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## Periodontal Implications of Hepatitis C Infection

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<http://dx.doi.org/10.5772/intechopen.76135>

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### Abstract

Periodontal tissues exhibit important vascular, lymphatic, and nervous connections with the rest of the body. Thus, periodontal inflammation caused by the interaction between the subgingival bacterial biofilm and the host immune response has an impact reaching further than the oral cavity. The concept of “periodontal medicine” reunites the bidirectional relationships that exist between periodontal disease and systemic conditions such as diabetes mellitus or cardiovascular disease. The chronic inflammation of hepatic tissues during hepatitis C virus (HCV) infection causes changes in the general homeostasis that can reverberate at periodontal level and influence periodontal inflammation. Various mechanisms such as insulin resistance or pro-inflammatory cytokines production could be the link between the two conditions. In addition, periodontal inflammation could impact HCV transmission, as HCV RNA molecules and antibodies have been found in infected patients’ saliva and gingival fluid. During periodontal inflammation, gingival bleeding is frequent, and the viral molecules could enter oral fluids while being carried by peripheral blood cells. Clinical particularities that suggest the onset of periodontal disease have also been frequently observed in HCV-infected patients. The connections between periodontal disease and hepatitis C need to take into consideration by practitioners of both specialties due to their important implications on clinical manifestations and treatment strategies.

**Keywords:** periodontal disease, hepatitis C, gingival crevicular fluid

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## 1. Introduction

The concept of “periodontal disease” comprises a group of inflammatory conditions that address the supporting tissues (periodontium) of the tooth. If left untreated, periodontal disease will lead to alveolar bone loss and subsequent decreased tooth stability, eventually causing tooth loss [1].

The main cause or determinant factor for periodontal disease (PD) is the subgingival biofilm, composed of bacteria, fungi, and other microorganisms that are all bound together within a matrix [2]. The periodontal pathogenic bacteria are usually found in the oral cavity even in a healthy person, but under special circumstances (such as low immune response or other local and systemic favoring factors), they overgrow in number and become over-aggressive [3]. The normal immune response of the body can be altered by systemic diseases, while the tissular architecture and strength of the periodontal tissues is genetically determined, thus varying the way in which each patient reacts to periodontal bacteria aggression.

## 2. Periodontal structures

The periodontal structures that surround and support each tooth are represented by gingiva, periodontal ligaments, cementum, and alveolar bone [4]. These are divided into two separate categories: the superficial periodontium (composed of gingival and gingival fibers) and the profound periodontium (composed of periodontal ligament, cementum, and alveolar bone). The histological characteristics of the periodontal tissues are genetically determined, resulting in a variety of periodontal phenotypes that share common features but are also different in some aspects, especially in strength and resistance against bacterial assault. This explains why PD is more frequent in some individuals than in others, despite universal distribution of the periodontal pathogens [5].

The anatomical constituents of the periodontium are divided as follows (**Figure 1**):

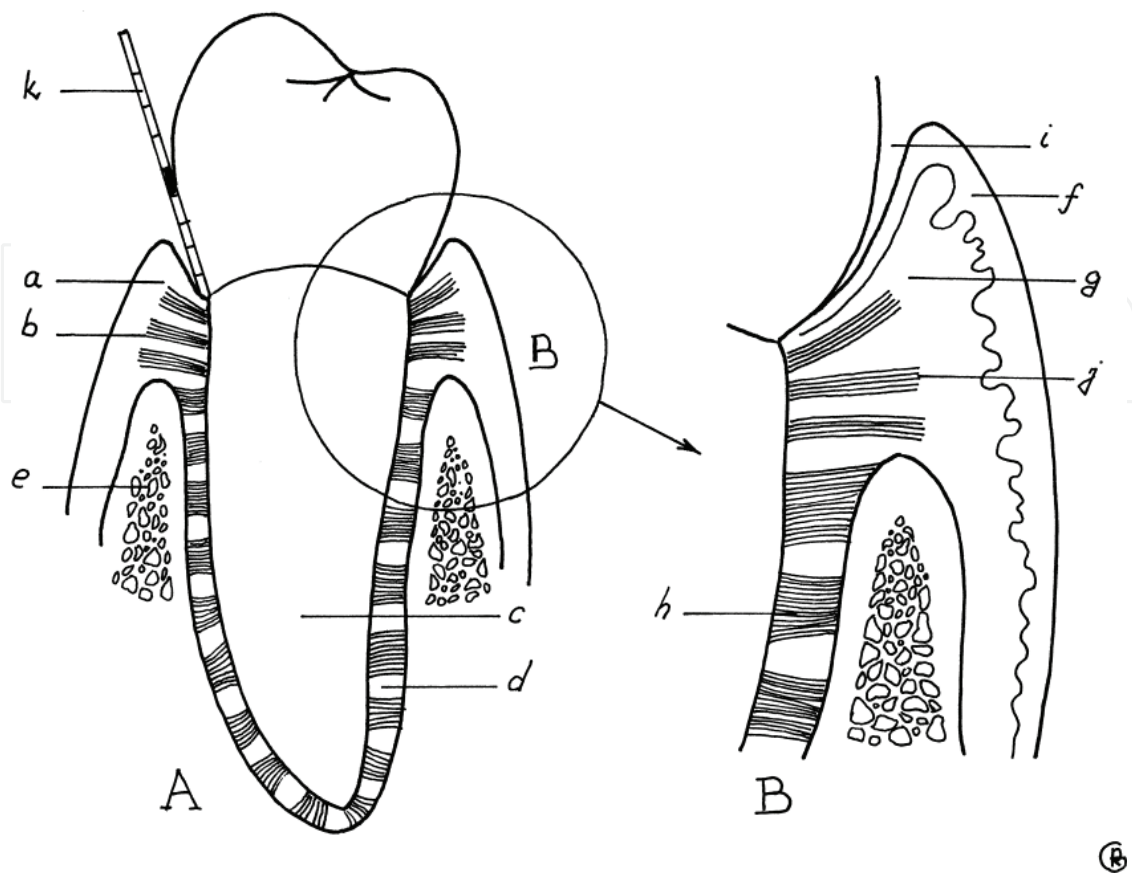
### 1. Superficial periodontium:

- gingiva: gingival epithelium + gingival connective tissue
- gingival fibers

### 2. Profound periodontium/attachment apparatus:

- periodontal ligament
- cementum
- alveolar bone

The gingiva protects and shelters the deeper structures of the periodontium (**Figure 1A(a)**). It is composed of a free, unattached area, called the marginal gingiva which surrounds each tooth,



**Figure 1.** (A) The tooth and its surrounding periodontal structures: a, gingiva; b, gingival fibers; c, cementum; d, periodontal ligament; e, alveolar bone; k, periodontal probe. (B) Detail from (A): f, epithelium; g, connective tissue; h, periodontal space; i, gingival sulcus; j, junctional epithelium.

an interdental area called the gingival papilla and an attached area, called the attached gingiva, which is closely bounded to the underlying periosteum and the alveolar bone.

The gingival epithelium is made out of multiple cellular layers that are strongly keratinized where important mechanical forces are applied during chewing. The vascular and nutritional support of the epithelium is provided by the underlying connective tissue. Special structures called papillae rise from the connective tissue inside the epithelium, improving the adherence between the two and enhancing nutritional supply (**Figure 1B(f,g)**) [6].

Between tooth surface and the free gingiva, a narrow space called gingival sulcus is formed (**Figure 1B(i)**). In a healthy gingiva, this sulcus is only 0.5–2 or 3 mm deep. The periodontal probe is a special instrument used for assessing the depth of the gingival sulcus, an important indicator of PD presence and evolution (**Figure 1A(k)**). The gingiva becomes attached to the tooth surface in the vicinity of the enamel-cementum junction with the help of the junctional epithelium (**Figure 1B(j)**), a specialized type of tissue with less cellular layers than the rest of the gingival epithelium, thus allowing rapid changes of molecules between the gingival sulcus and the connective tissue. However, the thin architecture of the junctional epithelium makes it more liable to penetration by bacteria and their toxins [7, 8].

The gingival fibers are collagen fibers that are distinct from the periodontal ligament and are found inside the gingiva. They are disposed in a circular manner in the gingival connective tissue and keep the gingiva in close contact to the tooth (**Figure 1A(b)**) [6].

The cementum is a type of mineralized connective tissue that covers the roots of the teeth (**Figure 1A(c)**). In comparison to other mineralized connective tissues such as the enamel or the bone, the cementum has a lower concentration of mineral substances, therefore making it less durable and resistant. In addition to this, the average root cementum thickness is about 100  $\mu\text{m}$ , making it predisposed to resorption. Nevertheless, the cementum can regenerate itself, as it is being stimulated by apposition forces like those used during orthodontic treatments and root planning [9].

The periodontal ligament fibers (**Figure 1A(h)**) are also made of collagen but these fibers are placed outside the gingiva, inside the narrow space between the root of the tooth and the alveolar bone called periodontal space (**Figure 1A(d)**). Therefore, they strongly connect the tooth inside its alveoli. Nevertheless, this connection is quite flexible and elastic, as it needs to adapt to various tooth movements that take place during chewing. Acting in a slingshot manner, the periodontal ligament fibers are anchored with one end in the root cementum and with the other in the alveolar bone, these ends of the fibers being called Sharpey fibers [4, 8].

The alveolar bone is composed of bony processes that extend from the base of the maxilla and the mandible, forming the sockets in which the teeth are placed (**Figure 1A(e)**). It is made out of spongy bone in its inside core and compact bone on the external and internal walls [8]. The alveolar bone attaches one end of the periodontal ligament fibers and distributes the masticatory forces from the teeth to the rest of the face and cranium. The existence of the bone is strongly related to the presence of teeth inside the sockets, as once the teeth are extracted the alveolar bone is quickly resorbed due to lack of stimulation by masticatory apposition forces [10].

### 3. Gingival crevicular fluid

When the periodontium is healthy, free of inflammatory conditions, the gingival connective tissue secretes a small quantity of clear, interstitial liquid inside the gingival sulcus, called the gingival crevicular fluid (GCF) [11]. The fluid is secreted as a result of different osmotic pressures between connective tissue vessels and the gingival sulcus content of bacteria [12]. When the subgingival bacterial plaque is matured and excessively grown, the fluid flow increases and changes its characteristics as periodontal inflammation unveils [11]. Thus, the gingival fluid will become rich in different types of cells such as epithelial, connective, bacterial, and host-immune cells.

The gingival fluid can be used for this reason as a mean to assess the severity and extent of PD and periodontal damage [11]. Moreover, the fluid contains a series of pro-inflammatory markers such as interleukins, enzymes (metalloproteinases (MMPs)), and growth factors that are all valuable indicators of PD activity. The quantitative and qualitative detection of these molecules in the gingival fluid is used as a method to assess the periodontal status during nonsurgical periodontal treatment [13], orthodontic therapy [14], and periodontal surgery [15].

## 4. Periodontal disease

The classification of periodontal diseases has been the subject of extensive scientific debate. For simplification reasons, it can be considered that periodontal conditions are divided into inflammatory diseases of the superficial periodontium (gingivitis) and those of the profound periodontium (periodontitis). These two main types of periodontal conditions have extended subtypes and various clinical forms, but the bacteria-generated ones are the most common.

### 4.1. Gingivitis

The extended accumulation of bacterial plaque in the close proximity of the free gingival margin or inside the gingival sulcus will lead to the onset of an inflammatory process. The bacteria express toxins such as their lipopolysaccharide (LPS) that can trigger the immunological reaction of the body. As a result, gingival blood vessels become enlarged, lymphocytes are drawn to the site of the reaction, and more pro-inflammatory markers are secreted [16]. Although the inflammatory reaction is meant to stop the bacterial aggression, the uninterrupted bacterial growth in the biofilm will continue, leading to a chronic self-sustained inflammatory reaction. As the inflammation unveils, the gingiva will display the typical signs of inflammation: changing color from pink to first bright and then dark red, increasing volume due to edema and bleeding spontaneously or on chewing or periodontal probing. As long as the bacterial plaque is undisturbed by professional cleaning, the inflammation will proceed [17].

Some local factors such as crowded teeth, incorrectly adapted dental fillings, crowns or bridges, orthodontic appliances, or gingival recessions can result in an inappropriate oral hygiene, by creating niches from where the bacterial plaque is more difficult to remove [18]. In addition, the gingival status of the patient can be influenced by a series of systemic factors such as disease, medication, hormonal variations, or nutritional status that have an impact on the behavior of the gingival tissues when confronted even with a limited quantity of bacterial plaque. For example, medication used for hypertension treatment, epilepsy or immunosuppression can cause the gingival enlargement due to hyperplasia. The treatment of gingivitis consists of the professional removal of bacterial plaque and improving the favoring factors, either local or systemic. An important part of the treatment is represented by patient education and motivation for a well-kept oral hygiene. Gingivitis has a reversible character, and the gingival tissues return to their initial situation prior to the onset of the disease in most cases [16].

### 4.2. Periodontitis

When bacterial plaque is not removed, it will continue to grow and mature inside the gingival sulcus. More aggressive, Gram-negative anaerobic bacteria will begin to appear inside the biofilm, as the local conditions (low oxygen) enable them to thrive and multiply. These bacteria include important and highly aggressive periodontal pathogens such as *Porphyromonas gingivalis*, *Treponema denticola*, or *Tannerella forsythia*. As a result of the continuous bacterial aggression, the gingival junctional epithelium will begin to migrate in an apical direction, as an immune adaptation. Consequently, the gingival sulcus will become deeper, allowing the

extended growth of the biofilm and its colonization with aggressive periodontal pathogens [19]. The moment when the junctional epithelium migrates away from its normal position—the enamel-cementum junction, the gingival sulcus becomes a periodontal pocket and the damage caused by PD becomes irreversible. Consequently, the collagen fibers of the periodontal ligament and those inside the matrix of the alveolar bone are degraded by collagenase enzymes secreted by bacteria or by lymphocytes as a result of the chronic inflammatory reaction. In addition, as the alveolar bone is no longer stimulated by periodontal ligament fibers that transmit the masticatory forces, its resorption will be even more accelerated [20].

Further empowered by leukocyte- and monocyte-secreted pro-inflammatory markers (chemokines, interleukins, tumor necrosis factors (TNFs)), the periodontal inflammation can last even for years, with few clinical symptoms (mostly gingival bleeding, receding gums, increased tooth sensitivity) until the loss of periodontal ligaments and alveolar bone is so extensive that the teeth increase their mobility and eventually are lost. The rate of progression and severity of periodontitis can be influenced by systemic disease that impair the normal immune response of the body and favor the aggressive actions of the bacteria and their debilitating impact on the periodontal tissues [21]. The periodontal therapy aims to remove all subgingival biofilms and to partially reconstruct the lost alveolar bone with the aid of bone grafts in order to increase tooth stability. Nonsurgical periodontal treatment, systemic and local antibacterial medication, and periodontal surgery methods are used during active treatment, but the patient needs to be frequently recalled for reassessment, monitoring, and clean-up in order to prevent any relapse of PD [19].

## 5. Periodontal disease and systemic conditions

Periodontal conditions can impact the general well-being of the patient and can help to improve the outcome of other systemic or distant diseases through their treatment. Over the past decades, based on the results of clinical and fundamental studies, scientific research has elaborated a new concept, “periodontal medicine,” which encompasses the bidirectional relationships that exist between periodontal diseases and some systemic conditions such as diabetes mellitus (DM), cardiovascular disease, or rheumatoid arthritis (RA) [22].

Diabetes mellitus associated to PD has received extensive and intensive research attention over time. Today, PD is officially recognized as the sixth complication of DM, alongside retinopathy, nephropathy, neuropathy, macrovascular disease, and modified wound healing [22]. The periodontal status of DM patients often includes overgrowth gingival tissues and the formation of gingival abscesses [23]. This chain of pathological events is strongly influenced by the glycemia level, as DM patients with well-controlled glycemia exhibit similar degrees of periodontal inflammation as non-DM ones [24]. Compared to healthy controls, DM patients exhibit an elevated risk for PD, by up to three times higher. DM history can also influence the onset of PD, as the major symptoms of periodontal destruction have been shown to manifest after 10 years of DM [25] or after the age of 30 for most patients [26].

Various mechanisms have been suggested in order to explain the impact of DM on periodontal status and PD onset and evolution. From a bacterial standpoint, it may seem that the increased glucose content of DM patients' saliva and GCF [27] could cause a change in the composition of the oral and periodontal microflora, favoring the development of periodontal pathogens such as *P. gingivalis* or *Aggregatibacter actinomycetemcomitans*. Another possible mechanism could reside in the impaired function of polymorphonuclear leukocytes (PMNs) that occur in diabetic patients. The cells' chemotactic, phagocytic, and adhesive capabilities are declined, facilitating debilitating defensive cellular mechanisms and periodontal pathogens infection of the periodontal tissues [28].

Pro-inflammatory markers play an important role in the onset, intensity, and extension of periodontal inflammation. In DM patients, significantly increased levels of pro-inflammatory cytokines produced by monocytes have been found [29]. This is believed to be caused by the hypersensitive monocyte/macrophage phenotype found in DM patients. This particular phenotype induces an overreaction to bacterial antigens, such as lipopolysaccharide (LPS). As a result, the production of cytokines is dramatically augmented [30]. For example, DM patients' monocytes produced 24–32 times higher quantities of TNF-alpha than non-DM monocytes, when stimulated by *P. gingivalis* LPS. Other cytokines are also produced in large amounts by DM monocytes subsequent to LPS stimulation: four times higher production of prostaglandin E2 (PGE2) and interleukin 1beta (IL-1beta) than non-DM monocytes [29]. When compared, the GCF levels of PGE2 and IL-1 beta were higher for DM patients'. Cytokines can activate the production of periodontal metalloproteinases (MMPs) (collagenase, gelatinase, elastase) [31] that subsequently impair the periodontal structures.

Coronary atherosclerosis disease (CAD) has been associated with dental infections [32], while ischemic heart disease has been correlated to the patient's history of missing teeth [33, 34]. Dental health was also found to be worse in myocardial infarction (MI) patients than in controls. Poor dental hygiene is also believed to increase twofold the risk of CAD. In addition, the Total Dental Index (TDI) can be considered as a predictor for CAD, according to some authors [35, 36].

In periodontal patients with more than 20% bone loss, the risk of CAD is increased by 50% [37]. Review articles of the existing literature on the subject mention advanced CAD risk in the presence of preceding PD, ranging from 14 to 222% [38]. The American Heart Association concludes that "periodontal disease is associated with atherosclerotic vascular disease independent of known confounders" [39], emphasizing that the direct causative correlation between PD and CAD has not yet been scientifically proven.

In the early stages of atheroma formation, monocyte cells adhere to the injured endothelial wall. The adhesion molecules that make this process possible are influenced by bacterial LPSs, prostaglandins, and pro-inflammatory cytokines. The increased levels of cytokines such as IL-1, TNF-alpha, and PGE2, which are found in periodontal disease's patients' serum, can facilitate the adhesion of the monocytes and therefore promote the formation of atheroma lesions. Periodontal therapy (scaling, root planning) has been shown to decrease the levels of pro-inflammatory cytokines and improve vascular health [40, 41]. The functional assessment of vascular endothelial function is also improved after periodontal therapy [40, 42].



Rheumatoid arthritis (RA) is a chronic inflammatory disease that leads to the dissolution of articular tissues (synovial membrane, bone, and cartilage). The disease is believed to be an autoimmune dysfunction in which the body's own immune system begins to target articular tissue's cells.

The bone destruction is mediated by matrix degenerative enzymes such as metalloproteinases (MMPs), oversecreted by fibroblast and phagocytes cells during chronic inflammation. The secretion of these MMPs is normally inhibited, but the impairment of the immune system that takes place in RA and PD cancels the inhibitory action. Therefore, the collagen matrix of the bone tissue is degraded and bone loss occurs. As a result, bone decline can be indirectly assessed through MMPs detection in both RA and PD [43, 44].

Inflammatory conditions such as RA and PD imply the secretion of elevated levels of cytokines and other inflammatory mediators. Despite the vast range of pro-inflammatory cytokines, the cytokine profiles found in RA and PD patients share certain common molecules. For example, the prostaglandin E2 (PGE2) responsible for cell damage in RA also expresses elevated levels in PD, where alveolar bone breakdown is frequent [45]. Moreover, as *P. gingivalis* has been associated as a susceptible factor for rheumatoid arthritis, other cytokines such as IL-1, IL-6, or TNF-alpha exhibit inflated levels in both RA and PD and may also be responsible for the impairment of normal bone formation mechanisms, which eventually trigger tissue degradation [46, 47].

## 6. Chronic hepatitis C infection from an oral health perspective

Hepatitis C is a liver disease caused by the infection with the hepatitis C virus (HCV). Due to the increased number of infected individuals globally, it is considered to be a major public health issue, requiring important financial and scientific resources for the development of a universally available treatment [48]. The infection affects such a large number of people, because in its early stages, it can have no visible symptoms, making the spread of the virus easier from unaware infected persons to healthy ones. As the liver inflammation caused by the virus unveils, it becomes chronic in most patients, eluting the immune system's protective mechanisms [49]. Through the years, the chronic inflammation impairs the normal functionality of the liver, healthy hepatic tissue, and hepatocytes being replaced by reactive, fibrotic tissue. As a result, the complications of chronic hepatitis C will develop, the most frequent and dangerous ones being liver cirrhosis and hepatocellular carcinoma, both with harmful consequences for the patient [50].

An important feature of the HCV virus is that it can be easily transmitted. After entering the human body, the virus needs a cellular host in order to multiply. It does so mainly inside hepatocytes but it also targets peripheral blood cells, which means that viral RNA strands are found in infected patients' blood. Consequently, this makes blood and blood products the main medium of viral infection. Most frequently, this arises when using infected needles (for medical purposes or drug abuse) or after blood transfusions involving infected patients. The virus can also disseminate through unprotected sexual contact when one partner is infected, or by using poorly sterilized medical instrument [51]. The fact that the initial stages of HCV

infection develop without many visible or notable symptoms can facilitate the spread of the virus. Certain studies have found that viral RNA molecules can be found in saliva and gingival crevicular fluid as well, being carried by peripheral blood cells that enter those fluids [52]. As the viral molecules can be hosted inside peripheral blood cells, these can be easily transported at the gingival level especially during gingival inflammation, when the blood flow in the small capillary vessels is expanded. The gingival connective tissue position (underneath the thin gingival junctional epithelium) supports the transfer of these HCV-infected white cells into the gingival crevicular fluid, along with other bacterial and own damaged cells. During inflammation, the quantity of secreted gingival fluid is increased. In addition, inflamed gums bleed easily, facilitating the transfer of the HCV virus into the oral fluids such as saliva and gingival fluid [53, 54]. The infectious potential of these fluids is still debatable and requires further research.

As no vaccine for HCV has been developed, the main strategy for preventing the spread of the infection is the early detection of infected patients and the proper management of blood products originating from such subjects. Considering that the acute phase of infection is manifested only in a limited number of patients (one-tenth) and the symptoms are not necessarily common to those of other hepatic conditions (e.g., jaundice), the infected patient can easily oversee the infectious event [55]. This aspect claims the need for frequent blood testing (i.e., hepatic transaminases) in order to detect early signs of liver function impairment, or serum anti-HCV antibodies assessment. In young patients, the infection may be cleared up by the immune system, but in most cases, it becomes chronic and associated to other risk factors such as alcohol consumption, an unhealthy diet, and lifestyle being able to make the shift toward liver cirrhosis [56].

Extrahepatic manifestations of the disease can also occur in some patients, due to the fact that the virus can be hosted by the blood. As such, cryoglobulinemia, an inflammatory reaction caused by the increased amount of antibodies in the infected patients' blood, can develop, as the infected cells travel along blood vessels. The chronic hepatitis C infection generates a lot of stress on the patients' immune system. Under these circumstances, it has been noted that a series of autoimmune conditions can develop as a consequence of chronic hepatitis C, due to the impaired function of the immune system and the alteration of normal pro-inflammatory molecule production. Such autoimmune conditions include non-Hodgkin lymphoma, autoimmune thyroiditis, porphyria cutanea tarda, and possibly diabetes mellitus and rheumatoid arthritis [57]. The chronic hepatic inflammation caused by HCV can also impact the normal cellular intake of glucose, by causing insulin resistance [58]. Other non-autoimmune extrahepatic manifestations impact the normal function of the kidney, heart, and central nervous system [57, 59].

Nowadays, intensive efforts are made for the limitation of HCV infection spread. This entails raising public awareness about virus transmission and therefore testing for HCV. As the detection of viral antibodies or viral RNA in blood samples can be overcomplicated and unavailable in some situations, easier diagnosis tools such as salivary oral kits have been created [60]. These can improve the screening of the patients for infection and decrease the chance of involuntary transmission of the virus. However, such methods are not yet fully developed or universally accessible. The treatment of chronic hepatitis C complications is

expensive and complex, including antiviral medication and liver transplant. This further enhances the need for a smooth diagnostic tool, able to intercept the infection in its early stages, despite the lack of evident clinical symptoms. In the future, perfected and well-calibrated oral fluid test kits could provide a solution for widespread screening of the infection and a hope for its prevalence and transmission rates decline [61].

Some extrahepatic manifestations of HCV infection such as Sjögren syndrome and oral lichen planus can also impact the status of the oral cavity [62, 63]. In Sjögren syndrome, the secretion ability of the lachrymal and salivary glands is impaired. The decrease in salivary volume causes a chain of oral health issues, which include soreness and friability of the oral mucosa, an increased number of dental caries, and sialadenitis of the main salivary glands [64]. Oral lichen planus is a type of mucous lesion that is not painful and thus can be easily unobserved by the patient, especially if settled in the posterior areas of the oral cavity. This fact has clinical significance, as the lesion can have malignant potential and needs to be identified and treated as soon as possible [65]. Some cases of oral-squamous cell carcinoma have been reported in HCV patients, stating a correlation between the two diseases [66]. HCV-infected patients should be closely monitored in terms of periodontal health, as the combined effect of chronic inflammation, both hepatic and periodontal, could have a negative impact on their life quality and general life expectancy. The common immunological, clinical, and epidemiological implications of the two conditions should raise awareness for practitioners, by offering the possibility of better understanding of their pathogenic mechanisms and therapeutic opportunities.

## **7. Connections between HCV infection and periodontal status**

HCV chronic infection can have important consequences on patient's life quality and influence the normal activity of defensive mechanisms, such as the host immune response. This can leave the patient vulnerable to the onset of other infections such as periodontal disease triggered by bacterial biofilm. Recent scientific data show that multiple-layered connections between HCV infection and periodontal disease could be possible, including transmission implications via oral fluids (saliva and gingival fluid), related clinical manifestations of the two conditions [63, 67–69], and common pathogenic pathways that may favor their evolution [68].

The proposed hypothesis claims that chronic hepatitis C can influence the onset of periodontal impairment. This connection could be possible through the HCV-mediated changes upon the patient's homeostasis. As it was recently suggested, one such mechanism could be insulin resistance [68]. Chronic inflammation or infections like hepatitis C have been shown to cause insulin resistance, meaning that cells become insensitive or unresponsive to insulin stimulation and thus with a decreased ability to absorb and metabolize the glucose [70]. Insulin resistance has also been noted in periodontal patients [71, 72], suggesting that preexisting HCV infection could create favorable conditions for the development of periodontal changes by altering the general cellular response to inflammation. Another explanation for the interaction between the two diseases and the way they are interconditioned is that the liver play an important role in the regulation of the immune response [73]. An impaired hepatic function caused by HCV

infection and its complications (liver fibrosis) can alter the general immune response by impaired neutrophil cell activity or overproduction of pro-inflammatory cytokines (interleukins, tumor necrosis factors) by the activated monocytes/macrophages. Such changes in the immune response have also been recorded during periodontal inflammation [74]. The similar immune response in the two conditions could suggest that, combined with the presence of subgingival bacterial biofilm, a preexisting inflammatory disease such as chronic hepatitis C could create the necessary immunological premises able to trigger the onset of periodontal damage in HCV patients [75, 76].

Similar pro-inflammatory cytokine profiles have been found in both chronic hepatitis C and periodontal disease. Various amounts of IL-1 (alpha and beta), IL-6, and TNF-alpha were found in HCV patients' serum [77, 78] as well as in periodontal patients [79]. A direct significant correlation emerged between serum levels of TNF-alpha, the degree of hepatic inflammation, and serum levels of adiponectin [80]. This association could further explain the impact of chronic hepatitis C on insulin resistance, since adiponectin serum levels can impact and correlate to insulin resistance and homeostasis glucose metabolism [80]. In saliva samples of periodontal patients, similar cytokine profiles to those in serum were found [81], while traces of viral RNA and anti-HCV antibodies were found in chronic hepatitis C patients' saliva [82, 83]. The gingival crevicular fluid exhibits similar characteristics to saliva in both cytokine profile in samples from periodontal disease sites [84] and HCV load with RNA molecules and antibodies [52, 53, 85]. As for other systemic periodontal comorbidities such as diabetes mellitus, cytokine profile plays an important role in the development of distant inflammation, mediated by pro-inflammatory markers triggered by other metabolic disease that impact the homeostasis [29].

The two most common hepatic enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), used for liver function assessment, can also be assessed in the gingival crevicular fluid and saliva. The level of these enzymes has been shown to fluctuate according to the inflammatory status of the periodontal tissues [86–88]. The fact that transaminases recorded a decreased activity subsequent to periodontal treatment suggests that the periodontal inflammation and the aggression caused by periodontal bacteria can have extending effects that exceed the periodontal tissues. Therefore, it could reach the liver and impact its normal function, being able to influence ongoing hepatic conditions such as chronic hepatitis. Thus, the relation between periodontal disease and HCV infection could be bidirectional, each of the two conditions having an impact upon the other one, both in terms of pathogenic mechanism, clinical manifestation, and therapeutic strategies.

The connection between HCV infection and periodontal disease is also suggested by some data that assesses its clinical impact on the manifestations of the two conditions. In a study comparing the periodontal status of patients with periodontal disease to those of patients with periodontal disease associating hepatitis C [89], the first group of patients exhibited a statistically significant larger number of remnant teeth than the second group. In addition, for the patients with periodontal disease and hepatitis C, the existing teeth were more frequently affected by periodontal pockets than the hepatitis-free patients, although not statistically significant. A statistically significant difference was recorded between the maximum periodontal

pocket depths of the groups, deeper periodontal pockets being found in HCV patients. Moreover, the gingival index (GI), assessing the degree of gingival inflammation, was also significantly higher for HCV and periodontitis patients than for hepatitis-free ones. A complementary study assessing the metabolic status of periodontal patients with or without comorbidities (chronic hepatitis and diabetes mellitus) [90] was set up in order to determine whether chronic hepatitis can impact the metabolic status in a similar manner that a well-studied and acknowledged periodontal comorbidity like diabetes mellitus does. The results showed that the metabolic status of HCV periodontal patients was different, similar to the changes that diabetes had caused on the metabolic status of periodontal patients. HCV patients could be more reluctant to seek dental treatment or could face a hesitant attitude among dental practitioners to perform complex surgical or rehabilitation treatments, due to the elevated risk of infection transmission. This opinion is enforced by a study showing that HCV patients exhibited a less favorable dental health status than a control group, with higher numbers of dental carries and missing teeth, but lower dental maneuvers such as fillings, crowns, or bridges [91].

As it has been previously suggested [68, 75, 76], the possible connection between periodontal disease and chronic hepatitis C becomes more than plausible. It seems that, given the holistic perspective on the pathogenic mechanisms of the human body, any disruption of its homeostasis caused by inflammatory processes ongoing even in distant territories like the periodontal and liver tissues has a general impact that reverberates across the entire biological structure and becomes relevant in terms of clinical manifestation. This aspect can help specialists to get a better understanding of the common pathophysiological mechanisms that govern these conditions and to provide better treatment strategies with a wider systemic perspective. Obviously, the matter still requires further scientific effort and research to provide comprehensive explanations to the issues that need to be addressed.

## 8. Conclusion

The periodontal implications of HCV impact the factors that favor the onset of periodontal inflammation such as the host immune response. The clinical manifestations of the periodontal disease (like gingival bleeding) influence the presence of the viral RNA molecules in the gingival fluid and saliva. Generally, hepatitis C patients can exhibit an impaired level of oral health and seek limited dental care, therefore creating additional premises for the onset of periodontal damage. These implications need to be further taken into consideration by both periodontists and hepatologists, in order to provide better oral health and health outcomes for their patients.

## Conflict of interest

None.

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