptible to develop peri-implantitis.

When compiling these data, it is difficult to conclude whether chronic liver infections by HBV or HCV could play a role in the etiopathogenesis or progression of periodontitis. The scientific evidence available on this theme is very scarce and only a few epidemiological studies have been published which did not address important factors. Notwithstanding, it is increasingly clear that the mammalian virome, which includes diverse commensal and pathogenic viruses, can evoke a broad range of immune responses. As part of this notion,
a two-way interaction between chronic hepatitis and other inflammatory conditions like rheumatoid arthritis has been assessed.81,82 These conditions have similarities with periodontitis, which push the periodontology to move forward in order to perform well-designed epidemiological and mechanistic studies to investigate possible link.

4.3 | Cirrhosis and Periodontitis

Liver cirrhosis is an end-stage CLD that is characterized by the formation of regenerative nodules surrounded by fibrous bands in response to several years of inflammation and fibrosis. Clinically, it can be presented in compensated or decompensated stages. Decompensated stage coexists with life-threatening complications, such as chickenpox hemorrhage, ascites, spontaneous bacterial peritonitis, and hepatic encephalopathy.31 Globally, the number of patients with cirrhosis is increasing, and currently it accounts for 1.16 million deaths per year, which makes it the 11th most common cause of death. In Western and industrialised countries NAFLD/NASH is overtaking chronic hepatitis as the primary etiology for cirrhosis, whereas in China and other Asian countries CHB continues to be a leading underlying cause.27,83

Cirrhosis develops following multiple lifelong injuries and can have several etiologies, including alcohol abuse, chronic hepatitis, and NAFLD/NASH,31 thereby the assessment of another risk factor, such as periodontitis in this process is not an easy task. Earlier studies reported poor oral hygiene to explain the higher prevalence, extent, and severity of periodontitis in patients with cirrhosis.84,85 However, the current evidence suggests this crosstalk can be far more complex, and periodontitis could impact the course of this liver disorder and vice versa.

In a Danish cohort study, Ladegaard Grønkjær et al86 followed 184 patients diagnosed with cirrhosis (most of them alcohol- or cholestatic-cirrhosis) for approximately 1 year and reported that the diagnosis of severe periodontitis at baseline predicted a higher cirrhosis-related mortality with an adjusted odds ratio of 2.29 (1.04-4.99). This study highlights the need for closer attention to oral health in the clinical care of patients with cirrhosis. The results of a recent systematic review showed increased association between cirrhosis without any distinguished underlying etiology and periodontitis, which could reach up to a OR of 2.28 (1.5-3.48).80 Notably, Costa et al87 reported that individuals with cirrhosis (72% due to alcohol abuse) exhibited two times increased prevalence of periodontitis than healthy controls independent of alcohol use status. These findings suggest that there might be a bidirectional effect between these two conditions and that the pro-inflammatory environment related to cirrhosis might impact periodontitis as well. In support of this, Jaiswal et al88 reported a strong positive correlation between periodontal breakdown and serum alkaline phosphatase level in cirrhotic patients with or without periodontitis.

Studies that evaluated the benefits of periodontal treatment for patients with cirrhosis are still scarce. Lins et al89 reported that subjects with cirrhosis (most of them due to CHC) that underwent periodontal treatment presented a lower mortality when compared to non-treated patients. In this study, they did not mention which periodontal treatment was performed, as well as the follow-up period, which limits a generalization of the findings. Notably, a recent clinical trial conducted by Bajaj and colleagues evaluated the impact of periodontal treatment on different hepatic parameters in cirrhotic patients with multiple underlying etiologies including CHC, alcohol abuse, and NASH.2 Periodontal intervention reduced serum levels of endotoxin, LPS binding protein, and IL-6, as well as salivary levels of IL-1β, principally in cases of cirrhosis with hepatic encephalopathy one-month post-therapy. In addition to this systemic immunomodulatory effect, an improvement in the cognitive functions was also reported after the therapy.27 The overall findings of this study underscore the periodontal treatment as a target to reduce inflammation and endotoxemia in these individuals, which needs to be further investigated in larger cohorts and long-term trials.

Remarkably, there is also evidence of possible crosstalk between the oral microbiota and liver function in cirrhosis. Jensen et al90 evaluated the subgingival microbiome of 21 patients suffering from cirrhosis and periodontitis and reported the abundance of Firmicutes and to a lesser extend Actinobacteria and Bacteroidetes. In the same study, bacteria considered as periodontal pathogens, like Porphyromonas gingivalis, T forsythia, and T denticola, were found in low abundance. The authors suggested that a compromised immune system in cirrhosis could lead to dysbiosis and render commensal bacteria pathogenic. In another study, Ghapanchi et al91 reported increased level of E coli in the saliva of cirrhotic patients when compared to age- and sex-matched healthy controls suggesting that oral cavity could possibly serve as a reservoir and alter the intestinal microenvironment. Consistently, Qin et al18 reported that major changes in the gut microbiota in individuals with cirrhosis could be associated with the invasion of the gut by oral bacterial species. The study showed a high proportion of denoted metagenomic species belonged to Veillonella and Streptococcus taxa in the gut microbiome of cirrhotic patients compared to healthy controls.18 While the origin of these species can be both oral cavity and small intestine, an elegant genetic tracking revealed that most of them were of buccal origin. It was further hypothesized that an altered epiphenomenon allowed by an impaired gastric acid and bile secretion that is prevalent in cirrhosis could render the gut more permissible or accessible to oral bacteria.18,92 Among the cirrhosis-enriched species in the intestine were S anginosus, Veillonella atypica, Veillonella dispar, Veillonella sp oral taxon, and Campylobacter concisus. Indeed, other studies also showed a higher abundance of Streptococcaceae and Veillonellaceae in the intestinal microbiome of chronic hepatitis and cirrhotic patients albeit the findings for Veillonellaceae seem to be conflicting.93-95 One of the major findings of these studies was to highlight the translocation of oral microbiota as a factor for the gut dysbiosis in cirrhosis. More recently, Dubinkina and colleagues reported increased oral microbes, S constellatus, S salivarius, V atypica, V dispar, and V parvula in the stool of cirrhotic patients. The authors also observed an increase of typical commensal species, namely
**Bifidobacterium** (B longum, B dentium, and B breve), Streptococcus (S thermophilus and S mutans), and Lactobacillus (L salivarius and L crispatus).\(^6^\) Consistently, Bajaj et al\(^7\) described that the salivary dysbiosis in cirrhosis is characterized by an increased abundance of Enterobacteriaceae, and reduction of autochthonous taxa (Lachnospiraceae, Ruminococcaceae). It was noted that this microbial composition could predict a higher rate of hospitalization regardless of disease severity, in a similar fashion to that reported for intestinal dysbiosis. Furthermore, in a proof-of-concept clinical trial, it was demonstrated that the periodontal treatment modulates the gut microbiome of patients with cirrhosis.\(^1\) Specifically, the authors reported reduced levels of Streptococcaceae and Enterobacteriaceae and increased proportion of Ruminococcaceae in patients’ faeces when compared to non-treated cirrhotic control. Streptococcaceae cluster was also decreased in the salivary microbiome.\(^1\) Increased levels of enterobacteria can weaken the gut barrier by reducing the expression of tight-junction proteins, which increases the permeability and translocation of intestinal bacteria and their products to the liver.\(^3^,^7\) Therefore, decreased levels of these bacteria as a result of periodontal treatment seem to provide beneficial effect. Intriguingly, the study also found higher levels of Veillonellaceae and Lactobacillaceae (commonly associated with a healthy periodontal status) and lower abundance of Porphyromonadaceae and Fusobacteria (commonly associated with a pathogenic periodontal environment) in the saliva of cirrhotic patients, which remained unaltered even after periodontal therapy.\(^1\) It is also of note that higher salivary levels of IL-6, IL-1\(\beta\), and secretory IgA along with lower levels of lysozyme and histatins in cirrhosis further indicate an overall mucosal-immune imbalance and strengthen the notion that oral-gut-liver axis can be an alternative source of inflammatory load in these patients.\(^1\)

### 4.4 Hepatocellular carcinoma and Periodontitis

Hepatocellular carcinoma (HCC) is the sixth most frequent neoplasia and the fourth leading cause of cancer-related deaths worldwide, causing over 800,000 deaths annually. About 80% of HCC cases is due to CHB and CHC infections and the rest involves alcohol abuse, NASH and NAFLD.\(^2^,^3^\) These factors can act independently or together to increase susceptibility for cirrhosis, which in turn creates an environment permissive for the development of HCC. Therefore, current screening recommendations focus primarily on patients with cirrhosis.\(^2^) In fact, around 90% of HCC cases exhibit cirrhosis, yet less than 5% of patients with cirrhosis progress to HCC. Emerging paradigm proposes that these end-stage liver diseases could originate from independent pathological responses controlled by different molecular mechanisms rather than a sequential series of events.\(^9^8\)

Epidemiological studies suggest a positive correlation between periodontitis and overall cancer risk including HCC with systemic inflammation serving as the main focus for biological plausibility.\(^9^9\) However, additional prospective studies are needed to better elucidate the strength of these relationships. A cohort based on NHANES III showed an association between severe periodontitis and mortality risk for oral digestive cancers including HCC, but the authors discussed that the study had limited power to evaluate mortality risks for specific cancers.\(^1^0^0\) To address this gap, a recent prospective study reported sufficient power to examine an association between tooth loss and liver cancer incidence. In a Finnish cohort with 29,096 male smokers who were followed up for 17 years, Yang et al\(^1^0^1\) reported that individuals presenting 11-31 permanent teeth loss or edentulism at the baseline (surrogate markers of periodontitis) were more likely to develop HCC; HR of 1.42 (1.01-1.98) and 1.45 (1.00-2.10), after adjusting for confounding factors, respectively. Since this study only included smokers, its generalizability is limited, albeit it outlines the impact of a possible history of periodontitis on hepatocarcinogenesis. One of the plausible mechanisms for this association might be the increased levels of oxidizing compounds in the circulation due to the inflammatory destruction of periodontal tissues.\(^4^6\) Consistently, a case-control study reported 25.8% higher levels of reactive oxygen species (ROS) in HCC individuals with moderate/severe periodontitis compared to those without periodontitis.\(^1^0^2\) Patients with periodontitis exhibited worse cancer staging and liver function when compared to non-periodontally affected controls, indicating poor prognosis.\(^1^0^2\) Yet, further studies are warranted to fully establish this association.

### 4.5 Liver transplant recipients and Periodontitis

Liver transplantation (LT) is a lifesaving procedure for patients with chronic end-stage liver disease and acute liver failure when there are no available medical and surgical treatment options. Most countries use the model for end-stage liver disease (MELD) score for LT listing and recipient selection. Globally, LT is the second most common solid organ transplantation.\(^2^7\) Cirrhosis accounts for most of the LTs performed in adults, although the underlying etiologies have changed over the past few years. According to the Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients (OPTN/SRTR) 2018 annual data, cirrhosis secondary to alcohol abuse or other/unknown factors (often NASH) contributed for 27.4% and 33.3% of the LTs, respectively. HCC is other well recognized indication for LT, accounting for about 16.9% of these procedures.\(^1^0^3\) In the past, chronic HCV infection was responsible for the largest number of LTs, but such cases have reduced dramatically due to the rapid advance in the treatment of HCV with highly effective and well tolerated drugs.\(^1^0^4\) At a long-term, 5 and 10-year patient survival outcomes have been shown more favorable for those with non-HCC diagnoses.\(^1^0^3\) Post-transplant long-term complications are highly related to the immunosuppressive treatment. Increased risk for osteoporosis or altered bone metabolism in LT recipients result from a combination of low bone mineral density before transplantation due to hepatic osteodystrophy, malnutrition, and steroid use after transplantation.\(^1^0^5\) The combination of tacrolimus, mycophenolate, and steroids is reported to be the predominant

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**References**: (Please provide the references for the citations mentioned in the text.)
regimen, and must be optimized according to each underlying etiology, as well as the control of each associated risk factor, in order to achieve the long-term success of the therapy.\textsuperscript{103}

Patients with end-stage chronic liver disease candidates for LT in general have worse periodontal indexes and higher prevalence of severe periodontitis.\textsuperscript{106,107} Thus, it is routine clinical practice to treat periodontitis prior to LT.\textsuperscript{108} This is based on the premise that untreated dental disease may pose a risk for infection and sepsis, although there is no evidence that this has occurred in LT candidates or recipients. Much more common, changes in periodontal tissues ensue following LT likely because of immunosuppressive treatment. LT is associated with an overall medical and functional recovery for most patients but a longitudinal improvement in periodontal parameters is unclear. Thus, the question to be answered is whether there could be any changes in the status of periodontal diseases in post-transplanted (post-LT) recipients. In this regard, Machtei et al\textsuperscript{109} evaluated the periodontal status of 17 post-LT patients in a non-interventional prospective study of 10 years and showed that periodontal probing depth was significantly lower within the post-LT group after the followed-up period. A clinical trial assessed the impact of the nonsurgical periodontal therapy on cyclosporine-induced gingival overgrowth. After 12 months intervention, total inflammatory cells, gingival vessels, and fibroblast proliferation rate were reduced in gingival biopsy specimens, indicating a strict biofilm control program as critical to maintain periodontal health in post-LT patients taking this immunosuppressant.\textsuperscript{110} Further, a recent observational study reported that pre- and post-LT patients have similar needs for periodontal treatment and comparable rates of moderate or severe periodontitis.\textsuperscript{111} Given that there is interplay between periodontal tissues and hepatic pathophysiology, it still remains to be determined the outcome of an uncontrolled periodontitis on LT survival.

5 | ORAL-GUT-LIVER AXIS

Considering the evidence from the epidemiological and clinical studies discussed above, it is plausible that an unbalanced oral-gut-liver axis could trigger further liver inflammation. Yet, while the precise source or direction of these pathological changes remains elusive, it is widely accepted that occurrence of dysbiotic microbiota coupled to dysregulated immune response drives the disease outcomes.\textsuperscript{112} One of the most important links between gut microbiota and extra-intestinal organs is the bidirectional gut-liver axis.\textsuperscript{114} This reciprocal interaction is established through the vascular route of the portal vein that carries gut-derived products directly to the liver, and the liver feedbacks by the route of bile acids and antibody secretion to the intestine.\textsuperscript{115} Thus, the liver shapes the intestinal microbiome which mutually impacts liver functions, especially in the context of dysbiosis.\textsuperscript{117} A dysfunctional gut microbiota weakens intestinal tight junctions and accordingly increases mucosal permeability, which enables bacterial metabolites and MAMPs/DAMPs to reach the liver via portal circulation and in several cases promote endotoxemia. These molecules then act directly on hepatocytes, Kupffer cells, and HSCs through activation of pattern recognition receptors, including TLRs and NOD-like receptors, hence triggering downstream pro-inflammatory cascades.\textsuperscript{97,113,118}

Therefore, given the role of an intestinal dysfunction in the pathological physiology of CLDs and considering the aforementioned data reporting gut microbiome associated changes linked to oral bacteria in patients with CLDs, it is likely that oral-gut-liver axis could trigger or substantiate hepatic inflammation which warrants further investigations. In this regard, pre-clinical assays using well-established disease models are useful tools to dissect the possible biological mechanisms linking oral cavity to liver pathology which will be discussed in the following sections.

6 | PLAUSIBLE MECHANISMS CONNECTING THE ORAL-GUT-LIVER AXIS

6.1 | Effect of periodontal pathogens on liver pathophysiology

Several studies have used in vivo disease models in mice, rats, and rabbits to assess the effect of major periodontal bacteria, particularly \textit{P gingivalis}, on liver tissues using various delivery routes such as oral gavage, or injection of live bacteria and/or bacterial components into dental pulp, intraperitoneal, intravascular, and intragingival spaces. The results of majority of these investigations support the hypothesis that keystone periodontal bacteria may in fact induce direct liver damage.\textsuperscript{58,59,60,119,120,121,122,123,124} In a murine model of NAFLD induced by high-fat diet, Yoneda et al\textsuperscript{60} noted increased body and liver weight accompanied by exacerbated lipid accumulation in liver tissues, and elevated ALT and liver triglyceride levels following injection of \textit{P gingivalis} Type II \textit{fimA} via jugular vein. These hepatic changes were not observed with other non-pathogenic periodontal bacteria such as \textit{S mutans}, \textit{S sanguinis}, and \textit{S salivarius}, suggesting that a NAFLD progression could be a \textit{P gingivalis}-specific event.\textsuperscript{60} In a similar model in rabbits, intragingival injection of LPS from \textit{P gingivalis} promoted progression from NAFLD to NASH by boosting hepatic lobular inflammation and serum levels of gamma-glutamyl transferase (GGT) which is a surrogate marker of liver injuries.\textsuperscript{124} In another study, Fujita et al\textsuperscript{125} tracked biodistribution of radiolabeled \textit{P gingivalis} LPS from gingiva to the brain, liver, kidney, and spleen and noted increased predilection of this endotoxin for the liver. The study also reported elevated lipid deposition, presence of large fat droplets, and focal necrosis with inflammatory cells, and numerous ballooning degenerations around the central vein which resemble histopathological characteristics compatible with NASH following gingival application of LPS.\textsuperscript{125} Corroborating the in vivo data, human HepG2 hepatocytes which were challenged with oleic acid to mimic NASH milieu and \textit{P gingivalis}-derived LPS exhibited increased accumulation of intracellular lipids, upregulation of MyD88 expression and phosphorylation of p65 and JNK, and increased release of pro-inflammatory cytokines (eg IL-1\beta, IL-8, and TNF-\alpha) compared to those cells that were not treated with LPS.\textsuperscript{126} Further, the
lipid accumulation was reduced following suppression of this signaling pathway which suggests a possible role of MyD88-NF-κB cascade in the NASH pathology associated to this pathogen.\textsuperscript{126}

In an odontogenic infection model that used high-fat diet fed mice and bacteria injection into the dental pulp, \textit{P. gingivalis} was able to exacerbate NASH lesions and increased the levels of MCP-1, TNF-α and IL-17 in the liver.\textsuperscript{59} There was also increased infiltration of liver parenchyma with Mac2\textsuperscript{+} (Galectin-3) M\textsubscript{φ}s, a marker which is considered as one of the most important molecules to induce liver fibrosis towards cirrhosis.\textsuperscript{127} Consistently, Nakahara et al\textsuperscript{58} reported upregulation of NLRP3 and Casp-1 in hepatocytes by \textit{P. gingivalis}-LPS which could potentially contribute to the overproduction of pro-inflammatory cytokines. It was noted that the disruption of liver metabolism by the bacterial infection and inflammatory microenvironment can lead to an increase in the proportion of oleic acid (C18:1) and palmitoleic acid (C16:1) which further contributes to the liver metabolism by the bacterial infection and inflammatory microbial outer membrane vesicles (OMVs).\textsuperscript{123} In fact, Arg-\textsuperscript{X} (RGP, Arg-gingipain) and Lys-\textsuperscript{X} (KGP, Lys-gingipain) specific proteases have been shown to participate in various other pathologies distant from the oral cavity including Alzheimer’s disease, rheumatoid arthritis, cardiovascular disease, diabetes, and even cancer.\textsuperscript{130} To the best of our knowledge, no study has yet evaluated whether this pathogen would have any specific role in the viral hepatitis chronicity or in the etiopathogenesis of HCC, although its role in the carcinogenesis of other types of cancer has already been described.\textsuperscript{131}

The oral cavity is a complex microbial ecosystem; thus, from the perspective of species-specific mechanisms, other bacteria hypothetically can have an important role in the regulation of liver functions. To assess this, germ-free mice were orally administered with either oral pathobionts (\textit{P. gingivalis}, \textit{Filifactor alocis}, and \textit{F. nucleatum}) or bacteria associated with periodontal health (\textit{Actinomyces naeslundii}, \textit{S. mitis}, and \textit{V. ragosae}) and monitored for bacterial accumulation, antibody levels and inflammatory mediator expression.\textsuperscript{122} The only bacteria isolated from liver specimens was \textit{F. nucleatum} whereas strong systemic antibody response was detected for \textit{P. gingivalis} and \textit{V. ragosae}. In addition, the endoplasmic reticulum stress-related gene DNA Damage-Inducible Transcript-4 was upregulated in the liver samples from the group orally infected with the pathogenic consortium.\textsuperscript{132} \textit{V. ragosae} was the only microorganism detected within the intestinal ecosystem. In fact, the oral commensal consortium increased the expression of TNF-α in small intestine samples, whereas pathogenic species upregulated IL-17a.\textsuperscript{132} Collectively, this finding shows that a symbiotic relationship between these bacteria and the host can be reached in the oral environment, but not in the intestinal mucosa, where their presence can cause an immune imbalance and possible pathology.

While all of these investigations are valuable to understand the mechanistic link between periodontitis and systemic complications, the results should be interpreted with caution. One key limitation of these preclinical studies is that putative periodontal pathogens are not part of the murine microbiota and the parenteral administration, and the high microbial concentration used in several assays may not be a good representation of the normal human physiology. Additionally, for future studies, it will be important to include control infections with other microorganisms to understand whether this effect is bacterial-specific or simply a widespread effect of bacterial inoculation.

6.2 | Effect of periodontal pathogens on liver pathophysiology via gut induced dysbiosis

The oral cavity harbors the second-largest and diverse microbiota after the gut and interacts with various microbial populations at
different sites of the body.\textsuperscript{77} Indeed, individuals with periodontitis may also present with intestinal dysbiosis, although the precise source or direction of this oral-gut dysbiosis route remains elusive.\textsuperscript{133,134} Studies with bacteria associated with periodontitis, especially strains of \textit{P. gingivalis} and \textit{A. actinomycetemcomitans}, have shown that these microorganisms can promote liver dysfunction by inducing gut dysbiosis with changes in the composition of the intestinal microbiota similar to those observed in patients with CLDs (Figure 3).

In mice with a normal diet, the oral gavage administration of \textit{P. gingivalis} increased intestinal abundance of \textit{Bacteroidetes} over \textit{Firmicutes} which was then followed by down-regulation of the tight junction proteins in the small intestine and up-regulation of the proinflammatory cytokines IL-6, IL-12\(\beta\), IFN-\(\gamma\), and IL-17c in the large intestine which collectively favor the breakdown of the gut barrier.\textsuperscript{119} Tracking a flow of events along a biological axis, \textit{P. gingivalis} infection also increased the number of lipid containing hepatocytes. There was also elevated number of transcripts of TNF and IL-6, as well as fat storage inducing transmembrane protein-2 and perilipin-2 in the liver, both of which strongly associated with lipid droplet formation.\textsuperscript{119} Another study used intravenous injection of sonicated \textit{P. gingivalis} in high fat diet fed mice and noted that lysates of the pathogen reduced the presence of \textit{Ruminococcaceae} in the gut, whereas \textit{L. johnsonii} and \textit{L. reuteri} became overrepresented.\textsuperscript{122} Notably, these gut imbalances induced by \textit{P. gingivalis} match with the clinical findings for most of the CLDs.\textsuperscript{93,135,136,137,138} Moreover, sonicated \textit{P. gingivalis} increased liver steatosis and upregulated the hepatic expression of acetyl-CoA carboxylase, glucokinase, glucose transporter-2, and glucose-6-phosphate, as well as of a set of genes related to fatty acid metabolism.\textsuperscript{122} A shift in the gut microbiota composition and increased liver steatosis were also observed during oral infection.

**FIGURE 3** Proposed role of oral microbiome in oral-gut-liver axis. Individuals with periodontitis present microbial dysbiosis in different compartments of the oral cavity, especially in periodontal pockets, which is also accompanied by dysbiosis in the intestinal microbiota. In cases of chronic liver diseases, particularly cirrhosis, swallowed bacteria of the oral niche can reach the intestine since an underlying reduction of gastric acid secretion can occur in these conditions. An overgrowth of oral bacteria in the intestine triggers an inflammatory response that increases the permeability of the intestinal mucosa. Then, MAMPs, particularly LPS, can cross the damaged gut epithelial barrier and reach the liver via portal circulation where they trigger or exacerbate pre-existing chronic liver inflammation. This figure was created using BioRender
with \textit{A. actinomycetemcomitans}. This periodontal pathogen impaired glucose tolerance and insulin resistance in mice feeding a normal or high fat diet.\cite{57} In addition, marked lipid accumulation was found in the liver, which consistently exhibited higher gene transcription of Acetyl-CoA carboxylase, an enzyme involved in hepatic lipid metabolism, and glucokinase, a master glucose sensor for regulation of insulin release.\cite{57} The results of these investigations are similar to those reported in \textit{P. gingivalis} infection model, and, by examining the intestinal microbiome following \textit{A. actinomycetemcomitans} infection, there was significantly less abundance of \textit{Turicibacter}, member from the phylum Firmicutes, in faeces.\cite{57}

Collectively, there is general agreement between clinical and experimental studies suggesting a specific role for some periodontal pathogens in the regulation of the oral-gut-liver axis, either through hematogenous or enteral route, especially in the context of NAFLD/NASH progression.

### 6.3 Host susceptibility in oral-gut-liver axis

As in any chronic inflammatory disease, it is the host response which dictates the clinical outcomes in the course of periodontitis and CLDs.\cite{13,139,140} Therefore, it will likely be the host which sets the relationship between these conditions as well. Yet, the studies are still scarce characterizing specific immune pathways in relation to oral-gut-liver axis. A study in which a cohort was followed over 8 years revealed an association between elevated serum levels of ALT, a well-known marker of liver injury, and higher periodontal probing depth.\cite{141} Consistently, using murine ligature-induced periodontitis model Mester et al\cite{142} reported extensive microvesicular steatosis around the central liver vein as well as expansion of the portal spaces with deposition of mature fibrous tissue. The study also revealed elevated levels of malondialdehyde (a marker of lipid peroxidation), and MMP8 in serum, gingiva, and liver.\cite{142} As these emerging investigations are starting to shed light on the possible immunological mechanisms which can favor the progression of liver diseases in patients with periodontitis, and vice versa, it will be important to carefully dissect the information from the existing literature for each individual condition and plan future studies to fully elucidate the interplay between oral and liver diseases (see Figure 4).

In the course of periodontal disease, circulating neutrophils (N\(_\phi\)) and monocyte-derived M\(_\phi\)s isolated from the peripheral blood of patients with periodontitis elicit a hyperinflammatory phenotype characterized by elevated basal expression of proinflammatory cytokines (eg IL-1, IL-6, TNF, CXCL8) and ROS.\cite{143-145} These responses are further aggravated upon priming of these cells with LPS.\cite{146,147} In addition, these cells also exhibit altered phagocytic activity,\cite{145} which is further decompenated by hyposensitiveness to chemotractants.\cite{145} Similarly, M\(_\phi\)s isolated from patients suffering with NAFLD also exhibit a hyperinflammatory phenotype and reduced phagocytic function.\cite{26,74} While the consequences of these cellular alterations on liver diseases are not yet known, these common pathways may likely drive the clinical pathology. Specifically, under the recent perspective an altered training of the innate immune response could mediate the association of periodontitis with other inflammatory comorbidities but we do not know yet if this applies to oral-gut-liver axis.\cite{13}

M\(_\phi\)s are considered as the major cells mediating NAFLD where resident Kupffer M\(_\phi\)s play essential role during the early phases of liver injury through the production of TNF-\(\alpha\) and chemoattractants. During the later stages of the disease, CCR2\(^+\) monocyte-derived M\(_\phi\)s are recruited from peripheral blood and acquire a pro-inflammatory phenotype that increase the susceptibility to endotoxemia and amplify the development of NASH and fibrosis.\cite{74,149,150,151} In addition, the overproduction of ROS metabolites is also a shared feature of the NAFLD lipotoxicity and hepatocarcinogenesis\cite{38,45} which can likely be a mechanism to accelerate the progression of NASH and HCC. Consistently, a recent study using a mass cytometry immunoassay in the peripheral blood of patients with moderate to severe periodontitis and healthy controls revealed that monocytes from periodontitis patients display a hyperinflammatory phenotype through the canonical activation of the NF-\(\kappa\)B/ERK pathway, while CD56\(^-\)CD16\(^+\) NK cells unexpectedly stay hypo-responsive characterized by reduced response to GM-CSF and TNF-\(\alpha\) challenge.\cite{152} Considering NK cells are effectors of virus clearance and cancer surveillance,\cite{153} it can be speculated that their anergy could contribute to HBV/HCV survival and HCC development. In fact, this overlapping feature could be further aggravated by the presence of other dysfunctions in the NK phenotype in CHB and CHC. For example, during chronic hepatic infections, NK cells display reduced capacity to produce IFN\(\gamma\), which is an important effector function for HCV control, and an upregulated expression of the apoptosis-inducing ligand TRAIL that can induce virus-specific CD8\(^+\) T cells depletion.\cite{154-156}

At the intersection of the innate and adaptive immune systems, it is worth noting that circulating CD14\(^+\) monocytes of periodontitis patients also induce CD4\(^+\) T cells to overproduce IL-17, prompting them to a Th17 response.\cite{157} Similarly, IL-17 is a known pro-fibrogenic interleukin in the pathophysiology of liver cirrhosis and its excess is also related to intestinal barrier dysfunctions associated with the disease.\cite{158} In fact, both cytotoxic and helper T cells appear to be altered in the peripheral blood of individuals with severe periodontitis and a recent study noted an increase in the population of both CD8\(^+\)CCR7\(^-\) and CD4\(^+\)CCR7\(^+\) central memory T cells.\cite{159} While the total number of CD4\(^+\) T cells is increased in individuals presenting with severe periodontitis, these cells exhibit reduced ability to produce IFN-\(\gamma\) even after stimulation with pathogens. In addition, the number of circulating CD4\(^+\)IFN-\(\gamma\) is also reduced in this patient population.\cite{160,161} IFNs are key for the immunity against viruses, and a deficiency in their synthesis could potentially compromise the antiviral immune defense in chronic hepatitis. HBV is termed as a "stealth virus" since its polymerase inhibits the transcription of Type I IFNs (IFN\(\alpha\) and IFN\(\beta\)), which together with type III IFNs (IFN\(\lambda\)) are major mediators of the antiviral immune system.\cite{162} Therefore, HBV has very strong interference mechanisms for the IFN response\cite{162,163} and CHB progression could be altered due to this unbalanced systemic environment existing in periodontitis patients.
Emerging evidence also implicates microRNAs as critical regulators of the immune response based on their ability to interfere with the post-transcriptional expression of multiple target genes. Periodontitis patients seem to have an altered systemic profile of microRNAs, and their serum or peripheral blood mononuclear cells exhibit an up-regulation of several of these small RNAs, including miR-9, miR-155, miR-203a, miR-182, miR-147, miR-664a, miR501, and miR-21.164,165 An array of microRNAs has also been reported in the pathophysiology of chronic hepatitis, progression from NAFLD to NASH, and hepatocarcinogenesis,166-168 and a differential expression of miR155 seems to be overlapping periodontal and liver diseases.164,167,168 Given that these small RNAs can elicit diverse effects by reaching distant organs, presumably they can be another source of interaction which deserves more attention in future research which evaluates oral and liver diseases.

7 | CONCLUSIONS AND PERSPECTIVE

Collectively, the clinical evidence shows an association between periodontitis, NAFLD/NASH and cirrhosis, although a causal relationship is unclear. To fill this gap in the knowledge, more mechanistic and clinical studies are needed to assess whether the control of periodontitis in these patients could have any beneficial effect on the clinical outcomes of the liver diseases. To date, periodontal treatment seems to alter the composition of the intestinal microbiota of cirrhotic patients and modulate their systemic immune response. Evidence also suggests that the intestinal exposure to oral commensal microbiome has the potential to exacerbate the gut dysbiosis underlying NAFLD and cirrhosis. This exposure can lead to an unprecedented increase in the abundance of oral species in the intestine, hence triggering an overstimulation of the immune response with reflexes in liver physiology via portal circulation. The periodontitis-associated dysbiosis seems to aggravate the liver pathology, but the mechanisms of ectopic colonization of the gut by oral bacteria are underexplored. Therefore, further studies are needed to clarify whether oral microorganisms can reach the liver via hematogenous route, or whether indirect modulation via oral-gut-liver axis prevails. In addition, it should be noted that similar to cirrhosis and NAFLD, periodontitis is also characterized by intestinal dysbiosis; thereby, it must be elucidated whether this microbial shift is a causal marker, or a consequence of a dysregulated inflammatory response shared by both diseases.

There is not enough evidence showing any relation between periodontitis and chronic viral hepatitis. It is therefore plausible that chronic hepatitis could offer another platform for exploring the role
of viruses in the etiopathogenesis of periodontitis. Similarly, the link between periodontitis and HCC is also not defined due to lack of epidemiological evidence. Further studies are needed to understand the mechanisms by which periodontitis can alter the process of hepatocarcinogenesis. In this regard the systemic role of ROS metabolites produced in excess by immune cells during the course of periodontitis deserves attention.

From an immunological point of view, much has to be done to clarify the association between periodontitis and CLDs. Hypothetically, the pro-inflammatory systemic profile found in periodontitis could promote catastrophic consequences on the liver pathophysiology under high oxidative stress or endotoxemia in cases of NAFLD/NASH and cirrhosis, or under chronic pathogenic challenge in cases of viral hepatitis. Recently, maladaptive bone marrow-mediated trained immunity has been hypothesized to occur in periodontitis which could potentially link it to inflammatory comorbidities. Whether and how this maladaptive immune training of bone marrow progenitors could alter the human hepatic environment is unclear and needs to be investigated.

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