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ASSOCIATION BETWEEN PERIODONTITIS AND LIVER DISEASE

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SUMMARY – Recent clinical and scientific evidence confirms the negative impact of long-term periodontitis on the clinical course and progression of various liver diseases. Periodontitis is a chronic, slow-progressing infectious disease of the tooth supporting tissues caused mainly by the gram-negative bacteria *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Treponema denticola* and *Tannerella forsythia*. These specific pathogens can be easily translocated from oral cavity to the intestine. Disruption of the intestine microbiota composition by orally derived periodontal pathogenic bacteria has recently been suggested to be a causal mechanism between periodontitis and liver disease. Furthermore, both diseases have the ability to induce an inflammatory response and lead to the creation of inflammatory mediators through which they may influence each other. Recent epidemiologic studies have demonstrated that individuals with liver cirrhosis have considerably poorer periodontal clinical parameters than those without cirrhosis. Periodontal therapy in cirrhosis patients favorably modulates oral and gut microbiome, the course of systemic inflammation, cirrhosis prognostic factors, and cognitive function. Therefore, future clinical researches should be focused on detailed examination of the biological mechanisms, strength and direction of the association between advanced liver disease and periodontitis.

Key words: *Inflammation; Liver diseases; Oral health; Periodontitis*

Introduction

Periodontitis is a chronic, slow-progressing infectious disease of the tooth supporting tissues that, if left untreated, leads to tooth loss. It is estimated that the global prevalence of periodontitis is high, 20%-50%¹, which ranks it at the very top, more precisely at the sixth place of the most common diseases of the population². The latest data show that as many as 11.2% of

the world's population suffer from the most severe forms of periodontal disease³. In adults, periodontitis develops as a result of loss of natural balance between oral microbiota and host resistance influenced by some lifestyle factors such as inappropriate oral hygiene and smoking, combined with compromised host defenses due to certain genetic changes or the presence of some systemic disease that adversely affects the host immune system⁴. Periodontal inflammation is localized in periodontal tissues and does not have very pronounced subjective symptoms, and often remains clinically unrecognized and thus untreated. As a consequence of untreated inflammatory changes, the epithelium of deep periodontal pockets disintegrates and

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becomes the *locus minoris resistentiae* for the entry of different microorganisms into systemic circulation. Systemic effects of periodontitis are believed to arise from a combination of disseminated toxins, bacterial insult, and the action of both innate and adaptive immunity⁵.

Chronic liver disease leads to a progressive, long-lasting deterioration of liver function due to different etiologic factors⁶. Various insults can injure the liver, including viral infections, toxins, alcohol abuse, metabolic and hereditary conditions, or autoimmune processes⁷. Chronic liver disease usually progresses to cirrhosis, which represents a final stage of liver disease. In the developed world, the most common causes of cirrhosis are nonalcoholic fatty liver disease (NAFLD), hepatitis C virus infection, and alcoholic liver disease⁸. It is estimated that more than 1.5 billion people in the world, taking the adult population, would be affected by chronic liver disease⁹. Liver cirrhosis is currently the 11th most common cause of death globally¹⁰.

Growing clinical and scientific evidence confirms the negative impact of long-term chronic periodontal infection on the clinical course and progression of various liver diseases such as NAFLD, development of cirrhosis and hepatocellular carcinoma, as well as on the success of liver transplantation¹¹⁻¹⁴.

The aim of this paper is to review the current knowledge about the possible mechanisms of the interaction between periodontal infection and liver diseases, in order to raise awareness of this issue within the health community. The method to conduct this narrative review used PubMed search for peer-reviewed articles related to periodontitis and liver disease utilizing periodontitis, liver disease, inflammation and oral health as searching terms.

Periodontitis as a Risk Factor for Systemic Diseases

A large number of bacterial species were found in subgingival plaque samples from individuals with periodontitis. It has been estimated that, under favorable conditions (anaerobic environment of deep periodontal pockets), the total number of periodontal pathogens can rise to up to 10¹⁰ bacteria in only one periodontal pocket¹⁵. Therefore, the existing periodontal infection (untreated gingivitis or periodontitis) represents a focus from which different pathogenic micro-

organisms can easily spread into circulation through the ulcerated epithelium of deep periodontal pockets and subsequently cause various changes in distant tissues and organs including liver tissue¹⁶.

Periodontal disease is often referred to as a 'mixed bacterial infection' to emphasize that the development of the disease is affected by multiple bacterial species, not just one. It is caused mainly by gram-negative bacteria, the so-called periodontal pathogens, including *Aggregatibacter (A.) actinomycetemcomitans*, *Porphyromonas (P.) gingivalis*, *Prevotella (P.) intermedia*, *Treponema (T.) denticola* and *Tannerella (T.) forsythia*¹⁷. These bacteria and their toxins activate the local inflammatory response leading to the formation and secretion of various inflammatory mediators (cytokines) that enhance the activity of tissue collagenases and matrix metalloproteinases resulting in destruction of the surrounding periodontal tissue¹⁸.

In the last twenty years, significant progress has been made in the field of identification and characterization of periodontal pathogens and their products, which enabled better understanding of their potential impact on systemic health. Two mechanisms have been proposed through which the existing periodontal disease can affect systemic health. The first is a direct consequence of dental plaque bacteria entering the bloodstream (bacteremia) and causing pathologic changes on the remote tissues in the body. This is the reason why people with damaged or artificial heart valves and other cardiac defects are at a high risk to suffer bacterial endocarditis if transient bacterial pathogens from bloodstream reach these heart areas where blood flow is chaotic¹⁹. The second mechanism is through the indirect influence of periodontally induced inflammatory mediators such as cytokines, prostaglandins and serum antibodies. The best example is two-way relationship between periodontal disease and diabetes mellitus. While diabetes predisposes oral tissues to further periodontal destruction, numerous studies have shown that periodontal disease contributes to weak glycemic control. Both conditions have the potential to cause an inflammatory response, which results in the release of inflammatory mediators. These proinflammatory cytokines such as interleukin (IL)-6 impair the glucose-stimulated release of insulin from the pancreas²⁰. Recent epidemiologic studies have found that patients with chronic periodontitis have higher glycemic levels compared to non-peri-

odontitis healthy individuals, and the improvement in oral hygiene has a beneficial effect on controlling glycemic levels²¹. Epidemiologic, microbiologic and immunologic studies are increasingly confirming that periodontal disease is a separate risk factor not only for cardiovascular disease and diabetes mellitus, but also for some other conditions and diseases such as respiratory diseases (acute bacterial pneumonia, chronic obstructive pulmonary disease (COPD)), preterm delivery, rheumatoid arthritis, cancer, and possibly liver diseases²²⁻²⁸. Periodontitis can be associated with the development of liver steatosis, since the bacteria, their toxins and proinflammatory cytokines released during inflammation can easily enter the bloodstream and reach liver tissue, leading to lipid peroxidation and oxidative stress, which are important factors involved in the development of steatosis²⁹. However, this is a bidirectional relationship because results of some studies have confirmed that advanced alcoholic cirrhosis increases the risk of developing advanced forms of periodontitis in these patients³⁰⁻³². They observed a negative impact of liver disease on periodontal health under the clinical features of advanced periodontal destruction with deep periodontal pockets and extensive loss of clinical attachment and alveolar bone. Furthermore, a study showed that patients with cirrhosis had poor oral hygiene³³. Such condition contributes to the development of serious oral infections that may have a negative impact on general health and consequently on poor control of an underlying disease such as cirrhosis.

The Oral-Gut-Liver Axis

Bacteria of the red complex (*P. gingivalis*, *T. forsythia*, *T. denticola*) play a major role in the pathogenesis of periodontitis and these bacteria can be found in large numbers in active periodontal lesions and deep periodontal pockets³⁴. These specific periodontal pathogens can be easily translocated from oral cavity to the intestine by swallowing and thus influence substantial change in intestinal microbiome³⁵. Disruption of the intestinal microbiota composition by orally derived periodontal pathogenic bacteria has recently been suggested to be a causal mechanism between periodontitis and systemic disease, especially liver disease³⁶⁻³⁸. Periodontitis may be of particular concern in liver cirrhosis patients due to translocation of oral bac-

teria and their toxins to the intestine and the likelihood of subsequent liver-related complications. Systemic endotoxemia, typically originating from the intestine, is associated with liver damage, progression of liver disease, and cirrhosis decompensation³⁹. Dysbiosis can cause an increase in the activation and production of TLR4 receptors and proinflammatory cytokines, which can lead to recruitment and activation of hepatic immune cells, contributing to the progression of liver disease⁴⁰. Some researchers believe that oral microbiota plays a substantial role in overall endotoxemia and systemic inflammation in cirrhosis patients due to the fact that patients with periodontitis have greater salivary dysbiosis⁴¹.

Rising evidence underpins the bidirectional relationship between the gut microbiome and the liver. The liver is receiving 75% of its blood supply from the intestines through the portal vein⁴², and is discharging bile acids into the biliary tract⁴³. Intestinal microbiota and bacterial products may contribute to the development of liver disease through multiple mechanisms including increased intestinal permeability, chronic systemic inflammation, production of short-chain fatty acids, and changes in metabolism⁴⁴. Dysbiosis, or an adverse alteration in the microbiome structure, is well known to occur in advanced liver disease and other intestinal abnormalities, with a decrease in autochthonous (*Firmicutes*) bacteria and an increase in other taxa (*Bacteroidetes*, *Actinobacteria*)⁴⁵. According to the studies by Ling *et al.*⁴⁶ and Tilg *et al.*⁴⁷, dysbiosis of the intestinal microbiome in liver cirrhosis patients is primarily caused by increased oral bacteria abundance in patients with some infectious oral disease such as periodontitis when compared to healthy controls. Salivary dysbiosis in these patients may be associated to an oral proinflammatory environment, systemic inflammation, and represent a risk of subsequent liver-related hospitalization⁴¹.

Periodontal Pathogens and Their Impact on the Liver

Yoneda *et al.*¹² were the first to report an association of periodontitis with NAFLD and suggest that infection with *P. gingivalis*, one of the major periodontal pathogens, could be a risk factor for the development and progression of NAFLD. In order to clarify the link between NAFLD and *P. gingivalis* infection, the au-

thors conducted multiple regression analysis in NAFLD patients and control group using different demographic variables. The results of the analysis showed a statistically significantly higher prevalence of *P. gingivalis* infection in NAFLD patients when compared with control healthy subjects, even after adjustment for age, presence of diabetes mellitus, and body mass index (BMI). The detection rate of *P. gingivalis* infection in NAFLD patients was 46.7%, which was significantly higher compared to 21.7% in control group. It is important to note that there were no significant differences in the incidence of infections caused by any other bacterial species between NAFLD patients and healthy controls. In NAFLD patients positive for *P. gingivalis*, a statistically significant decrease in serum albumin levels was observed, indicating liver function impairment. Furthermore, there was a tendency, but not significant, of an increase in the levels of hyaluronic acid and type IV collagen, which are indicators of the progression of liver fibrosis. These findings implicate that persistent *P. gingivalis* infection in patients with untreated periodontitis may accelerate liver tissue fibrosis and decrease liver function. This is in agreement with another study, the results of which led to a conclusion that *P. gingivalis* infection might be an independent predictor of NAFLD development⁴⁸.

Areas of fibrosis with hepatic stellate cell proliferation and collagen formation were observed in high-fat diet laboratory mice (C57BL/6J) with experimentally induced periodontal infection caused by *P. gingivalis*. The expression of toll-like receptor 2 (TLR2), one of the *P. gingivalis*-lipopolysaccharide (LPS) receptors, was significantly increased in steatosis-affected hepatocytes. Furthermore, *P. gingivalis*-LPS increased the levels of proinflammatory cytokine mRNA in these cells⁴⁹. These findings implicate that through stimulation of the *P. gingivalis*-LPS-TLR2 pathway and activation of proinflammatory cells, untreated dental infection may accelerate pathologic progression of non-alcoholic steatohepatitis (NASH) to fibrosis.

Komazaki *et al.*⁵⁰ examined the association of periodontitis and NAFLD by measuring the titer of IgG antibodies to periodontal pathogens (*A. actinomycetemcomitans*, *P. gingivalis* and *F. nucleatum*). The results of the study showed that the presence of *A. actinomycetemcomitans* increased hepatic steatosis. Oral administration of *A. actinomycetemcomitans* in experimental animals resulted in increased mRNA expres-

sion of acetyl-CoA carboxylase (an enzyme involved in liver lipid metabolism) and glucokinase. The results also showed that mRNA expression of tumor necrosis factor- α (TNF- α), IL-6 and IL-1 beta in the liver tissue did not show significant differences between control experimental animals and experimental animals with *A. actinomycetemcomitans*. Therefore, the authors concluded that the changes observed in liver function were not due to direct inflammatory changes, but to changes in the composition of intestinal flora, and concluded that *A. actinomycetemcomitans* infection was a potential risk factor for NAFLD.

Immune Aspects and Bidirectional Relationship

The pathogenesis of acute and chronic liver diseases is cytokine-driven as several proinflammatory cytokines (IL-1 α , IL-1 β , TNF- α and IL-6) are critically involved in inflammation, steatosis, fibrosis, and cancer development⁵¹. Systemic inflammation is mediated through the activation of all innate and adaptive immune cells, resulting in an increased production of proinflammatory cytokines and upregulated expression of cell activation markers⁵². In compensated cirrhosis, ligands released from necrotic hepatocytes may activate the immune system and cause sterile systemic inflammation⁵³. Besides that, cirrhosis causes a number of defects in the innate and adaptive immune response, such as impaired neutrophil function, reduced complement system efficiencies, decrease in the number and function of monocytes, natural killer cells and lymphocytes⁵⁴. This immune dysfunction in patients with liver cirrhosis is often referred to as immune paralysis. Therefore, it is possible that immune response deficiency, which is linked to higher susceptibility to a variety of infectious diseases, could also play a role in identifying higher periodontitis risk in these patients. It was observed that patients with cirrhosis had a significantly higher prevalence of periodontitis (62.2%) when compared to healthy individuals from the control group (41.8%). Multivariate analysis showed that cirrhotic patients had approximately 2 to up to 3 times higher chance of having periodontitis than healthy controls³².

The dominant features of gingivitis and periodontitis are inflammatory and immune reactions. Inflammation is visible both microscopically and clinically in the affected periodontal tissues and it is the host re-

sponse to dentobacterial plaque microorganisms and their products. Periodontitis is a result of the interaction between pathogenic bacteria from the biofilm and an exacerbated immune response with an onslaught of different inflammatory mediators, which has destructive effects on periodontal tissues. The inflammatory mediators produced as part of the host response which contribute to tissue destruction include proteinases, cytokines and prostaglandins. Matrix metalloproteinases (MMPs) are considered to be primary proteinases involved in periodontal tissue destruction by degradation of extracellular matrix molecules (collagen, gelatin, and elastin)⁵⁵. Other proteinases associated with periodontitis include neutrophil serine proteinases, elastase, and cathepsin G¹⁸. Besides them, two proinflammatory cytokines, IL-1 and TNF, appear to have a central role in periodontal destruction⁵⁶.

Communication between remote organs is an essential key point in understanding systemic effect that inflammation has on the entire body. While inflammatory processes in one organ are likely to cause pathologic changes in the neighboring tissues, the fact that circulating inflammatory mediators may cause inflammation changes in distant tissues within the body should not be ignored¹⁶. Periodontitis and liver disease have one thing in common, and that is the ability to induce an inflammatory response and lead to the creation of inflammatory mediators through which they may influence each other. Serum cytokines are elevated in patients with liver disease as a result of liver dysfunction. Elevated concentrations of cytokines represent a characteristic feature of chronic liver disease regardless of the underlying disease, suggesting that enhanced endogenous cytokine levels represent a consequence of liver dysfunction rather than of inflammatory disease. The cirrhotic group of chronic liver disease patients showed higher serum levels of IL-1 beta, IL-6, TNF and C-reactive protein than did non-cirrhotic cases and these differences were statistically significant⁵⁷. High serum levels of these enzymes may enhance periodontal destruction by increasing collagenase and MMP activity in periodontal tissues⁵⁸. This is consistent with epidemiologic findings showing that liver disease has a negative impact on periodontal health, manifested as advanced periodontal destruction with deep periodontal pocket depth, severe clinical attachment, and alveolar bone loss^{30,31,59}. Individuals with cirrhosis have considerably poorer

periodontal clinical parameters than those without cirrhosis, including fewer teeth, a higher mean plaque index score, higher mean number of sites with excessive bleeding upon probing, higher percentage of sites with deep periodontal pockets, and advanced clinical attachment loss³². Periodontal disease was found to be more common in healthy Japanese women with elevated serum levels of aspartate aminotransferase (AST), and cholinesterase⁶⁰. On the other hand, advanced periodontitis may have a harmful effect on liver health. Systemic inflammation due to advanced chronic periodontitis has negative impact on liver cirrhosis by affecting the function of tissue somatic cells and thus changing clinical manifestation of the disease. In other words, systemic inflammation promotes hemodynamic derangement of cirrhosis, which correlates negatively with disease prognosis⁶¹. These findings suggest that periodontal and liver disease, especially liver cirrhosis, could have a bidirectional adverse effect on each other due to inflammatory nature of these two diseases.

Periodontitis Related Liver Tissue Changes

Porphyromonas gingivalis and other periodontal pathogens have the capacity to translocate to the liver and internalize into hepatocytes⁶². These pathogens and their harmful products (LPS) cause parenchymal damage and subsequent release of alanine aminotransferase (ALT) from damaged cells. When bacterial LPS enter the bloodstream, they increase the levels of inflammatory cytokines, in particular TNF- α , which can lead to periodontal tissue destruction, as well as damage to liver parenchymal tissue. Thus, bacterial LPS and TNF may be important mediators in the relationship between periodontal and liver disease⁶³.

Several studies have shown that experimentally induced periodontitis in rats caused distinctive systemic damage, especially ultrastructural changes in the liver tissue⁶⁴⁻⁶⁶. Histopathologic evaluation of liver tissue in rats with periodontitis revealed degenerated and disorganized hepatocytes⁶⁷. Investigators observed substantial fatty accumulation in the hepatocytes, which is the main characteristic of steatosis, indicating liver tissue damage⁶⁸. More detailed electron microscopic examination at the cellular level showed significant increase in the size and number of lipid droplets, distance between the cisterns of rough endoplasmic reticulum,

mitochondria size, foamy cytoplasm, and glycogen accumulation in the liver of the periodontitis group compared to control group. Furthermore, serum levels of alkaline phosphatase, high-density lipoprotein, triglycerides and total cholesterol were significantly higher in the periodontitis group when compared with control group⁶⁴.

Beneficial Effect of Periodontal Therapy

In the vast majority of cases, periodontal treatment is a conventional, noninvasive procedure, thus relatively inexpensive, with undeniably positive effects in terms of improving oral and general health. Standard healthcare in the treatment of serious liver diseases such as cirrhosis usually does not include oral health care. However, recent clinical trials confirm that proper diagnosis and successful periodontal treatment may be of great help in reducing inflammation and toxins in the blood, while also enhancing cognitive function in patients with cirrhosis, especially those with hepatic encephalopathy⁶⁹. Hepatic encephalopathy is a brain dysfunction caused by liver failure, which allows substances such as ammonia to accumulate in the brain and produce deleterious effects on brain function⁷⁰. Periodontal therapy in those patients favorably modulates oral and gut microbiome, course of systemic inflammation, cirrhosis prognostic factors, and cognitive function over the span of 30 days. On the contrary, patients without periodontal therapy showed an increase in endotoxin and lipopolysaccharide binding protein over the same period of time⁶⁹.

According to the preliminary data, nonsurgical periodontal treatment in NAFLD patients improved liver function parameters such as serum levels of AST and ALT 3 months after treatment¹². As stated by some researchers, reduced ALT level indicates less hepatocyte damage and inflammation in the liver tissue⁷¹, but does not indicate changes in steatosis⁷².

These improvements in clinical parameters were associated with increased patient quality of life and cognition. Therefore, it is crucial to raise awareness within the medical and dental professionals and encourage interdisciplinary cooperation, so that patients with specific systemic disorders such as cardiovascular, pulmonary, metabolic and liver diseases can be timely referred to dental practitioners for examination, diagnosis and, if necessary, dental treatment.

Conclusion

Both liver diseases and periodontitis are important global health concerns among adult population. Results of recent studies suggest a possible link between these two pathologic conditions. In order to develop feasible and effective prevention strategies for liver diseases, better understanding of the relationship between these two disorders is of great importance. Therefore, future clinical researches in this field should be focused on detailed examination of the biologic mechanisms, strength and direction of the association between advanced liver disease and periodontitis.

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Sažetak

POVEZANOST PARODONTITISA I BOLESTI JETRE

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Rezultati novijih kliničkih i znanstvenih istraživanja potvrđuju negativan utjecaj parodontitisa na klinički tijek različitih bolesti jetre. Parodontitis je kronična, sporo napredujuća infekcija potpornih tkiva zuba uzrokovana uglavnom gram negativnim bakterijama *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Treponema denticola* i *Tannerella forsythia*. Ovi mikroorganizmi mogu vrlo lako iz usne šupljine dospjeti u crijeva uzrokujući promjenu crijevnog mikrobioma, što se smatra jednom od mogućih poveznica između parodontitisa i bolesti jetre. Nadalje, obje bolesti su upalnog karaktera i uzrokuju stvaranje različitih upalnih medijatora putem kojih mogu utjecati jedna na drugu. Nedavna epidemiološka istraživanja pokazala su da bolesnici s cirozom jetre imaju značajno lošiji parodontni status u odnosu na zdrave ispitanike. Uočeno je da parodontna terapija kod bolesnika s cirozom jetre pozitivno utječe na oralnu i crijevnu mikrofloru, tijekom upalnih procesa, prognostičke čimbenike i kognitivnu funkciju. Stoga se buduća klinička ispitivanja trebaju usredotočiti na proučavanje bioloških mehanizama, jačine i smjera povezanosti uznapredovale bolesti jetre i parodontitisa.

Ključne riječi: *Upala; Bolesti jetre; Oralno zdravlje; Parodontitis*