Chapter

Immunological Insights on Pathogenic Connections between Hepato-Digestive Disorders and Periodontal Conditions

Dora Maria Popescu, Dorin Nicolae Gheorghe, Flavia Nicolae, Lucian Paul Dragomir, Allma Pitru, Andrada Soanca, Cristina Florescu, Vasilica Toma, Liliana Foia, Alexandra Livia Roman, Petra Surlin and Ion Rogoveanu

Abstract

The oral cavity is an integral part of the digestive tract and thus significant diseases, including periodontitis, can have an important impact on the normal nutritional functions of the body. Certain diseases of the hepato-digestive system have an inflammatory component, such as chronic hepatitis, fatty liver disease, or gastric cancer. This inflammatory reaction is mainly driven by pro-inflammatory chemokines. This is also the case for periodontitis, a condition characterized by the inflammation of the supporting tissues of teeth. Thus, significant pathogenic connections mediated by pro-inflammatory chemokines could exist between periodontitis and diseases of the hepato-digestive system.

Keywords: periodontitis, periodontal medicine, periodontal conditions, hepato-digestive disorders, pathogenic connections, immunology, inflammation mediators

1. Introduction

Low-grade inflammation is defined as the continuous, low-grade production of inflammatory factors throughout the body. It is currently acknowledged as a risk factor for many chronic diseases, including cancer, cardiovascular, cerebrovascular, and neurodegenerative illnesses [1, 2]. Periodontitis is a chronic inflammatory multifactorial disease, that involves the tooth-supporting structures, the periodontium, and in developed countries is the most frequent reason for tooth loss. Despite being essential, the infection is insufficient for the occurrence of this disease, as the dysregulation of the immuno-inflammatory status is required also, thus leading to systemic low-grade inflammation [1]. Periodontal microbes and immunity engage in a battle, with the help of innate immunity (such as macrophages, dendritic

cells, natural killer cells, and neutrophils) and adaptive immunity (such as B and T lymphocytes), which leads to the release of pro-inflammatory molecules and enzymes (such as interferon-gamma, interleukin-17 (IL-17), tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), collagenases such as matrix metalloproteinases (MMPs) [2].

On the one hand, our body uses the inflammatory response as a type of defense against microorganisms getting within the deeper tissues (such as bone). The periodontium, on the other hand, is irreversibly destroyed if the inflammation persists and is not controlled, leading to the classic symptoms of periodontitis, including periodontal pockets, attachment loss, gingival recessions, tooth mobility, tooth migration, and tooth loss [1, 2]. The interface via which local inflammation can have an impact on overall health is represented by the dento-gingival epithelial surface area, which includes every pocket epithelium in direct contact with the subgingival biofilm. Pro-inflammatory mediators produced locally during periodontitis, such as IL-1, IL-6, TNF-α, and prostaglandin E2 (PGE2), may enter the systemic circulation and then have an impact on distant organs, causing an inflammatory state to worsen and/or persist. Thus, the theory that the systemic inflammation brought on by periodontitis may influence the subject's inflammatory burden develops [1, 3].

Periodontal disease is considered a risk factor for a number of chronic illnesses, such as diabetes, cardiovascular disease, neurodegenerative disorders, or several malignancies, where low-grade inflammation is mandatory for the development and progression of the disease [1]. The mechanisms that associate periodontitis to extra-oral comorbidities are in line with clinical observations that connect periodontitis to bacteriemias, low-grade systemic inflammation, increased myelopoiesis, and the ability of local periodontal therapy to attenuate systemic inflammatory markers and improve comorbid disease activity [1–3]. Patients with severe periodontitis have increased levels of pro-inflammatory mediators (including IL-1, IL-6, C-reactive protein (CRP), and fibrinogen), as well as increased neutrophil counts in the blood, in comparison with healthy controls [3]. This could be because of oral bacteria, mainly *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, which are partially responsible for periodontal disease and lead to a chronic inflammatory process, by damaging the fibroblasts, epithelial and endothelial cells, as they promote the release of inflammatory mediators, such as interleukin-1β (IL-1β), IL-6, IL-17, interleukin-23 (IL-23), TNF-α, and matrix metalloproteinases (MMP-8 and MMP-9) [2, 4].

Monocytes/macrophages, neutrophils, fibroblasts, and mast cells are the principal producers of IL-1β in the periodontium tissues in response to activation caused by lipopolysaccharide (LPS), the fundamental component of Gram-negative bacteria cell walls. Osteoclast development and bone resorption are brought on by IL-1β, which results in localized inflammation in the periodontium. Additionally, this cytokine induces the production of numerous MMPs, phospholipase A2, prostaglandins (PG), acute phase proteins, proinflammatory cytokine IL-6, and TNF-α. Regarding systemic malignancies, higher levels of this citokine are linked to tumor invasiveness, migration, and a more aggressive tumor phenotype. IL-1β creates an inflammatory milieu for angiogenesis and tumor growth [2, 4, 5].

IL-6 is a major pro-inflammatory cytokine. Numerous periodontal tissue cells produce it in response to stimulation when LPS and the pro-inflammatory cytokines IL-1 and TNF-α are present. In addition to causing bone resorption, IL-6 also promotes the production of acute phase proteins, chemokines, and PGE2. By boosting the production of matrix MMPs, IL-6 also influences the invasion and metastatic process [2, 4–6].

TNF-α, which is produced, among others, by monocytes/macrophages, neutrophils, fibroblasts, lymphocytes, and mast cells, is another important cytokine in the inflammatory response. In response to a variety of triggers, such as bacterial LPS, this cytokine is released. TNF-α significantly stimulates the formation of reactive oxygen species (ROS), leukotrienes, prostaglandins, and metalloproteinases and decreases the number of fibroblasts and osteogenic cells. Low dosages of this molecule are linked to tumor development as opposed to large concentrations of TNF-α, which are linked to tumor destruction. By stimulating the expression of MMPs and stimulating the production of several angiogenic factors, including interleukin-8 (IL-8) and basic fibroblast growth factor, TNF-α has been demonstrated to affect processes of motility and invasion [4, 5, 7]. A tumor phenotype can be induced by modest, persistent TNF-α production levels. The formation of reactive oxygen species and reactive nitrogen species (RNS), which may cause DNA damage and hence promote carcinogenesis, is the basis of a TNF-α tumor promotion mechanism. Cancer and TNF-α mediated inflammation are related [6, 7].

This chapter aims to exhibit the possible connections that may exist between periodontitis and some hepato-digestive disorders, mediated by means of pro-inflammatory chemokines. These diseases share an inflammatory component as part of their pathogenic mechanisms, and thus, mutual pro-inflammatory chemokines could play a significant influence on their onset and evolution, in terms of susceptibility and severity.

2. Cytokines' involvement in periodontitis-systemic conditions

2.1 Periodontitis and colorectal cancer

A prevalent inflammatory illness with infectious origins, periodontitis frequently turns into a chronic condition. In addition to its significance as a stomatological condition, chronic periodontitis has gained significance because it has been demonstrated that it can progress to a systemic condition marked by unresolved hyperinflammation, disruption of the innate and adaptive immune system,

dysbiosis of the oral and gut mucosa, and other conditions that may result in, coexist with or exacerbate other health problems while it is linked to increased morbidity and mortality. It is still up for discussion how the location's microbiota and other system-wide changes connect to the infectious, immunological, inflammatory, and systemic characteristics of periodontitis and gastrointestinal disorders [1, 2].

Similar to other diseases that we shall address later, systemic inflammation is considered to have an important biological function in these conditions as well. It is generally known that inflammation may have a significant impact on all stages of cancer. From the first cancerous cell to the first stages of tumor development, progression, and neoplasm spread, inflammatory and immunological mediation processes are well-known markers of cancer. Another developing idea in this context is that, similar to other complicated illnesses, cancer develops from systemic rather than local factors. A complicated process by itself, systemic inflammation involves interactions between immunological signals, energy metabolism, and functional linkages that, when combined with genetic instability, predispose people to cancer and control the aberrant conditions that support neoplastic illness [1–3].

In the western world, colorectal cancer (CRC) is the second most common cause of cancer-related mortality. The several stages of CRC formation are defined by

complicated interactions between environmental carcinogens, genetic changes, and the host immune system, which eventually lead to the uncontrolled expansion of altered cells. Chronic inflammation is a distinct risk factor for the development of CRC, just like it is for other prevalent malignancies (including gastric cancer, prostate cancer, and hepatocellular carcinoma). According to experimental models of inflammation-related colon carcinogenesis, cytokines produced by inflammatory cells can either directly or indirectly drive the development of cancer cells [8]. Moreover, a higher risk of colorectal cancer has been linked to plasma levels of certain pro-inflammatory cytokines, such as IL-8 and IL-6 [9].

In a research paper, tumor cells were shown to be a significant source of chemokines in CRC, and the gut microbiota was found to have a key role in chemokine synthesis and T cell recruitment in tumor tissue, both of which improved prognosis. This information may potentially pave the path for the creation of novel therapies focused on altering gut flora to encourage immune cell populations with positive prognostic relevance to infiltrate CRCs [10]. Chemokines primarily control angiogenesis, activate immune responses specific to tumors, and stimulate the tumor directly through autocrine or paracrine processes in cancer [11].

F. nucleatum, an periopathogen, can hematogenously spread to the colon, where it prefers CRC, as it directly binds to and invades host immune and cancer cells [3, 11]. This is because D-galactose-N-Acetyl-D-galactosamine (GAL-GalNAc), a carbohydrate moiety that the *F. nucleatum* lectin Fap2 binds, is overexpressed in CRC cells. This overexpression also triggers the release of prometastatic chemokines like IL-8 and chemokine family CXC-chemokine ligand 1 (CXCL1), which promote CRC migration and tumor-related angiogenesis. By activating E-cadherin-mediated Wnt—catenin signaling in a way that is reliant on annexin A1, which is increased in CRC, another *F. nucleatum* adhesin called FadA promotes the proliferation of CRC (but not non-cancerous) cells [3, 4].

For instance, when 13 cytokines, chemokines, and growth factors were examined in serum profiles from 116 CRC patients and 86 healthy controls, it was discovered that five of these proteins had statistically significant changes in their serum levels, including elevated levels of IL-6, IL-7, CXCL-8 (IL-8), and platelet-derived growth factor-subunit B (PDGFB) and decreased levels of chemokine ligand 2 (CCL2) [12]. Also, pro-inflammatory cytokines, such as IL-6, TNF-α, and IL-8, were found to be expressed more often in CRC patients than in the control group, and also more advanced CRC stages (stage III/IV vs. stage I/II cancers) are typically related with patients who have greater TNF-α concentrations [5]. In comparison to untreated mice, anti-TNF-treated animals showed considerably fewer colon tumors and lower histology scores of colon inflammation [13] while another study reported that the TNF-α serum level of the colorectal cancer group was statistically significantly lower than that of the control group [14].

Notably, IL-6 is one of the cytokines that are significantly higher in CRC patients compared to healthy controls and is much higher in metastatic cancer compared to non-metastatic disease, as it was reported that it causes CRC cells to proliferate, invade and migrate [7, 12, 15]. In comparison to IL-6 deletion tumors, those with IL-6 overexpression tended to develop more quickly, since angiogenesis is stimulated. Patients with increased IL-6 expression in CRC tissues had shorter overall survival (25.5 months on average) than those with lower IL-6 expression (46 months), as it was reported that IL-6 promotes chemotherapy resistance [5, 16]. When pro-inflammatory factors (IL-6, IL-1β, and TNF-α) were measured in the blood of patients with advanced cancer, IL-1β levels linked more significantly with clinical features than

IL-6 levels did [5]. Another research paper stated that, in CRC patients, IL-6 levels often correlate with tumor size, stage, and metastasis. In numerous kinds of cancer, circulating IL-6 levels are predictors of survival and response to therapy [16]. A postoperatively higher carcinoembryonic antigen (CEA) alone or in conjunction with carbohydrate antigen19–9 (CA19–9), chitinase-3-like-protein-1 (CHI3L1), CRP, or IL-6 may also signal individuals at high risk of relapsing, for CRC patients in stage II to IV who underwent radical surgery and received adjuvant 5-fluorouracil (5-FU)-based treatment [17].

2.2 Periodontitis and nonalcoholic fatty liver disease

The synthesis of inflammatory mediators is a characteristic of the systemic inflammatory response in periodontal disease, which is represented by periodontal infection associated with oral biofilm [18]. Even in the absence of other chronic systemic disorders, patients with chronic periodontitis have higher levels of proinflammatory mediators [19, 20]. It can be a bidirectional relationship between periodontitis and the majority of common noncommunicable diseases, including cardiovascular conditions, metabolic syndromes, diabetes mellitus and non-alcoholic fatty liver disease, cancer, and respiratory conditions [21].

Non-alcoholic fatty liver disease (NAFLD), is the most prevalent type of chronic liver disease globally. NAFLD is generally asymptomatic, and it is closely associated with diseases like obesity, diabetes mellitus type 2, and the characteristics of metabolic syndrome [22]. Scientific evidence strongly indicates that the gut microbiota contributes significantly to the pathogenesis of NAFLD and that *P. gingivalis* (P. g.) changes the composition of the intestinal microflora [23]. According to studies, P. g. infection is associated with various systemic disorders, such as diabetes mellitus, hepatic conditions, and gastric cancers [24]. Periopathogen bacteria such as P. g. can be detected, in association with a statistically significant decrease in serum albumin levels in NAFLD patients, indicating liver function impairment. Some studies concluded that P. g. infection could be an independent predictor of NAFLD development. These studies suggest that persistent P. g. infection in patients with untreated periodontitis may accelerate liver tissue fibrosis and decrease liver function [25].

A chronic low-grade inflammatory state is a pathological component of a variety of chronic conditions, including NAFLD [26]. Microvascular endothelial dysfunction, decreased immune responses, and chronic low-grade inflammation are all characteristics of the multisystem disease NAFLD [27]. A chronic low-grade inflammatory condition that is supported by the relationship between NAFLD, obesity, and type 2 diabetes increases the risk of atherosclerosis, dyslipidemia, systemic arterial hypertension, and acute myocardial infarction [28].

Simple steatosis and non-alcoholic steatohepatitis (NASH), which is marked by liver inflammation and hepatocyte ballooning with or without fibrosis, are also examples of NAFLD. NAFLD and NASH are linked to higher rates of morbidity and mortality across this broad spectrum of diseases [29].

Numerous variables, such as the patient's age and gender, ethnicity, frequency, amount of alcohol consumed daily, diet, hormonal status, genetic predisposition, microbiome, and metabolic status, have an impact on the heterogeneity in the clinic and the evolution of the fatty liver disease. There may be a differential impact on the contribution of these variables to each patient on the part or between patients, an impact that then changes the phenotype and evolution of the disease [30].

From in vitro, in vivo, and epidemiologic perspectives, the potential correlations between periodontitis and NAFLD have been studied, but the genetic and molecular processes of the relationship between periodontitis and NAFLD remain unknown [31]. According to epidemiological research, periodontitis and NAFLD together are increasing the occurrence of the condition, which could enhance the potential that it will advance to liver fibrosis as well [32]. However, alterations in the oral microbiome caused by periodontal disease could have an impact on the intestine microbiota and NAFLD's pathogenesis could be influenced by this gut microbiota [33].

The involvement of cytokines as important mediators of fibrosis, cirrhosis, and inflammation in NAFLD is generally accepted. Different inflammatory mediators, including IL-1, IL-6, TNF-α, CRP, and NOD-like receptor protein 3 (NLRP3) inflammasome, have been implicated in the pathogenesis and progression of NAFLD in previous studies [23, 34]. A systemic indicator of inflammation, CRP may be essential in detecting pathological alterations. The liver is the primary source of CRP but can also be secreted by adipose tissue, which acts as an endocrine organ that can secrete other inflammatory cytokines such as IL-6 [35]. A higher serum level of CRP has been identified in several studies as a significant risk factor for the development of NAFLD, and it appears to be a great marker for the prediction and diagnosis of NAFLD. A family of proteins known as pentraxin (PTX) is divided into two classes, short and long, depending on the length of their structural components. Serum amyloid P and CRP are two minor members of this family. One of the long proteins in this family, plasma pentraxin 3 (PTX3), is detected in significantly higher concentrations in patients with steatohepatitis than in those without [36]. Patients with more severe forms of NAFLD have higher serum concentrations of this protein, and higher levels of this protein are associated with more severe forms of hepatic fibrosis. Therefore, this could suggest that the serum PTX3 level might be used to diagnose the degree of hepatic fibrosis and to separate steatohepatitis and simple steatosis [37].

Particularly the pro-inflammatory cytokines IL-1 and TNF mediate important features of liver diseases including acute phase protein synthesis, lipid metabolism, cholestasis, and degree of fibrosis in different stages of liver diseases. These essential cytokines, which are mostly generated by mononuclear cells, influence all types of liver cells and control the generation of many other mediators essential in chronic liver diseases [38].

Other interleukins implicated in NAFLD disease include IL-8, IL-12, IL-18, and IL-34 [39]. Also, IL-32, which was first identified in 2005 and is one of several inflammatory biomarkers linked to obesity and NAFLD, is identified as a key regulator of obesity-driven inflammation and lipotoxicity [40].

According to some research, patients with NAFLD who ultimately progressed to critical condition had higher concentrations of IL-6, IL-8, and IL-10, than when establishing the diagnosis. IL-8 and IL-10 also seem to be significant prognostic biomarkers associated with recovery time [27]. IL-6 is often synthesized in immunologically activated adipose tissue, which is deeply associated with metabolic syndrome. This could be a possible explanation for the high prevalence of obesity in patients with NAFLD. Other studies did not find differences in IL-6 levels between non-obese and obese patients with NAFLD, suggesting other possible immunological mechanisms [27, 41].

The development of metabolic changes and an increased risk of liver damage associated with fibrosis during the evolution of NAFLD may be caused by inadequate modulation of IL-10 associated with IL-6, IL-12, and TNF [42]. Some

proinflammatory cytokines (including IL-6, IL-12, and TNF-α) are considered to contribute to inadequate modulation of IL-10, according to some studies. Since IL-10 concentrations indicated a strong correlation with IL-6 and other inflammatory markers, including CRP, this could be interpreted as an unsuccessful attempt to reduce the hyperinflammatory response and tissue damage. Additionally, immune cells that have been stimulated may become "IL-10 resistant," which would allow them to pass the anti-inflammatory effects of IL-10 signaling and increase the inflammatory response [43]. Higher IL-6 levels and a lower IL-10/IL-6 ratio have been reported in NASH patients, which may indicate inadequate anti-inflammatory compensation. Patients with NASH have also been found to have higher levels of circulating TNF than patients with steatosis or healthy controls [42].

When NAFLD first appears and progresses, cytokines may contribute, stimulating and controlling critical processes. Patients with non-alcoholic steatohepatitis may have a balance between proinflammatory (IL-1, IL-6, IL-12, and TNF) and regulatory (IL-10) cytokine concentrations, which have been associated with early metabolic abnormalities in the context of NAFLD [42]. Furthermore, it has been shown that TNF production may have a role in the first liver injury, causing the release of other cytokines including IL-12, which recruits inflammatory cells, destroys hepatocytes, and initiates a healing response, including hepatic fibrogenesis [44]. Because of its antioxidant and cytoprotective characteristics, IL-12 may be a protective biomarker for NAFLD. Regardless of the number of metabolic risk factors, IL-12 was inversely correlated with the prevalence of NAFLD and positively correlated with the specific rise in productivity bilirubin in patients with non-alcoholic steatohepatitis [45].

2.3 Periodontitis and chronic hepatitis C

Chronic hepatitis C (CHC) is caused by infection with the Hepatitis C Virus (HCV) and is a severe threat to the individual's life, with an estimated 700,000 deaths worldwide each year [46]. The spread of the virus is considered a global health hazard since it affects more than 200 million individuals globally, and it is especially difficult to battle because the disease has no symptoms in its early stages. As a result, infected individuals may be oblivious and easily infect others. Most individuals will develop chronic liver inflammation after the acute stage of illness. Hepatic function gradually deteriorates when hepatic tissue is replaced by fibrotic tissue and liver cirrhosis develops [47].

CHC is a potentially fatal illness if left untreated, leading to serious consequences such as hepatic cirrhosis (in 10–30% of CHC patients) and hepatocellular cancer (5 percent of CHC patients) [48]. Only 15% of individuals have clinical manifestations of the illness after infected contact with the virus. The initial inflammatory reaction generated by the presence of the virus is "chronicized" in the majority of cases, resulting in CHC, with the virus remaining detectable six months after the infected encounter [49].

Patients with CHC frequently experience significant oral health issues, which can have a negative impact on their quality of life, in addition to the pathological manifestations of liver disease and its complications [50]. CHC patients seeking dental treatments may encounter a variety of difficulties, such as high personal anxiety or altered healing and recovery processes following dental and periodontal surgery, which restrict the complexity of therapy alternatives [51]. CHC patients may have increased risk factors for the start of periodontitis, leading to its clinical presentation, which is driven by the buildup of subgingival bacterial plaque deposits, which is corroborated by probable behavioral differences [52].

As a chronic inflammatory disorder, CHC may have certain connections and interactions with Parkinson's disease, presumably through proinflammatory mediators released into the bloodstream of HCV patients [53]. Natural killer cells (NK), which may produce TNF-α, play a crucial role in the immunopathogenesis of CHC [54]. Certain cytokines, including IL-18 and IL-33, are employed as indicators of CHC disease activity and severity since these individuals have higher serological levels of these interleukins [55, 56]. Elevated levels of IL-1α have also been detected in blood samples of chronic hepatitis C patients, and have been linked to disease severity [57]. Furthermore, several proinflammatory mediators, including IL-1α, have been demonstrated to stimulate hepatic inflammatory processes in chronic hepatitis C patients, resulting in elevated blood levels [58].

In essence, both CHC and periodontitis cause a persistent inflammatory response, with proinflammatory mediators controlling the amount and intensity of the pathogenic process. Studies that focused on the gingival crevicular fluid (GCF) assessment of IL-1α and IL-1β's involvement in the pathogenic process of periodontitis patients with CHC, found that patients with both diseases had significantly worsened periodontal status and higher levels of these cytokines than non-CHC patients with periodontitis [59]. This suggests that hepatic pathology may have a negative impact on local periodontal inflammation.

Elevated gingival fluid levels of IL-1α and IL-1β, detected in periodontal patients compared to healthy controls, have been demonstrated to decrease following periodontal therapy, supporting their critical involvement in the development of periodontal disease [24, 59]. A statistically significant difference in GCF cytokine levels between the CHC and periodontitis groups was also highlighted. Because both groups of patients had periodontal disease with equal degrees of severity and progression, the greater GCF cytokines levels in periodontitis patients with CHC might be explained by the added chronic hepatic inflammation that these individuals exhibit. This fact can also influence the severity of the inflammatory periodontal response [59].

The levels of GCF cytokines in chronic periodontitis patients correlate with the degree of periodontal inflammation. The clinical markers used to measure periodontal condition (such as the number of missing teeth, periodontal pocket depth, or gingival attachment loss) were associated to increased GCF levels of IL-1α and IL-1β in periodontal patients with CHC [59]. There was also a modest positive connection between these clinical measures in periodontal patients with no systemic disease and GCF cytokine levels, indicating that systemic chronic inflammation might have an extra influence on such patients' periodontal health [59].

Periodontal and hepatic chronic inflammatory responses may interact because they are both fueled by the same proinflammatory cytokines, IL-1α and IL-1β [60]. Hepatic chronic inflammation has a significant detrimental influence on periodontal condition in terms of the strength of the periodontal inflammatory reaction [61]. Elevated levels of IL-1α and IL-1β, which have significant consequences in the pathogenic processes of both periodontitis and CHC, might suggest that chronic hepatitis C has a deleterious influence on periodontal patients' inflammatory status, as measured by IL-1α and IL-1β GCF detection.

The notion of the "inflammasome" molecule has opened up new perspectives for periodontal inflammation research. The NLPR3 inflammasome is a critical component of this inflammatory response, serving as the first triggering mechanism upon interaction with bacterial antigens such as *P.g's* LPS [62]. Substantial variations in

GCF NLRP3 levels between the periodontitis and control groups were reported, as well as between patients with CHC and periodontitis and CHC-only ones, suggesting that periodontal pathological events cause a significant rise in NLRP3 expression [63]. This concept was also evaluated and supported by a recent study on the issue, which indicated that periodontal disorders are characterized by an increase in inflammasome expression and a decrease in their inhibitor proteins [64, 65]. In terms of hepatic disease, NLRP3 has been shown to activate inside white and red blood cells when triggered by HCV infection [66]. Furthermore, the *in vitro* presence of the virus dictated cellular pyroptosis within infected hepatocytes, an event primarily mediated by NLRP3 and caspase-1 (CASP1) activity [67, 68]. Together with IL-1, NLRP3 is implicated in the initiation of the chronic hepatic inflammatory response caused by HCV infection. As a result, CHC patients are likely to have higher blood NLRP3 levels [67].

According to research on the issue of NLRP3 inflammasome involved in the periodontitis and diabetes connection, the findings revealed substantial correlations between GCF NLRP3 levels and blood glucose levels of the participating patients [63, 69]. This result supports the pathogenic relationships that exist between periodontitis and insulin resistance. Similar pathogenic links exist between CHC and insulin resistance. These findings imply that this pathologic mechanism may be able to bridge the gap between chronic hepatitis and periodontitis due to the significant influence and bi-directional repercussions it has on the inflammatory response [69].

The immunological analysis produced equivalent results on the average values of CASP1 in periodontitis patients' GCF samples, which were considerably greater than those of healthy controls [65, 69]. CASP1 is largely expressed in gingival epithelial cells, keratinocytes, and connective tissue cells, and is essentially non-existent when periodontal tissues are not inflamed [70]. Furthermore, key periodontal bacteria (*Aggregatibacter actinomycetemcomitans* and *P. g.*) have been found to induce caspase expression in epithelial cells and macrophages [71]. CASP1 is also implicated in the pathology of CHC, since HCV-infected cells may synthesize and release the NLRP3 inflammasome [68]. The findings revealed that CHC + periodontitis patients had higher average GCF CASP1 levels than non-CHC periodontitis patients. There were also significant variations in the average values of CHC patients with and without periodontal disease. These findings imply that chronic inflammation, whether hepatic or periodontal, can have a considerable influence on CASP1 levels [65, 69].

IL-18 has also been proposed as a potential marker for periodontal structural degradation [72]. GCF IL-18 levels in periodontal patients were substantially greater than in healthy controls. Furthermore, the statistical analysis revealed substantial associations between GCF IL-18 levels and periodontal disease severity measures (periodontal probing depth, clinical attachment loss, and gingival bleeding index) [63, 69]. In line with this observation, CHC + periodontitis patients had substantially higher GCF IL-18 levels, indicating an unfavorable clinical periodontal state [64, 69]. Concerning hepatic illness, IL-18 has immunological and clinical repercussions for CHC, as affected individuals frequently have much higher levels of this mediator than healthy controls [73]. Significant variations in GCF IL-18 levels were seen between the CHC+ periodontitis patients and non-CHC periodontitis ones, confirming the deleterious influence that HCV infection can have on periodontal status in comparable periodontal pathological circumstances [69]. This can exacerbate gingival pathogenic events and cause a more severe periodontal inflammatory response.

PTX is a protein family that participates in inflammatory pathways by serving as pattern-recognition receptors (PRRs) [74]. PTX, also known as acute-phase proteins (APP), play a key role in the initiation of inflammation, primarily by protecting against pathogenic bacteria via complement activation. This role is supported by the fact that in GCF samples originating from patients diagnosed with periodontitis, PTX3 levels were significantly elevated, as compared to control groups [36, 75]. These elevated GCF PTX3 levels also correlated with clinical periodontal parameters, suggesting an early up-regulated synthesis of this mediator by neutrophil cells, in response to periodontal bacterial aggression [36]. It is known that PTX3 is pre-stored in neutrophil cells to be accessible for quick release and action [75]. It was highlighted that GCF PTX3 levels rise proportionally to the severity of periodontitis. At baseline, GCF PTX3 levels were higher in periodontitis patients than in controls, and these levels considerably decreased as soon as two weeks following scaling and root planning (non-surgical periodontal therapy—NSPT) on these patients [76]. However, a higher fall in GCF PTX3 levels was found in smoking patients, indicating that smoking had a major influence on this parameter. GCF PTX3 levels in smoking patients remained increased even after NSPT [76].

CRP is a short pentraxin, whereas PTX3 belongs to the long pentraxin branch. Both proteins are increased in severe infections and inflammation, indicating their importance in bacterial or viral diseases (such as periodontitis and CHC) [77]. GCF CRP levels express lower association strength and, as a result, less periodontal clinical significance than the PTX3 mediator [36, 76]. GCF and CRP levels are considerably higher in periodontitis patients' samples compared to healthy controls [78]. However, there was no statistically significant difference in marker levels between periodontitis patients with and without CHC [36]. GCF CRP levels dropped after NSPT in CHC + periodontitis patients but increased somewhat in periodontitis-only patients. GCF CRP levels are associated with patients' age and the dental plaque index, indicating that it may be more important to senior patients, who have poorer dental hygiene. GCF CRP levels were also associated with the bleeding on the probing index [36]. These factors match the profile of CHC patients, who had much higher bleeding on probing than non-CHC individuals. This feature can be explained by the hepatic nature of CRP, which, unlike PTX3, is not locally pre-synthesized and may take a longer time to reach critical quantities in the GCF. This idea was supported by a study highlighting that, while NSPT improved periodontal clinical parameters such as plaque index (due to improved oral hygiene) and pocket depth/attachment loss (due to decreased inflammation), serum CRP levels did not decrease significantly after a one- and two-month recall [79]. Putative participation of hepatic disease in the local inflammatory processes of periodontitis necessitates more investigation in the future, similar to a larger perspective on the role of the CRP mediator in a shared periodontitis-CHC scenario.

3. Conclusions

Periodontitis is characterized by a low-grade inflammation, which triggers the local up-regulation of significant pro-inflammatory mediators, similar to that of certain systemic diseases (**Table 1**). Given that many hepato-digestive disorders have an important inflammatory component, the two types of conditions could exert a significant influence on each other, by means of mutual pro-inflammatory chemokines.

Inflammatory marker	Periodontitis/colorectal cancer	Periodontitis/ nonalcoholic fatty liver disease	Periodontitis/ chronic Hepatitis C
CASP1			*
CCL2	*		
CRP		*	*
CXCL1	*		
GAL-GalNAc	*		
IL-1		*	
IL-1α			*
IL-1β	*		*
IL-6	*	*	
IL-7	*		
IL-8	*	*	
IL-10		*	
IL-12		*	
IL-18		*	*
IL-32		*	
IL-33			*
IL-34		*	
NRLP3		*	*
PTX3		*	*
TNF-α	*	*	*

**-existing relevant information on implications in periodontitis and systemic diseases (CASP1 – caspase1; CCL2-chemokine ligand2; CRP – C Reactive Protein; CXCL1- CXC-chemokine ligand 1; GAL-GalNAc - D-galactose-N-Acetyl-D-galactosamine; IL – interleukin; NRLP3 - NOD-like receptor protein 3; PTX3 – pentraxin3; TNF-α – tumor necrosis factor-α.*

Table 1.
Synopsis of mediators' inflammation in the association of periodontitis and hepato-digestive disorders.

Conflict of interest

The authors declare no conflict of interest.

Author details

Dora Maria Popescu[1], Dorin Nicolae Gheorghe[1*], Flavia Nicolae[1], Lucian Paul Dragomir[2], Allma Pitru[3], Andrada Soanca[4], Cristina Florescu[5], Vasilica Toma[6], Liliana Foia[7], Alexandra Livia Roman[4], Petra Surlin[1] and Ion Rogoveanu[8]

1 Faculty of Dental Medicine, Department of Periodontology, University of Medicine and Pharmacy of Craiova, Craiova, Romania

2 Faculty of Dental Medicine, Department of Fixed Prosthodontics, University of Medicine and Pharmacy of Craiova, Craiova, Romania

3 Faculty of Dental Medicine, Department of Oral Pathology, University of Medicine and Pharmacy of Craiova, Craiova, Romania

4 Faculty of Dental Medicine, Department of Periodontology, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

5 Faculty of Medicine, Department of Internal Medicine and Cardiology, University of Medicine and Pharmacy of Craiova, Craiova, Romania

6 Faculty of Dental Medicine, Department of Pedodontics, "Gr. T. Popa" University of Medicine and Pharmacy, Iasi, Romania

7 Faculty of Dental Medicine, Department of Biochemistry, "Gr. T. Popa" University of Medicine and Pharmacy, Iasi, Romania

8 Faculty of Medicine, Department of Gastroenterology, University of Medicine and Pharmacy of Craiova, Craiova, Romania

*Address all correspondence to: dorinngheorghe@gmail.com

IntechOpen

References

[1] Cecoro G, Annunziata M, Iuorio MT, Nastri L, Guida L. Periodontitis, low-grade inflammation and systemic health: A scoping review. Medicina (Kaunas, Lithuania). 2020;**56**(6):272

[2] Martínez-García M, Hernández-Lemus E. Periodontal inflammation and systemic diseases: An overview. Frontiers in Physiology. 2021;**12**:709438

[3] Hajishengallis G, Chavakis T. Local and systemic mechanisms linking periodontal disease and inflammatory comorbidities. Nature Reviews. Immunology. 2021;**21**(7):426-440

[4] Karpinski TM. Role of oral microbiota in cancer development. Microorganisms. 2019;**7**(1):20

[5] Kasprzak A. The role of tumor microenvironment cells in colorectal cancer (CRC) Cachexia. International Journal of Molecular Sciences. 2021;**22**(4):1565

[6] Landskron G, De la Fuente M, Thuwajit P, Thuwajit C, Hermoso MA. Chronic inflammation and cytokines in the tumor microenvironment. Journal of Immunology Research. 2014;**2014**:149185

[7] Kraus S, Arber N. Inflammation and colorectal cancer. Current Opinion in Pharmacology. 2009;**9**(4):405-410

[8] De Simone V, Franzè E, Ronchetti G, Colantoni A, Fantini MC, Di Fusco D, et al. Th17-type cytokines, IL-6 and TNF-α synergistically activate STAT3 and NF-kB to promote colorectal cancer cell growth. Oncogene. 2015;**34**(27):3493-3503

[9] Momen-Heravi F, Babic A, Tworoger SS, Zhang L, Wu K, Smith-Warner SA, et al. Periodontal disease, tooth loss and colorectal cancer risk: Results from the nurses' health study. International Journal of Cancer. 2017;**140**(3):646-652

[10] Cremonesi E, Governa V, Garzon JFG, Mele V, Amicarella F, Muraro MG, et al. Gut microbiota modulate T cell trafficking into human colorectal cancer. Gut. 2018;**67**(11):1984-1994

[11] Casasanta MA, Yoo CC, Udayasuryan B, Sanders BE, Umaña A, Zhang Y, et al. Fusobacterium nucleatum host-cell binding and invasion induces IL-8 and CXCL1 secretion that drives colorectal cancer cell migration. Science Signaling. 2020;**13**(641):eaba9157

[12] Tuomisto AE, Mäkinen MJ, Väyrynen JP. Systemic inflammation in colorectal cancer: Underlying factors, effects, and prognostic significance. World Journal of Gastroenterology. 2019;**25**(31):4383-4404

[13] Yang Y, Gharaibeh RZ, Newsome RC, Jobin C. Amending microbiota by targeting intestinal inflammation with TNF blockade attenuates development of colorectal cancer. Nature Cancer. 2020;**1**(7):723-734

[14] Coşkun Ö, Öztopuz Ö, Özkan ÖF. Determination of IL-6, TNF-α and VEGF levels in the serums of patients with colorectal cancer. Cellular and Molecular Biology (Noisy-le-Grand, France). 2017;**63**(5):97-101

[15] Zhang X, Hu F, Li G, Li G, Yang X, Liu L, et al. Human colorectal cancer-derived mesenchymal stem cells promote colorectal cancer progression through IL-6/JAK2/STAT3 signaling. Cell Death & Disease. 2018;**9**(2):25

[16] Hu F, Song D, Yan Y, Huang C, Shen C, Lan J, et al. IL-6 regulates autophagy and chemotherapy resistance by promoting BECN1 phosphorylation. Nature Communications. 2021;**12**(1):3651

[17] Hermunen K, Soveri LM, Boisen MK, Mustonen HK, Dehlendorff C, Haglund CH, et al. Postoperative serum CA19-9, YKL-40, CRP and IL-6 in combination with CEA as prognostic markers for recurrence and survival in colorectal cancer. Acta Oncologica. 2020;**59**(12):1416-1423

[18] Hatasa M, Yoshida S, Takahashi H, Tanaka K, Kubotsu Y, Ohsugi Y, et al. Relationship between NAFLD and periodontal disease from the view of clinical and basic research, and immunological response. International Journal of Molecular Sciences. 2021;**22**(7):3728

[19] Popescu DM, Pitru AR, Florescu C, Gheorghe DN, Ionele CM, Rica AM, et al. Implications of lipid and carbohydrate metabolism in periodontal disease associated with diabetes, cardiovascular and nonalcoholic fatty liver disease. Medical Surgical Journal. 2021;**125**(3):513-520

[20] Bartold PM, Van Dyke TE. Host modulation: Controlling the inflammation to control the infection. Periodontology 2000 2000. 2017;75(1):317-329

[21] Cardoso EM, Reis C, Manzanares-Céspedes MC. Chronic periodontitis, inflammatory cytokines, and interrelationship with other chronic diseases. Postgraduate Medicine. 2018;**130**(1):98-104

[22] Arsenie C, Săndulescu D, Popescu DM, Gheorghe DN, Mârțu A, Foia L, et al. Periodontal changes, and the non-alcoholic fatty liver disease. International Journal of Medical Dentistry. 2018;**22**(3):280-287

[23] Ponziani FR, Bhoori S, Castelli C, Putignani L, Rivoltini L, Del Chierico F, et al. Hepatocellular carcinoma is associated with gut microbiota profile and inflammation in nonalcoholic fatty liver disease. Hepatology. 2019;**69**(1):107-120

[24] Gheorghe DN, Camen A, Popescu DM, Sincar C, Pitru A, Ionele CM, et al. Periodontitis, metabolic and gastrointestinal tract diseases: Current perspectives on possible pathogenic connections. Journal of Persian Medicine. 2022;**12**(3):341

[25] Rinčić G, Gaćina P, Virović Jukić L, Rinčić N, Božić D, Badovinac A. Association between periodontitis and liver disease. Acta Clinica Croatica. 2022;**60**(3):510-518

[26] Minihane AM, Vinoy S, Russell WR, Baka A, Roche HM, Tuohy KM, et al. Low-grade inflammation, diet composition and health: Current research evidence and its translation. The British Journal of Nutrition. 2015;**114**(7):999-1012

[27] Papic N, Samadan L, Vrsaljko N, Radmanic L, Jelicic K, Simicic P, et al. Distinct cytokine profiles in severe COVID-19 and non-alcoholic fatty liver disease. Life (Basel). 2022;**12**(6):795

[28] Tilg H, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: The multiple parallel hits hypothesis. Hepatology. 2010;**52**(5):1836-1846

[29] Surlin P, Didilescu AC, Lazar L, Arsenie CC, Camen A, Popescu DM, et al. Evaluation through the optical coherence tomography analysis of the

influence of non-alcoholic fatty liver disease on the gingival inflammation in periodontal patients. Diabetes Metabolic Syndrome Obesity. 2021;**14**:2935-2942

[30] Eslam M, Sanyal AJ, George J. International consensus panel. MAFLD: A consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology. 2020;**158**(7):1999-2014.e1

[31] Wanqiu X, Zhengwei Z, Lihong Y, Bing X, Hualei X, Xiumei W, et al. Exploration of shared gene signatures and molecular mechanisms between periodontitis and nonalcoholic fatty liver disease. Frontiers in Genetics. 2022;**13**:939751

[32] Kuroe K, Furuta M, Takeuchi K, Takeshita T, Suma S, Shinagawa T, et al. Association between periodontitis and fibrotic progression of non-alcoholic fatty liver among Japanese adults. Journal of Clinical Periodontology. 2021;**48**(3):368-377

[33] Di Ciaula A, Bonfrate L, Portincasa P. The role of microbiota in nonalcoholic fatty liver disease. European Journal of Clinical Investigation. 2022;**52**(7):e13768

[34] Duan Y, Pan X, Luo J, Xiao X, Li J, Bestman PL, et al. Association of inflammatory cytokines with non-alcoholic fatty liver disease. Frontiers in Immunology. 2022;**13**:880298

[35] Yun CH, Jhuang JR, Tsou MT. Pericardial fat, thoracic peri-aortic adipose tissue, and systemic inflammatory marker in nonalcoholic fatty liver and abdominal obesity phenotype. Scientific Reports. 2022;**12**(1):1958

[36] Gheorghe DN, Popescu DM, Salan A, Boldeanu MV, Ionele CM, Pitru A, et al. Non-surgical periodontal therapy could improve the periodontal inflammatory status in patients with periodontitis and chronic hepatitis C. Journal of Clinical Medicine. 2021;**10**(22):5275

[37] Hadizadeh F, Faghihimani E, Adibi P. Nonalcoholic fatty liver disease: Diagnostic biomarkers. World J Gastrointest Pathophysiol. 2017;**8**(2): 11-26

[38] Niederreiter L, Tilg H. Cytokines and fatty liver diseases. Liver Research. 2018;**2**(1):14-20

[39] Fricker ZP, Pedley A, Massaro JM, Vasan RS, Hoffmann U, Benjamin EJ, et al. Liver fat is associated with markers of inflammation and oxidative stress in analysis of data from the Framingham heart study. Clinical Gastroenterology and Hepatology. 2019;**17**(6):1157-1164.e4

[40] Dali-Youcef N, Vix M, Costantino F, El-Saghire H, Lhermitte B, Callari C, et al. Interleukin-32 contributes to human nonalcoholic fatty liver disease and insulin resistance. Hepatological Communication. 2019;**3**(9):1205-1220

[41] Han MS, White A, Perry RJ, Camporez JP, Hidalgo J, Shulman GI, et al. Regulation of adipose tissue inflammation by interleukin 6. Proceedings of the National Academic Science USA. 2019;**117**(6):2751-2760

[42] Fontes-Cal TCM, Mattos RT, Medeiros NI, Pinto BF, Belchior-Bezerra M, Roque-Souza B, et al. Crosstalk between plasma cytokines, inflammation, and liver damage as a new strategy to monitoring NAFLD progression. Frontiers in Immunology. 2021;**12**:708959

[43] Islam H, Chamberlain TC, Mui AL, Little JP. Elevated Interleukin-10 levels in COVID-19: Potentiation of pro-inflammatory responses or impaired

anti-inflammatory action? Frontiers in Immunology. 2021;**12**:677008

[44] Schwabe RF, Brenner DA. Mechanisms of liver injury. I. TNF-alpha-induced liver injury: Role of IKK, JNK, and ROS pathways. American Journal of Physiology. Gastrointestinal and Liver Physiology. 2006;**290**(4):G583-G589

[45] Tian J, Zhong R, Liu C, Tang Y, Gong J, Chang J, et al. Association between bilirubin and risk of non-alcoholic fatty liver disease based on a prospective cohort study. Scientific Reports. 2016;**6**:31006

[46] Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. International Journal of Medical Sciences. 2006;**3**(2):47

[47] Bataller R, Brenner DA. Liver fibrosis. The Journal of Clinical Investigation. 2005;**115**(2):209-218

[48] Sarhan MA, Pham TN, Chen AY, Michalak TI. Hepatitis C virus infection of human T lymphocytes is mediated by CD5. Journal of Virology. 2012;**86**(7):3723-3735

[49] Capone F, Guerriero E, Colonna G, Maio P, Mangia A, Castello G, et al. Cytokinome profile evaluation in patients with hepatitis C virus infection. World Journal of Gastroenterology. 2014;**20**(28):9261-9269

[50] Coates EA, Brennan D, Logan RM. Hepatitis C infection and associated oral health problems. Australian Dental Journal. 2000;**45**(2):108-114

[51] Carozzo M. Oral health in patients with hepatitis C virus infection: An underestimated problem? Oral Diseases. 2001;**7**(5):267-270

[52] Alavian SM, Mahboobi N, Mahboobi N, Karayiannis P. Oral conditions associated with hepatitis C virus infection. The Saudi Journal of Gastroenterology. 2013;**19**(6):245-251

[53] Cacoub P, Comarmond C, Domont F, Savey L, Desbois AC, Saadoun D. Extrahepatic manifestations of chronic hepatitis C virus infection. Therapeutic Advances in Infectious Disease. 2016;**3**(1):3-14

[54] Yoon JC, Yang CM, Song Y, Lee JM. Natural killer cells in hepatitis C: Current progress. World Journal of Gastroenterology. 2016;**22**:1449-1460

[55] Wang J, Zhao P, Guo H, Sun X, Jiang Z, Xu L, et al. Serum IL 33 levels are associated with liver damage in patients with chronic hepatitis C. Mediators of Inflammation. 2012;**2012**:819636

[56] Sharma A, Chakraborti A, Das A, Dhiman RK, Chawla Y. Elevation of interleukin 18 in chronic hepatitis C: Implications for hepatitis C virus pathogenesis. Immunology. 2009;**128**(S1):e514-e522

[57] Tawfik AK, Amin AM, Yousef M, El Sayd NM, Elashry H, Elkadeem M, et al. IL 1α correlates with severity of hepatitis C virus related liver diseases. Journal of Inflammation Research. 2018;**11**:289-295

[58] Vanis N, Mehmedović A, Mesihović R. Use of serum levels of proinflammatory cytokine IL 1α in chronic hepatitis C. Collegium Antropologicum. 2015;**39**:75-79

[59] Surlin P, Gheorghe DN, Popescu DM, Martu AM, Solomon S, Roman A, Lazar L, Stratul S.I, Rusu D, Foia L. Interleukin-1α and -1β assessment in the gingival crevicular fluid of periodontal patients with chronic hepatitis C. Experimental and Therapeutic Medicine 2020;**20**:2381-2386

[60] Reis C, Costa DA, Guimarães JT, Tuna D, Braga AC, Pacheco JJ, et al. Clinical improvement following therapy for periodontitis: Association with a decrease in IL 1 and IL 6. Experimental and Therapeutic Medicine. 2014;**8**:323-327

[61] Jia HY, Du J, Zhu SH, Ma YJ, Chen HY, Yang BS, et al. The roles of serum IL 18, IL 10, TNF alpha and sIL 2R in patients with chronic hepatitis C. Hepatobiliary & Pancreatic Diseases International. 2002;**1**:378-382

[62] Isaza-Guzmán DM, Medina-Piedrahíta VM, Gutiérrez- Henao C, Tobón-Arroyave SI. Salivary levels of NLRP3 inflammasome-related proteins as potential biomarkers of periodontal clinical status. Journal of Periodontology. 2017;**88**(12):1329-1338

[63] García-Hernández AL, Muñoz-Saavedra AE, González-Alva P. Upregulation of proteins of the NLRP3 inflammasome in patients with periodontitis and uncontrolled type 2 diabetes. Oral Diseases. 2019;**25**(2):596-608

[64] Aral K, Berdeli E, Cooper PR. Differential expression of inflammasome regulatory transcripts in periodontal disease. Journal of Periodontology. 2020;**91**(5):606-616

[65] Isola G, Polizzi A, Santonocito S, Alibrandi A, Williams RC. Periodontitis activates the NLRP3 inflammasome in serum and saliva. Journal of Periodontology. 2022;**93**(1):135-114

[66] Chen W, Xu Y, Het L. HCV genomic RNA activates the NLRP3 inflammasome in human myeloid cells. PLoS One. 2014;**9**(1):e84953

[67] Negash AA, Ramos HJ, Crochet N. IL-1β production through the NLRP3 inflammasome by hepatic macrophages links hepatitis C virus infection with liver inflammation and disease. PLoS Pathogens. 2013;**9**:e1003330

[68] Burdette D, Haskett A, Presser L, McRae S, Iqbal J, Waris G. Hepatitis C virus activates interleukin-1β via caspase-1-inflammasome complex. The Journal of General Virology. 2012;**93**(2):235-246

[69] Surlin P, Lazar L, Sincar C, Gheorghe DN, Popescu DM, Boldeanu VM, et al. NLRP3 inflammasome expression in gingival crevicular fluid of patients with periodontitis and chronic hepatitis C. Mediators of Inflammation. 2021;**19**:6917919

[70] Pradeep AR, Suke DK, Prasad MR. Expression of key executioner of apoptosis caspase-3 in periodontal health and disease. Journal of Investigative and Clinical Dentistry. 2016;**7**(2):174-179

[71] Cheng R, Liu W, Zhang R, Feng Y, Bhowmick NA, Hu T. Porphyromonas gingivalis-derived lipopolysaccharide combines hypoxia to induce caspase-1 activation in periodontitis. Frontiers in Cellular and Infection Microbiology. 2017;**7**:474

[72] Figueredo CM, Rescala B, Teles RP. Increased interleukin-18 in gingival crevicular fluid from periodontitis patients. Molecular Oral Microbiology. 2008;**23**(2):173-176

[73] Niu Z, Zhang P, Tong Y. Association of plasma interleukin-18 levels and polymorphisms in interleukin-18 gene with outcomes of hepatitis C virus infections: A metaanalysis. Journal of Immunoassay. 2015;**36**(3):221-232

[74] Du Clos TW. Pentraxins: Structure, function, and role in inflammation.

International Scholarly Research Notes. 2013;**2013**:379040

[75] Pradeep AR, Kathariya R, Raghavendra NM, Sharma A. Levels of pentraxin-3 in gingival crevicular fluid and plasma in periodontal health and disease. Journal of Periodontology. 2011;**82**:734-741

[76] Mohan M, Jhingran R, Bains VK, Gupta V, Madan R, Rizvi I, et al. Impact of scaling and root planing on C-reactive protein levels in gingival crevicular fluid and serum in chronic periodontitis patients with or without diabetes mellitus. Journal of Periodontalogical Implantation Science. 2014;**44**:158-168

[77] Pradeep AR, Manjunath RG, Kathariya R. Progressive periodontal disease has a simultaneous incremental elevation of gingival crevicular fluid and serum CRP levels. Journal of Investigative and Clinical Dentistry. 2010;**1**:133-138

[78] Bian Y, Liu C, Fu Z. Application value of combination therapy of periodontal curettage and root planing on moderate-to-severe chronic periodontitis in patients with type 2 diabetes. Head & Face Medicine. 2021;**17**:12

[79] Sun J, Zheng Y, Bian X, Ge H, Wang J, Zhang Z. Non-surgical periodontal treatment improves rheumatoid arthritis disease activity: A meta-analysis. Clinical Oral Investigations. 2021;**25**:4975-4985