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Review

Non-Alcoholic Fatty Liver and Periodontal Disease: Is there a Relationship? A Contemporary Review

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Abstract

Periodontal disease is a common inflammatory disease and is known to be related to other systemic diseases. This bidirectional relation between periodontal disease and other disease processes has led to outstanding research recently. In addition, periodontal disease has been advocated to exacerbate metabolic disorders including non-alcoholic fatty liver disease (NAFLD). In this traditional review, general characteristics of periodontal diseases, general characteristics of NAFLD/ Nonalcoholic steatohepatitis (NASH), and their causality were discussed for treatment providers. The collected data significantly corroborate a greater incidence of periodontal disease among individuals with NAFLD in comparison to the general healthy population. Healthcare professionals need to be aware of the association between NAFLD and periodontal disease thus patient management effectiveness can be enhanced.

Keywords: Periodontal diseases, non-alcoholic fatty liver disease, causality, steatohepatitis

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The Non-alcoholic fatty liver disease (NAFLD) it's a term used for several conditions caused by fat accumulation in the liver. One-fourth of the world's population is faced with this clinical situation. It is mostly seen in South America and the Middle East, and least in Africa.[1] Nevertheless, when considering its prevalence within the community, this malady emerges as one of the most frequently encountered liver diseases, demonstrating a notable association with elevated rates of liver-related mortality and morbidity.[2] By definition, NAFLD is a clinical picture in which insulin resistance, histopathological more than 5% steatosis of hepatocytes, or dense fat fractions by radiographic techniques are detected. This clinical situation is examined under two main headings non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (steatosis coexists with liver-cell injury and inflammation).[3, 4] NAFLD has 4 stages for developing; simple fatty liver (steatosis), non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis, and may liver cancer.[5] In advanced phases, this may result in liver transplantation. The patients with NAFLD show similar histological damage to alcoholic liver disease.[6] Oxidative and inflammatory responses play crucial roles in the shared pathogenesis of both NAFLD and nonalcoholic NASH.[7] Lifestyle is an important point for developing this disease.

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For an exact definition of these diseases, NAFLD/NASH necessitates the exclusion of viral, autoimmune genetic, and so on liver diseases (alcohol abuse, hepatotoxic medications, etc.).[8]

The definitive diagnosis of NASH is established through a liver biopsy. The accurate characterization of NAFLD necessitates the consideration of daily alcohol consumption, which should be less than 30 grams for men and less than 20 grams for women. Physical examination often reveals no discernible local or systemic signs. However, manifestations such as fatigue, right upper quadrant pain, or dullness may be evident. Conversely, mild to moderate hepatomegaly may be observed.[9] NAFLD generally shows insulin resistance as an important clinical finding. In addition to this, obesity, hyperglycemia, low HDL (high-density lipoprotein), cholesterol, hypertension, and hypertriglyceridemia levels are symptoms that occur in metabolic syndrome.[6]

NAFLD patients often present with increased liver function tests. It is detected incidentally. Although hepatic transaminases are normal in two-thirds of patients, transaminase levels are increased in one-third of patients, typically higher alanine aminotransferase (ALT). However, for diagnosis, conditions that cause toxic hepatitis such as viral hepatitis that increases hepatic transferases, autoimmune hepatitis, alcoholic hepatitis, Wilson's disease, hemochromatosis, alpha-1 antitrypsin deficiency, corticosteroids, antiretroviral therapy, and tamoxifen use must be excluded.[10]

Periodontal diseases may be important in the formation and development of some systemic diseases/conditions. A robust correlation is probable to exist between periodontal diseases and systemic diseases/conditions. Periodontal diseases are often affiliated with cardiovascular problems adverse pregnancy outcomes diabetes, respiratory system disorders, metabolic syndrome, osteoporosis, rheumatoid arthritis, neurological disorders gastrointestinal disorders, urological (e.g., prostatitis), and renal diseases.[11-13]

This review aims to delineate the features of periodontal disease and impairments associated with NAFLD/NASH for healthcare providers and explore potential interrelationships between them. Relevant citations were identified through searches on PubMed, Google Scholar, and the Cochrane Library databases, encompassing references in the English language from January 2010 through December 2023. The search strategy incorporated Medical Subject Headings (MeSH) for the following: Fatty liver-periodontal, hepatic steatosis-periodontal, liver steatosis-periodontal, and non-alcoholic steatohepatitis-periodontal. Only English papers were included. After determining the articles the current review was performed.

Periodontal Problems and the General Systemic Health

It is always useful to examine the health status of the periodontal tissues since periodontal diseases can be a sign of systemic diseases. Bleeding on probing, erythema, edema, attachment, and bone loss were not observed in the clinically healthy periodontium.[14] Periodontal disease formation be related to microbial dental plaque (sub-, supragingival plaque), host-related local factors (periodontal pocket, existing restorations, tooth position-anatomy), and general factors (host response, genetic and systemic conditions)] and environmental factors (relates to smoking, drugs, etc.) as presented by "Lang et al".[15] Periodontal diseases are examined under two main topics. In the case of gingivitis, only the gingival tissue is affected. Gingivitis may persist for years without progression to periodontitis, especially when inflammatory events are prevented.[16] Periodontitis, is an inflammatory clinical disease in which in addition to the gingiva the periodontal ligament and alveolar bone are affected resulting in their destruction.[17] The main clinical findings of periodontitis are characterized by attachment loss, alveolar bone destruction (radiographic), periodontal pocket formation, and bleeding on probing.[18] Microorganisms in dental plaque are an essential component in the progression of periodontitis.[19] Although bacteria are required for periodontal disease, a susceptible host is also required for the disease to occur.[20]

Periodontal disease is common in the community. In the evaluations, it was stated that periodontal disease is not present in 9.3% of adults, 9.7% of elderly individuals, and 21.2% of adolescents.[21] In research conducted in Saudi Arabia, it was shown that 100% of individuals aged 18-40 years had plaque-related gingivitis. A systematic review and meta-regression analysis (which was conducted between 1990-2010) showed that 11.2% of the world population had advanced periodontitis.[22] Again, in the studies performed on individuals over the age of 65 in the USA, differences were observed in cases in different states, and the incidence of periodontitis was found between 62.1% and 74.2% in some states. Severe periodontitis cases were observed in ~12% nationwide.[23]

Oral hygiene plays a major role in the progression of the periodontal disease. In the treatment of periodontal disease, considerations include factors such as oral hygiene and dental care. Periodontal therapy can be managed through effective mechanical periodontal therapy, including surgical procedures, and regular professional care, especially the control of biofilm and modifiable risk factors.[24] There are surgical and non-surgical periodontal treatments available based on the etiologic factor. The efficacy

of antimicrobials, probiotics, and host modulation-based treatments in the treatment of periodontal diseases are currently periodontal treatment research topics.[25]

The primary etiological factor in periodontal diseases is microbial dental plaque. Generally, periodontal disease is caused by a dysbiosis of the commensal oral microbiota and the activation of the host's immune mechanisms.[26] In individuals, especially with advanced periodontitis bleeding lesions show an ulcerated and inflamed pocket epithelium.[27] Inflamed and ulcerated pocket epithelium is considered to be a place where microorganisms enter the body.[28] It was stated that proinflammatory cytokines produced in periodontal tissues may increase in pathogenic amounts and affect the systemic state by participating in the circulation.[29]

The concept of focal infection should be mentioned hereby. Mechanisms that may cause focal infection were described by Thoden van Velzen et al.[30] These mechanisms encompass metastatic infection resulting from transient bacteremia, metastatic inflammation induced by immunological injury, and metastatic damage initiated by microbial toxins.

Periodontal Problems and Non-Alcoholic Fatty Liver Disease

The systemic effect of the oral cavity through the different pathways mentioned above is remarkable. Periodontal diseases share common risk factors and systemic diseases/conditions with NAFLD/NASH. Possible associations with several disorders of NAFLD have been explored in a review. Within this framework, NAFLD has been associated with a spectrum of health conditions, encompassing chronic kidney diseases, colorectal cancer, psychological dysfunction, gastroesophageal reflux disease, obstructive sleep apnea syndrome, hypothyroidism, adult growth hormone deficiency, polycystic ovarian syndrome, urolithiasis, and periodontitis.[31] Clinical studies revealed some collected works that investigate the possible relationship between fatty liver, periodontitis, and periapical (endodontic) lesions.[32-34]

There is enough data to suggest that periodontitis is associated with a higher incidence of NAFLD. Treatment and prevention of periodontal disease may be important in reducing the risk of NAFLD.[35] Data on the treatment of periodontitis in studies has shown promising results for obesity, diabetes, and NASH, but the data are not yet at the desired level for humans.[36] Further to that it was stated that the presence of hepatobiliary pathology in substance abusers and smokers enhances the risk of periodontal disease.[37] A meta-analysis revealed a noteworthy association between periodontitis and NAFLD. However, this relationship lost its significance when various metabolic parameters were taken into account. Predisposing factors for NAFLD were metabolic conditions, not periodontitis itself.[38]

Liver abnormalities with metabolic syndrome (MetS) were together examined with periodontal parameters [Probing pocket depth (PPD), clinic attachment loss (CAL), and oral hygiene index (oral hygiene index-simplified)] in a study. Deep pocket depth and the coexistence of elevated alanine aminotransferase (ALT) and MetS in males with low alcohol consumption were shown.[39]

G-glutamyl transferase (GGT) and ALT levels were increased in persons with periodontal pockets. Additionally, Morita et al. observed a significant correlation between periodontal pockets and GGT. It was underlined that periodontal disease is associated with liver function, independently of alcohol-using habits.[40] It was shown that elevated ALT is a potential risk hallmark for periodontitis in healthy young men. Fruta et al. suggested that to prevent cases of periodontitis, liver abnormalities should be monitored and better understood, particularly in the young adult population.[41] Nevertheless, the previously reported associations between periodontitis and NAFLD, particularly concerning ALT levels, were not replicated in Hispanic/Latin men and women. The inconsistency in findings was attributed to the utilization of transaminases to characterize NAFLD in the study.[42]

Periodontitis was associated with incident liver disease independent of different factors in a study with additional adjustments for alcohol use, smoking, metabolic risk, serum GGT, dental care habits, lifestyle, and socioeconomic status. Periodontal disease can be considered a modifiable risk factor for chronic liver disease.[43] It was suggested that chronic periodontitis may play a role in hepatic damage and liver steatosis, and its mechanism may be related to the oral-intestinal-liver axis and SCD1/AMPK signaling activation in the liver.[44] In a study group aged 35-64 years the presence of liver fibrosis and periodontitis were addressed. After a follow-up period, the development of liver fibrosis was %10.6. The periodontal parameter CAL was significantly associated with liver fibrosis and obesity.[45] Representative data of the Korean population showed that "Fatty Liver Index (FLI)" was higher and related to a higher prevalence of periodontitis which was diagnosed on the "Community Periodontal Index (CPI)".[46] In a study conducted on a Korean population periodontal status was determined by the CPI. NAFLD was detected with FLI and hepatic steatosis index (HSI). A statistical evaluation was made between the existing pocket depths and indices in individuals. In conclusion, periodontal pocket was found to be independently associated with NAFLD.[47] Results shown in another study have suggested that hepatic steatosis is related to periodontitis

in Japanese women.[48] In a US nominal study population, it was seen that NAFLD was significantly relevant with tooth loss, moderate-severe forms of periodontitis, and after adjusting some socio-demographic factors with dental caries.[49] Akinkugbe et al have reported that periodontitis showed a higher probability of NAFLD.[50] They have proposed that elevated serum C-reactive protein (CRP) levels and weighted CRP genetic scores exhibit a positive association with an increased prevalence odds of coinciding NAFLD and periodontitis. A Chinese study evaluated databases for periodontal and liver diseases. As a result, it revealed a positive association with NAFLD, increased transaminase level, liver cirrhosis, and liver cancer with tooth loss and periodontal disease.[51] A population-based survey and a patient-based study were performed to examine biopsy-proved NAFLD and underwent periodontal examination. Appreciations revealed an important association between periodontitis and NAFLD. Even when controlling diabetes, a connection was observed with significant liver fibrosis.[52]

Ultrasound diagnosed the NAFLD patient group, and periodontal parameters like PPD and number of teeth were recorded. The results have shown a possible risk factor for PPD≥4 mm. This was statistically significant.[53] Ultrasonic liver examination was performed in individuals in whom periodontitis was detected by the percentage, clinic attachment level, and pocket depth. Incidence of NAFLD, relative to participants without clinic attachment level ≥3mm, <30% of sites slightly increased and ≥30% of sites moderately increased in affected participants.[54] On the other hand, optical coherence tomography findings between the three study groups revealed that NAFLD could be an aggravating factor for inflammation in periodontal disease.[55]

A noteworthy correlation was established between elevated CAL and obesity among participants. However, such associations were not evident among non-obese individuals. The heightened CAL was conjectured to be linked with an elevated probability of liver fibrosis in obese adults with NAFLD.[45]

In an evaluation, it was seen that teeth loss in men was associated with NAFLD. The same relationship was not observed in female patients.[56] A similar tendency was shown in a distinctive study.[57]

A study revealed an inverse relationship between tooth brushing frequency (≥2 per day) and NAFLD. Oral hygiene habits as a modifiable factor can be considered as a method that can be applied to reduce the risk for NAFLD, especially in smokers and diabetic patients.[58] The findings from a particular study indicate that an exercise regimen may improve the oral environment of patients with NAFLD. This improvement is attributed to an increased diversity of oral microflora and a reduction in LPS-producing periodontal bacteria, along with their functional capacity.[59]

Aggregatibacter actinomycetemcomitans (Aa) administrations to mice reveal changes in gut microbiota. It's shown that Aa effects in NAFLD mice downregulation of fatty acid degradation and upregulation of fatty acid biosynthesis.[60] In additional review and studies the periodontopathogen *Porphyromonas gingivalis* (Pg) was considered as an extra risk factor for the development/progression of NAFLD/NASH.[61, 62] It's shown in a study that Pg has the potential to change the gut microbiota and initiate steatosis and metabolic disease.[63] Again Pg endotoxin-induced periodontal infection is believed to play an important role in the progression of NASH.[64] In a case report, a morbidly obese patient with cirrhosis due to NASH who died of sepsis due to a dental infection of Pg was reported. Oral care, including oral assessment and eradication of Pg may be important in patients with NAFLD.[65] A cross-sectional study suggested an involvement between Pg infection and alanine ALT levels in women.[66] Intravenous injection of sonicated Pg creates glucose tolerance, insulin resistance, and fatty liver in mice fed high-fat diets.[67] A new-dated trial has investigated current periodontal treatment results within the possible changes in endotoxin levels and treat Pg infection to show the improvement status in NAFLD patients.[68] Pg odontogenic infection exacerbates the disease of NASH by hepatic stellate cells (HSCs) activation by way of transforming growth factor-β1 (TGF-β1) and Galectin-3 [(Gal-3); a protein of the galectin family] boost the production from HSCs and hepatocytes.[69] Similarly, it was introduced that Pg derived lipopolysaccharide (LPS) may play an important role in the lipid accumulation in HepG2 cells (immortal cell line derived from the liver tissue) via activating nuclear factor kappa B (NF-κB) and c-Jun N-terminal kinase (JNK) pathways in the advancement of NAFLD.[70] Late elimination of Pg by intracellular lipid accumulation can cause long-term inflammation and cellular damage, suggesting that it's one of the risk coefficients for the progression and development of NAFLD.[71]

In a study, systemically and locally, macrolide (Azithromycin) was applied to the "high-fat-diet NASH" mouse model with Pg odontogenic infection, and markers such as TNFα, Il-1β, galectin-3, and phosphorylated Smad2 (pSmad2; key signaling molecule of TGF-β1), and the number of hepatic crown-like structures (hCLSs) were examined. The results showed that NASH progression was inhibited by Pg elimination.[72] It has been shown in the literature that consumed periodontopathic bacteria exacerbate NAFLD pathology due to dysregulation of gene expression and subsequent efflux of intestinal bacteria and/or bacterial products, possibly by inducing intestinal dysbiosis.[73]

Systemic effects of induced periodontitis caused by the increase in oxidative stress and lipid peroxidation were shown with differentiation in hepatic tissues (such as microvesicular steatosis). Findings show an association between ligature-induced periodontitis and liver disease with reduced pericytes in rats.[74] In a rat model one or two ligatures were enforced to generate periodontitis. The two models did not show differences from each other. Both were eligible to produce a similar amount of fatty liver.[75] It was shown that in ligature ligature-induced periodontitis rat model a high-fat diet provokes liver disease.[76]

Dos Santos Carvalho et al show that periodontitis-induced microvesicular steatosis in rats is reversible after ligature removal. It has been hypothesized that this may be related to the increase in oxidative stress and lipid peroxidation in the liver.[77]

A rabbit model that introduces an LPS-induced model of periodontal disease evaluates the effect of periodontal interventions on atherosclerosis, hyperlipidemia, and NASH. Poor periodontal health had the potential accompany to dyslipidemia and induce NAFLD progression.[78] The application of LPS and proteases to periodontal pockets has been demonstrated to induce a lesion reminiscent of NAFLD. In rats with periodontitis, elevated serum LPS levels led to increased levels of tumor necrosis factor-alpha (TNF-α) and 8-hydroxydeoxyguanosine (8-OHdG) in the liver.[79] Similarly, the localized application of LPS and proteases to the gingival sulcus has been shown to escalate liver deterioration and induce oxidative damage in rats subjected to a high-cholesterol diet.[80] Ahn et al. showed a streamed result with Pg on fatty liver disease in obese mice through the upregulation CD36-PPARγ pathway.[81]

Pg-LPS injected via the oral mucosa in the maxilla has been reported to induce the onset of NASH in the liver of rats fed a high-fat diet.[82] In general prevention and/or elimination of Pg infections with dental treatment may have a beneficial effect on NASH. This may happen through upregulation of the P.g.-LPS-TLR2 pathway and activation of inflammasomes.[83] The findings suggest that oral Pg administration directly causes NAFLD in mice, which causes dysregulated microbial metabolism and may be due to ferroptosis of liver cells, which also occurs through Th17/Treg imbalance. Therefore, optimizing periodontal health may be a new treatment strategy for the prevention of NAFLD.[84] Pg can cause ferroptosis and inflammation in hepatocytes, further aggravating liver damage. The mechanism of ferroptosis in hepatocytes is thought to depend on the NF-κB signaling pathway.[85] Pg. infected hepatocytes exhibited heightened cell proliferation and migration, coupled with reduced doxorubicin-mediated apoptosis. These alterations were impeded upon the knockdown of Integrin β1. The hypothesis posits that Pg.-related odontogenic infection could potentially advance the development of neoplastic nodules through integrin signaling and tumor necrosis factor-alpha (TNF-α)-induced oxidative DNA damage.[86] Tomofuji et al indicate in a rat model that tooth brushing decreased serum LPS concentrations and suppressed liver injury.[87]

Periodontitis probably affects the progression of NAFLD by increasing insulin resistance and hepatic inflammation in sphingolipid metabolism. Data also showed that acid sphingomyelinase with imipramine improved NAFLD by reducing insulin resistance and hepatic inflammation.[88]

One study found that food restriction in rats reduced oral damage as well as alveolar bone changes hepatic, blood, and associated with ligature-induced periodontitis.[89] In a ligature-induced periodontitis model study, bromelain was administrated to rats. It was shown that bromelain improved the steatosis scores. On the other hand, bromelain reduces oral inflammatory parameters (Gingival bleeding index, mobility, alveoli bone height, and probing depth) and some compounds like malondialdehyde, myeloperoxidase, and blood parameters.[90]

Conclusion

This review provides a comprehensive overview of the interplay between NAFLD and periodontal disease, suggesting the potential exacerbation of NAFLD by periodontal disease. The gathered data crucially confirm a higher prevalence of periodontal disease in NAFLD patients compared to the healthy population. The review underscores the significance of oral health in systemic well-being, particularly for individuals with NAFLD. Clinicians should be mindful of the relationship between NAFLD and periodontal disease, and dentists, equipped with this knowledge, can optimize periodontal treatment. Further research is imperative to elucidate the connection between periodontal disease and NAFLD, aiming to establish the overarching concept that oral health plays a pivotal role in systemic health, especially in individuals with NAFLD.

Disclosures

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