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Impact of Liver Disease on Oral Health

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Abstract

The liver is the second-largest organ in the human body, which has the ability to regenerate after an injury or any inflammation. The liver diseases can be classified as an acute or chronic and infectious or non-infectious origin. Almost all the liver diseases produce oral manifestations like petechiae, Excessive bleeding in the cause of any minor trauma, inflammation. Oral Manifestation like gingival bleeding, glossitis, sialadenitis, hyposalivation are most commonly associated and perioral rashes, more prone to dental caries, Candidiasis are associated rarely with liver cirrhosis. Dry mouth, Sjogren syndrome both are commonly associated with all liver disease, hyposalivation leads to changes in the oral mucosa like alteration in taste, burning sensation in the tongue, bad breath etc., There are changes seen in oral mucosa, Candidiasis, fissured tongue, aphthous ulcers, bald tongue and halitosis due to compounds like Aliphatic acid, hydrogen sulfide, produced as a result of liver damage and they have a characteristic mousy odour. The common oral manifestations that are associated with Hepatocellular carcinoma include increased incidence of dental caries, loss of the tooth, Gingival bleeding, increased bone loss, chronic periodontitis, oral thrush, Candidiasis and oral lichen planus. Liver diseases have many implications in a dental setting and should carefully take a brief medical history. This study will provide better knowledge in understanding the association between liver disease and oral hygiene, Effective treatment planning in a dental setting also for liver diseased patients. Dental practitioners should know the oral manifestations commonly associated with liver diseases so that treatment can be accordingly made. With this background, the present study aims to review the impact of liver disease on oral health and its management in a dental setting.

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INTRODUCTION

The second-largest organ in the human body is Liver, which has the ability to regenerate after an injury or any inflammation, but in some vulnerable conditions like chronic alcohol abuse, microbial infection liver loses the ability to regenerate. The liver diseases can be classified as an acute or chronic and infectious or non-infectious origin. Almost all the liver diseases produce oral manifestations from small fatty liver to hepatocellular carcinoma produces/affects the oral health of an individual. The

changes seen in the oral cavity is due to poor oral hygiene which makes it susceptible to all infections, compromise periodontal health, malignant lesions, diseases like Candidiasis, lichen Planus etc (Grau-García-Moreno, 2003).

The liver disease patient suffers an Imbalance in homeostasis maintenance, Which leads to oral manifestations like Petechiae, Excessive bleeding in the cause of any minor trauma, inflammation. There is also an increased risk of cross-infection in Hepatitis B, highly prevalent in a dental setting, dental professionals should have necessary safety precautions and measures. Identification Of the liver disease by oral manifestations like poor oral health, chronic periodontitis, worst periodontal status, increased bone loss is more in comparison with healthy individuals. This may be due to immune suppression associated with liver diseases like liver cirrhosis, making it more susceptible to bacterial infections (Novacek *et al.*, 1995).

Common oral Manifestation associated with liver cirrhosis are gingival bleeding, glossitis, sialadenitis, hyposalivation are most commonly associated and perioral rashes, more prone to dental caries, Candidiasis are associated rarely with liver cirrhosis. Hepatitis is a chronic liver disease caused by Hepatitis viruses, which has a primary role in the immune system. Liver dysfunction due to hepatitis, produces oral lesions, oral lichen planus. These are characterised by the degeneration of the epithelial cells and lymphocyte infiltration. The oral manifestations seen in hepatitis include Sjogren syndrome, lichen planus, petechiae, rashes, sialadenitis, Gingival bleeding. Hepatocellular carcinoma is caused due to Hepatitis or Liver cirrhosis. There is an increase in serum Reactive Oxygen Species (ROS) along with oral manifestations. The oral manifestations associated are gingival bleeding, Petechiae are usually associated. There reports of exophytic lesions or tumours seen in the mandible, gingivitis is due to metastasis which is a rare phenomenon (Nagao, 2008).

Dry mouth, Sjogren syndrome both are commonly associated with all liver disease, hyposalivation leads to changes in the oral mucosa like alteration in taste, burning sensation in the tongue, bad breath etc., Especially in hepatitis, the salivary flow is severely decreased and the person suffers difficulties in speaking, swallowing. There are changes seen in oral mucosa, Candidiasis, fissured tongue, aphthous ulcers, bald tongue and halitosis due to compounds like Aliphatic acid, hydrogen sulfide, produced of liver damage and they have a characteristic mousy odour.

Liver diseases have many implications in a dental setting and should carefully take a brief medical history. Any suspect of liver disease the following tests should be taken to confirm the presence of liver diseases Liver Function Test, Complete Blood Count, Prothrombin Time, Thromboplastin time, the Bleeding time is to be evaluated prior treatment. Care should be taken during the prescription of drugs as certain drugs cannot be metabolised, which might result in toxicity. Administration of amine-containing Local anaesthetic should also be avoided as they are metabolised in the liver, due to impaired liver function it will not get metabolised (Buratti and Lavine, 2002).

This study will provide better knowledge in understanding the association between liver disease and oral hygiene, Effective treatment planning in a dental setting also for liver diseased patients. Dental practitioners should know the oral manifestations commonly associated with liver diseases so that treatment can be accordingly made. With this background, the present study aims to review the impact of liver disease on oral health and its management in a dental setting.

Association Between Lichen Planus And Hepatitis

Lichen planus is a chronic, inflammatory mucocutaneous disease. It can occur on any surface like skin, oral cavity, any extra-oral site and they are accordingly named. Oral Lichen Planus (OLP) is a condition where the lesions occur in the mucocutaneous area of the oral cavity. There are different lesions like reticular, plaque like Erosive, multiple Symmetric lesions and are associated with different conditions. Erosive type of lesions is associated with the oral cavity. The association between OLP and Hepatitis prevalence varies according to the geographical location. The rate of prevalence in a previous study was reported as 35% in Egypt, Japan, Southern Europe; 5 -30 % in North Africa, East & Central Asia; less than 1.5 % in Northern America and Northern Europe. In a study by Carrazo et al., demonstrated the high frequency of Human Leukocyte Antigen - Antigen D related 6 (HLA-DR6) allele in patients with hepatitis associated with OLP compared to Patients without OLP (Carrozzo *et al.*, 2001). The pathogenesis Behind OLP and hepatitis is still unclear however, the association between the two is well documented in previous literature. Few theories have been put forth to explain the pathogenesis in previous studies. In Hepatitis, the immunological changes are produced due to direct interference with the replication cycle and produce lesions in OLP. Few antibodies present in hepatitis

individuals are directed against Basal keratinocytes in the oral mucosa, which leads to OLP. In a study by Naga et al., it was reported that Hepatitis C infection is the main pathogenic factor in Oral Lichen Planus and a strong association between the two diseases was also noted (Nagao and Sata, 2012).

Conversely, a study conducted by Stojanovic et al., among 173 OLP patients concluded that only 12 % had anti HCV antibodies and there was no association between both the disease. Another study by Song J et al., in China, also concluded that anti HCV antibodies were found only in 0.7 % and there was no association between OLP and Hepatitis (Song, 2016). Interferon-alpha, in combination with Ribavarin, is the standard treatment for Hepatitis. In a study by Naga O et al., wherein the effectiveness of directly acting Antiviral drugs in patients with Hepatitis associated with OLP concluded that there was complete resolution 4 weeks from OLP. Corticosteroids, Calcineurin inhibitors are also effective up to a certain extent (Nagao, 2017).

Hepatitis And Sjogren Syndrome

Sjögren's syndrome is an autoimmune disease that causes dryness of the mouth since the exocrine salivary glands are affected. Usually, Sjögren's syndrome is a triad of conjunctivitis, dryness of mouth with or without salivary gland enlargement and Rheumatoid arthritis. Hepatitis C Virus is an RNA virus which is one of the main underlying causes for Sjogren syndrome. The association between Sjogren syndrome and Hepatitis was reported in early 1992. The main changes seen in the oral cavity include mucosal dryness, Soreness, increased bacterial infections, enlargement of salivary glands. A study by Britto et al. reported that patients with Sjogren syndrome, the HCV had driven autoimmune response dominated by the presence of mixed cryoglobulins in 2/3rd of the sample population Hepatitis C and Sjogren syndrome (Rajeshkumar and Kumar, 2018). The patients with Hepatitis C associated with Sjogren syndrome had been reported with Autoantibodies against the ribonucleoproteins in low frequency compared to the patients without Sjogren syndrome in Hepatitis C. In a study comparing the association between Sjogren syndrome and HCV concluded that there is a high frequency of association between Sjogren syndrome and Hepatitis C, no SS-A or SS- B specific autoantibodies were present in the serum despite the presence of specific clinical and laboratory features. In addition, the HCV - RNA was detected in the saliva of the patients associated with Sjogren syndrome, confirms a positive association. There is a strong association between the two diseases however, the underlying pathogenic mechanism is still unclear. But an interesting fact that is known from the previous literature is the SS-B antibody is the target in Sjogren Syndrome, which has a molecular weight of 50-52kDa and RNA binding protein. However, future studies. Since the underlying pathogenic mechanism is unclear, there are no clear treatment protocols. But currently used drugs in management includes Corticosteroids (Methylprednisolone), Cyclophosphamide, Rituximab are employed clinically for the treatment and are also effective to an extent (Stefanski, 2017; Rajeshkumar *et al.*, 2018).

Liver Cirrhosis In Association With Periodontitis

Periodontitis is a multi microbial origin disease which gets aggravated by the immune response effects which are evoked as a result of Biofilms forming bacteria in the supragingival and subgingival areas. The bacteria associated in the biofilm formation in periodontitis are P.gingivalis, T.forsythria and T.denticola, these bacteria are called Red complex bacteria as a whole (Socransky, 1998). The mechanism of association between liver cirrhosis and periodontitis is not explained still and should be explored in future studies. However few studies report that there is immunosuppression as a result of liver dysfunction, which leads to increased bacterial attack and accumulation in the oral cavity which causes infections which leads to periodontitis (Grønkjær, 2018). The presence of increased alveolar bone loss and subgingival calculus worsens more the periodontal destruction. When this continues over a period of time, there will further bone loss and mobility of the tooth and the tooth might get exfoliated. In periodontitis patients, saliva contains around > 10^{12} bacteria, each day these bacteria enter the gut as a result from the saliva which is swallowed each day and it causes alterations in the liver microbiota and gut microbiota. This microbial alteration leads to several other diseases and also adverse effects in the body (Åberg *et al.*, 2014). The microbiota like Proteus sp., Klebsiella, aciduric lactobacillus - Bifidobacterium is usually associated with liver cirrhosis and periodontitis. Lactobacillus gasseri is increased in periodontitis condition indecently on Liver Cirrhosis. The elevation of IL-1β, IL-6, IL-8 and TNF -α usually increases the rate of destruction of periodontal tissue and aggravates the disease progression in periodontitis. C-reactive protein acts a sensitive biomarker which is increased in the Condition of Liver Cirrhosis associated with Periodontitis. The mechanism of association is given in two different ways in previous literature as (i) As a result of Liver Cirrhosis, there are abnormalities produced like an impaired neutrophil function because of the immune response (both Innate and

adaptive) (ii) The number and function of monocytes is decreased due to the defect in the complement system pathway and finally produces Dysfunction of the T and B lymphocytes and Liver cirrhosis patients experience other oral complications like Petechiae, rashes, Xerostomia, Candidiasis etc., in addition to periodontitis. There are not only alterations to the gut and liver microbiome there are also alterations in the stool microbiome. In a study by Qin et al., it was reported that there was a higher expression of Streptococcus and Veillonella species in the stool when compared to normal healthy individuals (Qin, 2014). A study comparing the oral gut liver axis and the oral microbiome in liver cirrhotics, there was an increased load of Enterobacteriaceae sp. in saliva along with inflammation in the oral cavity which might be due to the impairment of non-specific defence mechanism (Bajaj, 2015). Many studies end up as alterations in the microbiome that play a major role in the disease progression and complicate the effects. When the effects of cirrhosis are experimented by modulating microorganisms with probiotics and antibiotics helps in the reversal of the microbiome. When lactobacillus is given to a liver cirrhotic, the Enterobacteriaceae count has reduced significantly in eight weeks time, the inflammatory mediators and endotoxins were also reduced (Acharya *et al.*, 2017).

Hepatocellular Carcinoma And Periodontitis

The 6th most common cancer reported across the globe is hepatocellular carcinoma. Cohort effect of Hepatitis is One of the common reasons for the increasing prevalence of Hepatocellular carcinoma, whereas Non-alcoholic fatty liver is the most common risk factor associated. In most cases, the underlying pre-existing or damaged liver tissues as in various liver diseases like liver cirrhosis, liver failure, chronic hepatitis, hemochromatosis etc., leads to hepatocellular carcinoma as the last effect of any particular liver disease (Han *et al.*, 2016). There are many studies which suggest the positive correlation between Periodontitis and Hepatocellular Carcinoma. In a Japanese study by Timaki et al., demonstrated the association between the various stages of Hepatocellular carcinoma and periodontitis, where Japanese Integrated Staging (JIS) system was used for the demonstration, concluded that the JIS score was significantly increased when hepatocellular carcinoma is associated with Periodontitis when compared with normal healthy individuals (Tamaki, 2011). The underlying pathogenic mechanism between the association of Periodontitis and Hepatocellular carcinoma is still unclear and is an area to be explored in future. The common oral manifestations associated are increased dental caries, loss of the tooth, Gingival bleeding, increased bone loss, chronic periodontitis, oral thrush, Candidiasis and oral lichen planus are usually associated. Liver transplantation is the only treatment of choice for hepatocellular carcinoma. Even for receiving a liver transplant, there are set criteria for eligibility. in a study conducted by Santos et al., evaluating the oral health status in liver transplant receiving participants concluded that there increased prevalence of Oral diseases like Periodontal disease, Gingival overgrowth, Petechiae, angular cheilitis, Ulceration, Candidiasis etc. (da Silva Santos *et al.*, 2012).

Oral Manifestations In Liver Diseases

The oral manifestations associated with hepatitis includes Cryoglobulinemia, Porphyria cutanea tarda, Lichen Planus, erythema multiforme, oral cancer, Sjogren syndrome, oral cancer, gingival bleeding due to defective coagulation factors, dental caries, oral leukoplakia, Cheilitis are generally associated however their chances for the prevalence of other oral diseases also. In general, all liver diseases possess a common set of oral manifestations like dry mouth due to Xerostomia, salivary secretion decreased up to 50 %, gingival bleeding, oral aphthous ulcers, increased dental caries, gingivitis, oral thrush and stomatitis are associated with all the liver diseases. In a study by Kannan et al., where the prevalence of the oral manifestations was ordered as Dental caries as highly prevalent (56 %), Periodontitis (40 %), Glossitis (34 %), Xerostomia, Fissured tongue (10 %), oral submucous fibrosis (8 %) (Kannan *et al.*, 2020).

Changes in Microbiome with Different Liver Diseases

A strong association between the various liver diseases and oral dysbiosis Is studied and proved in different studies. There are clinical studies which demonstrate the association between periodontitis and liver pathos like Non-alcoholic fatty liver, Hepatocellular carcinoma. When non-alcoholic fatty liver disease is associated with periodontitis, there is an increase in Porphyromonas gingivalis, a prime pathogen in Periodontitis which suggests the positive association with Periodontitis. In liver cirrhosis, the concentration of Bacteroidetes is Decreased, increased level of fusobacteria and Proteobacteria (Kumar *et al.*, 2015). In addition, the beneficial bacteria are severely affected. Alterations in the microbiome of the liver lead to metabolic endotoxemia which is associated with inflammation and other diseases. Inflammation is produced as a result of the Oral Gut liver axis cascade activation in the liver cirrhotic patients. Oral biome dysregulation

produces changes in the intestinal pH, decreases in Bile secretion are usually associated. The investigation for oral microbiome is by RNA sequencing of the 16s ribosomal RNA. In cirrhosis, When the tongue is coated, it can also be used for investigation. When the coated tongue is investigated, it resulted in an abundance of Oribacterium and Fusobacterium (Zarco *et al.*, 2012).

Dental Management of Liver Diseased Patients

Dental treatment for a liver cirrhotic patient intervenes with bleeding, care should be taken during the treatment In dental setting (Lakshmi, 2015). The dental practitioner should identify the presence or any indication for liver disease based on oral manifestations. In case, the presence of any liver disease, adequate prophylactic measures is to be taken. Antibiotics can be given prior treatment to avoid any complications and to reduce the incidence of renal failure, toxicity, risk of bacterial endocarditis. In addition, liver cirrhosis patients have low coagulation factors due to poor synthesis and absorption of Vitamin K. The drugs, anaesthesia are to be carefully selected and should be prescribed to avoid impaired, metabolism and cytotoxicity due to the drugs. Anaesthetics which do not get metabolised in the liver should be selected because of liver dysfunction. All precautionary measures are to be taken in hepatitis infection due to blood spill injury, contamination leads to cross-infection etc., (Golla *et al.*, 2004).

CONCLUSIONS

Since the oral cavity is the mirror of the other systemic diseases, in conditions of asymptomatic liver diseases, the first change is seen in the oral cavity. From this study, it is evident that there is a strong association between liver diseases and oral health. The knowledge about the association is of great significance as it will be supportive during treatment planning. In a dental setting, it will help in early diagnosis of the diseases, since oral health is the mirror of systemic health.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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