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# The Relationship Between Periodontitis and Hepatitis C

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## Abstract

**Background**: Hepatitis C virus (HCV) infection affects 3% of the global population. The liver plays an important role in the balance of the immune system, so hepatitis C can cause disturbances in this system. These changes also manifest orally, making hepatitis C patients more susceptible to inflammatory diseases of the oral cavity, such as periodontitis.

**Objective**: This study was conducted to determine the pathogenesis of chronic hepatitis C, the pathogenesis of periodontitis, and the relationship between the pathogenesis of chronic hepatitis C and periodontitis.

**Methods**: This study was conducted using a literature review method with Google Scholar as the database.

**Results**: HCV infection causes a decline in the oral health of infected patients. Increased levels of IL-1α and IL-1β, which have significant implications in the pathogenic processes of periodontitis and chronic hepatitis C.

**Conclusion**: Chronic hepatitis C and periodontitis have a two-way relationship that influences each other. The inflammatory process is the key underlying the relationship between the two.

**Keywords:** Inflammation; Hepatitis C; Periodontitis; Immune System

## 1. Introduction

According to the World Health Organization (2024), approximately 10.3 million people in Southeast Asia are chronically infected with the hepatitis C virus (HCV). Viral hepatitis continues to pose a major public health challenge in the region, with an estimated 410,000 deaths each year. Remarkably, around 78% of these deaths are related to liver cancer and cirrhosis resulting from hepatitis B and C infections. In Indonesia, the 2013 National Basic Health Research (*Riset Kesehatan Dasar*, Riskesdas) reported that about 2.5 million individuals were infected with HCV (Ministry of Health, 2021). Furthermore, surveillance data from the Hepatitis and Gastrointestinal Infection Information System (SIHEPI) documented 2,950 anti-HCV–positive cases in referral hospitals across West Java between November 2018 and November 2023. These data indicate that the burden of HCV infection remains high and highlight the urgent need for strengthened screening, prevention, and comprehensive treatment strategies in the region [24].

Beyond its hepatic manifestations, HCV infection also has implications for extrahepatic organs, including the oral cavity. One of the most relevant conditions is periodontitis, a chronic inflammatory disease caused by the accumulation of subgingival biofilm. The prolonged presence of pathogenic bacteria promotes colonization by virulent microorganisms and the production of toxins that penetrate gingival tissues, initiating the characteristic inflammatory response of the disease. The impact of periodontitis is not limited to local tissue destruction, as the periodontium is highly

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interconnected with vascular, neural, and lymphatic systems throughout the body. Hence, systemic pathological changes can influence periodontal health, while periodontal inflammation may also affect systemic conditions. This bidirectional relationship has led to the concept known as "periodontal medicine" [21].

HCV infection can disrupt metabolic balance and immune regulation due to the liver's central role in maintaining these systems. Such disturbances may negatively affect oral health, making HCV-infected individuals more susceptible to inflammatory periodontal diseases [6]. Periodontal inflammation increases gingival crevicular fluid (GCF) flow and gingival bleeding frequency. This fluid contains serum, inflammatory mediators, and microbial components derived from the vascular network of periodontal tissues, facilitating the translocation of viral particles from systemic circulation into the periodontal environment through exudation and infiltration of peripheral blood cells [18].

Several studies have demonstrated that HCV RNA can be detected in higher concentrations in GCF than in saliva, suggesting that GCF may act as a potential viral reservoir in the oral cavity. These findings highlight the complex interaction between systemic inflammation, microbial dysbiosis, and immune dysfunction in disease mechanisms. Therefore, multidisciplinary collaboration between dentistry and hepatology is essential to improve the diagnosis and management of patients infected with HCV [20].

### 1.1. Periodontitis

Periodontal health is maintained through a balanced homeostatic immune response and a symbiotic microbiota. Periodontitis is a condition associated with a dysbiotic polymicrobial community, in which keystone pathogens, aided by accessory pathogens, disrupt the host immune system and promote the emergence of a dysbiotic microbiota. Under these circumstances, commensal microorganisms may transform into pathobionts, triggering an excessive inflammatory response that leads to tissue destruction. This inflammation further aggravates dysbiosis by providing nutrients derived from tissue breakdown products, thereby creating a positive feedback loop that perpetuates the chronic nature of periodontitis. Several risk factors contribute to this process, including the presence of bacteria capable of evading host immune responses, systemic diseases, smoking habits, aging, high-fat diet, and immune deficiencies. These factors can act independently or synergistically to promote dysbiosis and contribute to the pathogenesis of periodontitis [8].

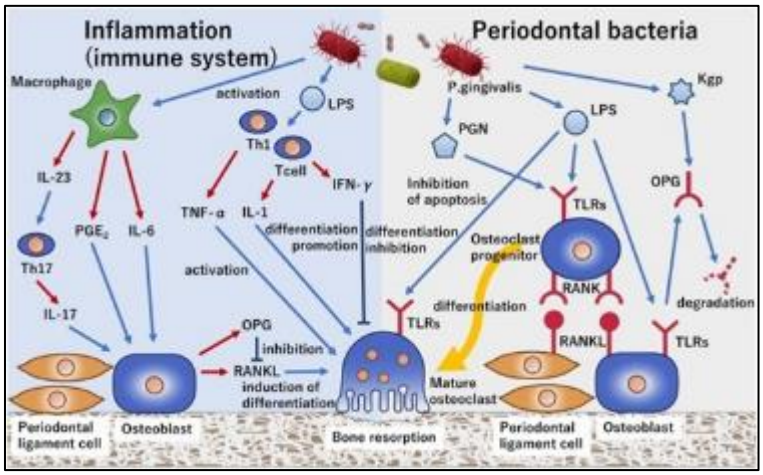


**Figure 1** Pathogenesis of Periodontitis: Interaction Between Periodontal Bacteria and Host Immune Response [26]

One of the key cellular players in the pathogenesis of periodontitis is the neutrophil, which functions not only as a phagocytic effector cell but also as an important regulator of adaptive immunity. For instance, by releasing chemokines such as C–C motif ligand 2 (CCL2) and C–C motif ligand 20 (CCL20), neutrophils can recruit Th17. Th17 cells, a subset of $CD4^+$ helper T cells that secrete interleukin-17 (IL-17) at inflammatory sites, represent an osteoclastogenic population that links T-cell activation with inflammatory bone resorption in periodontitis. Moreover, neutrophils secrete B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL), two key cytokines that promote B-cell survival, proliferation, and differentiation into plasma cells. The synergistic activation of complement pathways and Toll-like receptor signaling in antigen-presenting cells further enhances IL-17 production by adaptive immune cells (Th17). IL-17, in turn, acts primarily on innate immune and stromal cells to amplify inflammatory responses.By stimulating granulocyte colony-stimulating factor (G-CSF), IL-17 regulates neutrophil production in the bone marrow and their mobilization into circulation. Through the induction of CXC chemokines, IL-17 facilitates chemotactic

recruitment of neutrophils into the periodontium. In addition, IL-17 activates macrophages and promotes the degradation of connective tissue and alveolar bone by inducing the production of matrix metalloproteinases (MMPs) and receptor activator of nuclear factor-κB ligand (RANKL) from stromal cell types [8, 14].

### 1.2. Chronic Hepatitis C

Hepatitis C virus (HCV) infection is complex and exhibits a high degree of genetic diversity due to its existence as a heterogeneous population known as quasispecies. This genetic variability plays a crucial role in the virus's ability to adapt to host immune pressure and antiviral therapy. Mutations occurring in the Replication Enhancing Domain (ReED) of the nonstructural protein 5A have been shown to increase the replication efficiency of the HCV genome, resulting in variants with high replicative fitness. These variants are predominantly found in immunosuppressed individuals, such as liver transplant patients, and are associated with more severe disease progression. This condition indicates that high replication capacity strengthens viral pathogenicity, whereas low replication favors chronic infection persistence through evasion of the host immune response [21].

In addition, chronic HCV infection is often accompanied by systemic metabolic alterations such as hepatic steatosis, insulin resistance, and lipid dysfunction. Recent studies have shown that although total cholesterol and low-density lipoprotein (LDL) levels tend to increase after viral elimination through direct-acting antiviral therapy (DAA), significant improvements are observed in cardiovascular parameters, including reductions in carotid plaques and intima–media thickness. However, the degree of metabolic recovery largely depends on pre-existing metabolic disturbances prior to therapy, emphasizing that HCV infection is not only hepatotropic but also affects systemic metabolic homeostasis [4].

Chronic hepatitis C virus (HCV) infection induces persistent hepatic inflammation and promotes progressive fibrogenesis through activation of various inflammatory signaling pathways. The innate immune response triggered by HCV strongly activates the NF-κB pathway, enhancing the production of proinflammatory cytokines and chemokines, including type III interferons (IFN-λ), which contribute to maintaining an inflammatory hepatic microenvironment [22] Chronic HCV infection leads to dysfunction of cytotoxic T cells ($CD8^+$), characterized by reduced effector activity and immunological exhaustion, including increased expression of inhibitory receptors and diminished proliferative capacity. This condition compromises the immune system's ability to eliminate the virus, allowing HCV to persist despite adaptive immune activation [1]. The cycles of hepatocyte injury and regeneration occurring during chronic hepatitis C result in oxidative stress and genomic alterations such as somatic mutations and epigenetic dysregulation, which cumulatively accelerate genetic instability and increase the likelihood of hepatocellular transformation into liver carcinoma [11, 27].

Mitochondrial dysfunction–induced oxidative stress increases reactive oxygen species (ROS) production, which subsequently activates the NLRP3 inflammasome and TGF-β/SMAD signaling pathways, contributing to hepatic stellate cell activation and differentiation into fibrogenic myofibroblasts [5, 27].

Activation of hepatic stellate cells (HSCs) represents a key mechanism in the development of liver fibrosis caused by hepatitis C virus (HCV) infection. Under chronic inflammatory conditions, HSCs transition into myofibroblast-like cells expressing α-smooth muscle actin and secreting extracellular matrix proteins such as type I collagen, which accumulates in the hepatic parenchyma and promotes fibrosis progression toward cirrhosis [13]. Experimental evidence indicates that endoplasmic reticulum (ER) stress and activation of the Wnt/β-catenin pathway can persist even after viral eradication through direct-acting antiviral (DAA) therapy, signifying the presence of lasting molecular alterations that contribute to hepatocarcinogenic risk [15]. Further molecular studies have reported that patients who have achieved virological cure still exhibit altered gene and epigenetic expression associated with inflammatory and fibrogenic pathways, including activation of NF-κB, IL-6, and oxidative stress mediators [23]. Moreover, inhibition of the Wnt/β-catenin pathway has been shown to suppress HSC activation and reduce the expression of COL1A1 and α-SMA, underscoring the central role of this pathway in maintaining fibrogenic activity during chronic HCV infection [10]. Overall, the synergy between ER stress, Wnt/β-catenin activation, proinflammatory NF-κB signaling, and collagen secretion by HSCs forms the molecular basis for the progressive inflammation and fibrosis characteristic of chronic HCV infection.

Activation of interferon (IFN) signaling pathways constitutes a major component of the immune response against chronic hepatitis C infection. However, the specific cell types that secrete IFN and the subsets responsible for inducing its release remain incompletely understood, partly due to the limitations of existing immunocompetent in vivo HCV infection models that can accurately mimic the complex interactions between parenchymal and non-parenchymal liver cells under physiological conditions. Furthermore, overexpression of T lymphocytes (LT) can trigger chronic hepatitis

through modulation of NF-κB signaling in both hepatocytes and T cells. Activation of hepatic stellate cells (HSCs) and liver fibrogenesis is associated with acetylation of HMGB1 by extracellular osteopontin (OPN), a stress-sensing protein elevated in liver disease and found at high levels in the serum of patients with chronic HCV infection. Acetylated HMGB1 interacts with HDAC1/HDAC2 to induce type I collagen expression by HSCs, thereby enhancing collagen deposition in hepatic tissue. An additional mechanism involves upregulation of the Gas6/Axl pathway in HSCs, which contributes to their activation and accelerates liver fibrogenesis. Collectively, the combined activation of IFN pathways, T lymphocyte overexpression, and HSC modulation through HMGB1 and Gas6/Axl signaling plays a critical role in the pathogenesis of chronic hepatitis and liver fibrogenesis in patients with HCV infection [2].

## 2. Discussion

### 2.1. Relationship Between Periodontitis and Hepatitis C Disease

The possible pathological mechanisms explaining the association between chronic hepatitis C and periodontal conditions are related to insulin resistance (IR) and chronic hepatic inflammation. Insulin resistance is a pathological condition in which body cells fail to respond optimally to insulin, and it is closely associated with diabetes mellitus and obesity. Periodontal disease has been linked to metabolic syndrome, including IR, while the association between HCV infection and IR has also been scientifically demonstrated. Given the interrelationship between chronic hepatic inflammation and IR, the inflammatory response in periodontal tissues may be altered in individuals with HCV infection, particularly when accompanied by hepatic fibrosis and obesity. Increased IR due to chronic HCV infection occurs through mechanisms involving metabolic syndrome and systemic inflammation, which stimulate the release of several proinflammatory cytokines such as TNF-α, adiponectin, and IL-6. These cytokines play crucial roles in the initiation and progression of periodontal disease, as well as in the interaction between periodontitis and insulin resistance [6].

Pathophysiologically, chronic HCV infection increases the production of proinflammatory cytokines such as TNF-α and IL-6, while reducing adiponectin levels, a hormone involved in glucose metabolism. This imbalance disrupts insulin signaling, impairs hepatic function, and exacerbates inflammatory conditions in periodontal tissues that are sensitive to proinflammatory mediators. Thus, HCV-induced cytokine elevation represents a key mechanism linking insulin resistance, systemic inflammation, and the progression of periodontitis [9].

The liver plays a fundamental role in systemic immune regulation and the formation of effector cells in host defense. Hepatic dysfunction due to chronic inflammation leads to immunological imbalance that may impair neutrophil and complement system functions, thereby enhancing defensive antibody responses. The synergy between neutrophils and the complement system is a critical component of defense against periodontal pathogens. Therefore, the relationship between periodontitis and liver diseases such as chronic HCV infection is thought to be mediated by increased proinflammatory mediators and oxidative stress, both of which may exacerbate these conditions [6].

The relationship between periodontitis and liver diseases, including chronic hepatitis C, is believed to be mediated by several biological factors such as bacterial components, proinflammatory mediators, and oxidative stress. In individuals with chronic periodontitis, cytokine levels in the gingival crevicular fluid (GCF) exhibit a positive correlation with the severity of periodontal inflammation. Periodontal status parameters, including pocket depth (PD), attachment loss (AL), and recession (RT), have been reported to be associated with increased levels of IL-1α and IL-1β in the GCF of patients with chronic hepatitis C and periodontitis. In chronic hepatitis, activation of immune responses and systemic inflammatory processes contribute to the elevated levels of IL-1α and IL-1β. Similarly, increased IL-1β levels are frequently observed in cases of chronic periodontitis. These findings suggest that elevated concentrations of IL-1α and IL-1β in the GCF may represent a pathogenic mechanism linking periodontitis with chronic hepatitis C. This association appears to be bidirectional, as chronic inflammation in both the liver and periodontal tissues may mutually exacerbate one another. Furthermore, insulin resistance is hypothesized to act as a potential pathogenic mechanism mediating the interaction between periodontitis and chronic hepatitis C [25].

The periodontal inflammatory process may also serve as a potential route for HCV dissemination within the oral cavity. HCV particles can be detected in saliva and GCF through peripheral blood cells involved in inflammation. This indicates that the oral cavity may act as a potential reservoir for the virus, especially when gingival bleeding occurs. Viral particles released with blood may contribute to the detection of HCV RNA in oral fluids and aggravate local immune responses and tissue inflammation [19].

Subjective oral symptoms such as xerostomia, pain, and burning sensations on the mucosa have been reported more frequently in HCV-infected patients than in control groups. Reduced salivary gland function leads to moderate to severe oral dryness, increasing the risk of caries, oral candidiasis, and discomfort during oral functions. This strengthens the

evidence that chronic HCV infection is associated with impaired salivary secretion and an elevated risk of secondary oral complications [3].

In addition to immune and metabolic mechanisms, hormonal factors also play a role in the interaction between periodontitis and chronic HCV infection. Periodontal tissues express receptors for sex hormones such as testosterone, estrogen, and progesterone, the presence of which is influenced by hormonal levels in the body. Altered hormonal profiles in the saliva of chronic HCV patients may affect the biological activity of periodontal tissues. Reduced testosterone levels enhance osteoclastic activity and alveolar bone resorption, while estrogen receptors help maintain soft tissue homeostasis through periodontal fibroblasts. Progesterone also modulates the production of inflammatory mediators such as TNF-α, angiogenic factors, and prostaglandin $E_2$ ($PGE_2$). A reduction of up to 52% in progesterone levels in the saliva of HCV patients is thought to activate glucocorticoid receptors in osteoblasts, inhibit osteoclast apoptosis, and accelerate bone resorption [16].

Overall, literature evidence indicates that the relationship between chronic hepatitis C and periodontal disease is multifactorial and bidirectional, involving immunological mechanisms, systemic inflammation, hormonal alterations, and local oral factors. A comprehensive understanding of these interactions is essential for the prevention and management of HCV patients with periodontitis, aiming to minimize systemic complications and improve quality of life.

## 3. Conclusion

Chronic HCV infection exerts a significant impact on oral health, particularly by exacerbating periodontal inflammation through elevated levels of proinflammatory cytokines such as IL-1α and IL-1β. These cytokines play a crucial role in the pathogenic mechanisms underlying both periodontitis and chronic hepatitis C, suggesting that systemic HCV infection negatively influences interleukin-mediated inflammatory processes within periodontal tissues. Consequently, individuals with chronic hepatitis C tend to exhibit more pronounced structural and inflammatory alterations in periodontal tissues compared to systemically healthy individuals. Understanding this bidirectional relationship holds important implications for integrated management strategies and future research on the interplay between systemic viral infections and periodontal diseases.

## Compliance with ethical standards

### *Disclosure of conflict of interest*

No conflict of interest to be disclosed.

### *Statement of informed consent*

Informed consent was obtained from all individual participants included in the study.

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