

The Linking Mechanisms Between Liver and Periodontal Diseases

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Abstract

A variety of systemic diseases in the past decade have been shown to have a relationship with periodontal diseases. The present literature points to a relationship between liver diseases and periodontal diseases. In this review, we attempted to identify, whether liver diseases have a detrimental effect on the periodontal health and vice versa. We have also attempted to identify the possible biological mechanisms that link the two diseases. Electronic databases of Medline, Pre-Medline, and Medline Daily Update were searched for articles published in English from 1964-2013 to identify variables associated with periodontitis and liver diseases. We found the studies to show that the patients with liver diseases have more periodontal attachment and alveolar bone loss. More plaque and calculus and a higher amount of virulent periodontal bacteria were found in periodontal pockets of liver disease patients compared to the controls. It was also shown that post-liver transplantation patients maintained stable clinical periodontal parameters for long periods. In addition, possible biological linking mechanisms were withdrawn from the studies. However, as the majority of the studies were cross sectional and lack the necessary power to elucidate the relationship, further researches are necessary with better study design and the exclusion of the confounding factors. This article is the first known attempt to review the bidirectional relationship and at the same time the possible mechanisms that link the two diseases.

Keywords: Liver disease; Periodontitis; Liver transplant; Periodontium; Immunosuppressive agent

Background

Periodontitis is a polymicrobial disease aggravated by self-damaging effects of the immune response elicited to supra- and sub-gingival bacteria colonizing as biofilms [1,2]. The major pathogens associated with these biofilms include the Gram-negative anaerobes *P.gingivalis*, *T.denticola* and *T.forsythia* - together known as the 'red-complex' bacterial consortium [3]. Periodontitis has a local impact that leads to tooth loss [4,5]. In addition to significant pathologic alterations in the systemic status of the host. For instance, there appears to be a link between chronic periodontitis and diabetes mellitus. Recent epidemiological studies have found that patients with chronic periodontitis have higher glycemic levels compared to non-periodontitis healthy individuals, and the improvement in oral hygiene has a beneficial effect on controlling glycemic levels. Furthermore, pneumonia, preterm birth, obesity and rheumatoid arthritis have been found to be more prevalent among those with periodontitis when compared to healthy individuals [6-9].

The physiological function of the liver is the removal of pathogens from blood, protein synthesis and food metabolism. Clearance of antigens from the blood occurs mainly by sinusoidal endothelial cells through very efficient receptor-mediated endocytosis. Liver sinusoidal endothelial cells constitutively express all molecules necessary for antigen presentation (CD54, CD80, CD86, MHC class I and class II and CD40) and can function as antigen-presenting cells for CD4+ and CD8+ T cells [10]. Liver also produces cytokines in response to infection which elicits immune response. For instance, it produces C reactive protein, an acute-phase protein, which is found in the blood plasma, the levels of which rises in response to inflammation. It binds to phosphocholine expressed on the surface of dead or dying cell in order to activate complement system via the C1Q complex [11].

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Liver diseases can range from inflammation, hepatitis, to the destruction of the liver tissue and its replacement by fibrous tissue as in liver cirrhosis or cancers. If treated early, the liver is capable of natural regeneration of the lost tissue.

Liver diseases and Periodontitis-Rationale of the relation

The oral cavity is a reservoir of more than 700 bacterial species. These bacteria especially the periodontopathic bacteria can spread through blood and reach further organs. The most important function of the liver is to remove bacteria from the blood. Therefore, bacteremia produced from periodontitis could be a serious source of infection to the body in persons with liver disease.

Secondarily, as periodontitis results due to interplay of the pathogenic bacteria biofilm and the aggravated immune response which concurrently has self-damaging effects on the periodontium. An onslaught cytokines production is involved in the inflammatory process. On the other hand, liver diseases can result in the increase of cytokines production too. Therefore, these two diseases could have a detrimental effect on each other and the body.

Therefore, this review attempts to answer the following questions; Do liver diseases influence the initiation or the progression of periodontal diseases? What is the possible mechanism that links the two diseases? In addition, what effect does periodontitis have on liver diseases?

Materials and Methods

Search protocol, data Source and search strategy: The search strategy was defined to include randomized control clinical trial (RCT), longitudinal, cohort, cross sectional and case control. Variables associated with periodontitis and liver disease were searched in electronic databases of Medline, Pre-Medline, and Medline Daily Update from 1964-2013.

Inclusion and Exclusion criteria: The studies included where those investigating relationship between the liver diseases and periodontal diseases as measured by probing depth, clinical attachment loss, radiographic bone loss, gingival inflammation, bleeding and oral hygiene indices. Animal studies and articles published in other than English language were not considered.

Results

We found 193 articles; however, only 42 articles fulfilled the selection criteria. 33 were cross sectional studies and 9 case reports.

Most studies showed an adverse effect of liver diseases on the periodontal health, which is presented as increased severity of periodontitis, in particular, increased pocket depth, clinical attachment loss and alveolar bone loss. The number of virulent periodontal bacteria was more in liver disease patients compared to the healthy. Histologically, poorer blood circulation in mucogingival region was found in liver cirrhosis patients compared to healthy patients.

Few studies suggested a detrimental effect of the periodontal disease on the liver health. These studies were case reports and the effect was represented as periodontal bacteria that caused liver abscesses.

The research highlighted the possible mechanisms by which these two diseases relate. These are

1. The inflammatory process natures of the two diseases
2. The defect of the microcirculation of the gingiva in liver disease patients which leads to more periodontal destruction
3. The decrease in the function of the liver to clear bacteria which leads to more periodontal bacterial growth.
4. The psychological factor and poorer oral hygiene practice of liver disease a patient which leads to more periodontal destruction

Discussion

For better organization of the articles, they were grouped in four tables. Each table looked for the bidirectional relationship and the mechanisms that connect both diseases.

Author	Study Design	Findings
Susanne Movin [12]	Cross sectional	Liver cirrhosis patients have more attachment loss as well as plaque and calculus.
Oettinger-Barak O [13]	Cross sectional	Liver cirrhosis patient demonstrated greater pocket depth and attachment loss compared to healthy control.
Oettinger-Barak O [14]	Cross sectional	Liver cirrhosis patients exhibited more bone loss. Restoring liver function seems to reverse some of the radiographic changes.
Funatsu K [15]	Cross sectional	Blood flow of the mucogingival junction was significantly decreased in patients with liver cirrhosis.
Raghava KV [16]	Cross sectional	Liver cirrhosis patients demonstrated greater alveolar bone loss and increased periodontal destruction.
Sayyar F [17]	Cross sectional	Chronic liver disease demonstrated more clinical attachment loss than the healthy subjects with the same Plaque index and gingival bleeding.
AC Anand [18]	Cross sectional	Alcoholic abuse and bad oral hygiene rather than cirrhosis is a major predisposing factor for periodontal disease.
Novacek G [19]	Cross sectional	Cirrhosis is not a predisposing factor periodontal disease. In alcoholics, the diseases appears to be caused by bad oral hygiene .
Bensley L <i>et al.</i> [20]	Cross sectional	People with severe periodontal disease are likely to have more chronic diseases like liver disease.

Table 1: Liver and Periodontal disease-Clinical and Histological findings.

Table-1 included articles that generally focused on the relation between the two diseases, periodontitis and liver diseases. These studies confirmed the existence of a relationship between periodontitis and liver diseases. Patients with liver disease have more severe periodontitis compared to healthy controls. The depth of the periodontal pockets and the loss of the clinical attachments were more significant in liver disease patients. Likewise, the amount of bone loss was more in liver disease patients compared to controls.

The question that should be answered now is; what is/are the possible mechanism (s) by which these two diseases correlate? According to the articles, the possible answer is as the following;

First, liver cirrhosis patients and as a consequence of liver dysfunction have elevated levels of serum cytokines. These might be involved in the destructive process of the periodontal disease probably through enhancement of collagenase and metalloproteinase activity [21].

Secondly, in liver cirrhosis patients, capillaries in the periodontium and oral mucosa were decreased in number compared to that in the control. This microcirculatory disturbances is indeed an important factor in the diminish of the self defensive mechanism of the periodontium and therefore the progression of the periodontal disease [15].

Finally, some studies showed that the depressed psychological state which advanced liver disease patients might experience, can lead to the negligence of the oral hygiene. And the bad oral hygiene is responsible for the periodontitis [12,18,19,22].

However, not all liver disease patients practice poor oral hygiene. Some studies showed that liver disease patients with equal plaque and the bleeding indices compared to healthy people, still demonstrate more clinical attachment loss. This suggests that liver disease by itself is a risk factor for periodontal diseases [17].

Table (2) included articles that searched for the relation between the two diseases, but this time not by assessing the clinical outcomes as in Table (1). Table (2) searched microbiologically.

These studies showed that bacteria which are found in periodontal disease are found systematically causing liver abscesses.

For instance, the anaerobic orange complex bacterium, *F. nucleatum*, which is commonly found in periodontitis, has been reported to cause liver abscesses [25,26]. Furthermore, *trponema denticola*, *prevotella intermedia* and *porphyromonas gingivalis* also caused liver abscess [28].

Author	Study Design	Findings
Alix Ashare [23]	Cross sectional	Liver cirrhosis patients have prolonged bacteremia.
Masato Yoneda [24]	Cross sectional	<i>Porphyromonas gingivalis</i> was higher in number in non-alcoholic fatty liver disease compared with normal patients.
Yoneda, Masato [25]	Case report	Liver abscess was caused by periodontal bacteria- <i>Fusobacterium nucleatum</i> .
Crippin JS [26]	Case report	<i>Fusobacterium nucleatum</i> was cultured from both dental disease and liver abscesses.
Wagner KW [27]	Case report	<i>Streptococcus intermedius</i> (oral bacteria) was isolated from oral smear and liver.
Ohyama <i>et al.</i> [28]	Case report	<i>Fusobacterium nucleatum</i> , <i>trponema denticola</i> , <i>prevotella intermedia</i> and <i>Porphyromonas gingivalis</i> were found in pyogenic liver abscess.
Kim YH <i>et al.</i> [29]	Case report	<i>Fusobacterium nucleatum</i> caused of liver abscess
Lins <i>et al.</i> [22]	Cross sectional	Poor oral health status observed in most chronic liver disease patients may represent a source of systemic infections T

Table 2: Liver Disease and Periodontal Disease - The Microbial Findings.

Liver disease, on the other hand, can affect the ability of the periodontium to fight bacteria. The study by Yoneda [24] showed that the detection of *P. gingivalis* in periodontal pockets was higher in non-alcoholic fatty liver disease compared with healthy patients.

Therefore, according to table 2, periodontal bacteria can thrive better in liver disease patients due to the decreased capability of the diseased liver to clear bacteria from tissues and blood and this is a another mechanism by which liver and periodontal diseases link together.

Author	Study Design	Finding
Chambers DA [30]	Cross sectional	(AST30) was elevated at sites with new attachment loss, and at sites with past attachment loss or gingivitis.
Furuta M [31]	Cross sectional	There is association between ALK elevation and deeper pocket in young males.
Imrey PB [32]	Cross sectional	There is relationships between ASP in gingival crevicular fluid and clinical indices of human periodontal disease
Sweetijain [24]	Cross sectional	Serum AST increased with severe periodontitis. Serum ALT increased significantly in moderate periodontitis.
Jaiswal [33]	Cross sectional	Strong positive correlation between periodontal breakdown and serum alkaline phosphatase level in liver cirrhosis patients.
Lu Q [34]	Cross sectional	Human gingiva is able to produce CRP in situ that may be associated with IL-6 activity.

Table 3: Liver Disease and Periodontal Disease- The Biological Markers.

AST: Aspartate aminotransferase; ALK: Alkaline phosphatase

Table (3) focused on the relationship between periodontal diseases, as indicated by clinical parameters, and liver diseases, as indicated by the increase of the liver enzymes which are alkaline phosphatase and aspartate aminotransferase. These studies showed again that more attachment loss, deeper periodontal pockets and more severe gingivitis or periodontitis are associated with liver disease patients as indicated by the increase of liver enzymes compared to controls.

Author	Study Design	Findings
Machtei [35]	Cross sectional	Post-liver transplantation patients maintained stable clinical periodontal parameters during a 10-year period.
Alphonse V Gargiulo [36]	Case report	Liver cirrhotic patients demonstrated severe periodontal disease that does not improve with solo periodontal treatment. After 3 month post-liver transplant, the patient exhibited marked improvement in gingival health.
Gu L Q Wang [37]	case report	Suggests that liver transplant patients can be successfully rehabilitated with dental implants.
Sheehy EC [38]	Cross sectional	The oral health of the children undergoing liver transplantation was inadequate. Implementation of an oral health care program must become a priority
Lin YT [39]	Cross sectional	Children administered cyclosporine after liver transplantation showed gingival enlargement.
Wondimu B [40]	Cross sectional	35% of children taking cyclosporine exhibited gingival overgrowth.
Somacarrera ML [41]	Cross sectional	Forty-three percent (43%) of the patients taking cyclosporine developed gingival overgrowth.
Guggenheimer [42]	Cross sectional	Intervals of more than 1 year since the last dental visit, smoking, and diuretic therapy appear to be the most significant determinants of dental disease and the need for a pre-transplantation dental screening and evaluation in liver transplant candidates.
Hosey MT [43]	Cross sectional	Gingival overgrowth was related to the duration of cyclosporine therapy in patients with liver transplant
Oettinger-Barak O [44]	Cross sectional	The majority of liver transplant patients had insufficient 25(OH)D(3) serum levels. Changes in calcium-regulating hormones were correlated with alveolar bone loss
Akiko Morimoto [45]	Case report	A protocol was proposed and found to be effective in a patient receiving liver transplant. The patient had all the necessary dental treatment before transplant.
Barbero [46]	Cross sectional	Dentists, after, surgery must be also prepared to deal with excessive bleeding related to a severe liver dysfunction
Diaz-Ortiz ML [47]	Cross sectional	In liver transplant patient taking immunosuppressive drugs; 22% of the dentate patients showed gingival overgrowth, while half of those with teeth had gingival recessions, and 34% presented some type of tooth mobility.
Ferrazzano GF, <i>et al.</i> [48]	Cross sectional	High caries and gingival diseases among children showed the need for prevention program for liver transplant patients
Tamaki, <i>et al.</i> [49]	Cross sectional	Hepatocellular carcinoma pts with periodontitis have higher reactive oxygen species than patients without periodontitis.
Huang, <i>et al.</i> [50]	Case report	Gingival tumor as a first sign of advanced hepatocellular carcinoma on FDG PET/CT.
Greenstein [51]	Case report	Hepatocellular carcinoma can metastasis to maxillary attached gingival
Davidovich E, <i>et al.</i> [52]	Cross sectional	There is high incidence of calculus in post transplant patients due to increased oral PH and that necessitate particular attention to liver transplant children.
Helenius, <i>et al.</i> [53]	Cross sectional	Chronic liver transplant recipients presented with low salivary flow.

Table 4: Liver Transplant and the Periodontal Status.

Table (4) focused on the periodontal condition before and after liver transplant. The studies showed that patients who had liver transplant restored and maintained good periodontal health for long period of time. For instance, Machtei 2010, did a periodontal examination before liver transplant and then after 10 years of the transplant. During this period, the periodontal treatment performed was scaling and root planning twice a year (at least once). He found that liver transplant patients maintained good periodontal health and a reduction of pocket depths. The only drawback was a reduction of alveolar bone level, which is a common side effect of the medications taken after the transplant on the bone of the body in general [35].

However, this can be partly overcome if Vitamin D supplement is taken as shown by Oettinger-Barak 2007 [44].

It is important to mention that there was not any randomized control or longitudinal studies that searched and compared different periodontal modalities in liver transplant patients compared to healthy. In fact, they were cross sectional studies that examined patients periodontally before and after liver transplants and found the results mentioned above.

Therefore, since restoring liver function has a positive effect on the periodontal health, this confirms that a healthy liver is crucial for the health of the periodontium.

Therefore, these studies answered an important question-Is it possible to improve the periodontal health if we treat the liver? The answer is yes, controlling the liver disease is essential and has significantly better result on the health of the periodontium [36]. Moreover, and liver transplant patients could have successful dental implant therapy [37].

However, periodontally, it is important to notice that post transplant patients could have low salivary flow and quick calculus formation [52,53].

The studies highlighted the importance of an oral health program that should be implemented before and after liver transplant [38,45]. Because patients who need liver transplantation might be in a terrible psychological condition and neglect their oral hygiene and since they take immunosuppressive medications, gingival overgrowth is expected.

These studies in table (4) stressed the importance of pre-transplant dental screening to decrease the chance of any dental infection. Great attention should be implemented by dentists to deal with dental bleeding as those patients suffer from decreased clotting factors. Attention also should be paid to the possibility of cross infection with hepatitis virus as it might be the cause of the liver disease. Furthermore, gingival tumors could be a metastasis of liver cancers.

Conclusion

Periodontal and liver diseases, especially liver cirrhosis, have a bidirectional adverse effect on each other. This is due to in part to the inflammatory nature of the two diseases as well as the essentiality of the liver in clearing of bacteria from the body. This review also highlighted the adverse effect of liver cirrhosis in the normal blood supply to the gingiva. On the other hand, periodontitis can results in liver abscesses.

Liver transplant has a positive effect on the health of the periodontium. This further proves the existence of a connection between the liver and the periodontium in health and disease.

However, it would be necessary to set randomized control and longitudinal studies to further and better investigate the relationship as the studies found were cross sectional and case reports.

Finally, an important recommendation that could be drawn from this review is that dentist must pay more attention to the liver condition of their patients if a comprehensive and thorough periodontal treatment outcome is desired.

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