87809_Auto_Edited.docx

WORD COUNT 3092
TIME SUBMITTED 07-OCT-2023 08:51PM
PAPER ID 103302556

Name of Journal: *World Journal of Hepatology*
Manuscript NO: 87809
Manuscript Type: ORIGINAL ARTICLE

Prospective Study

High incidence of periodontitis in patients with ascitic decompensated cirrhosis, but lack of detectable *P. gingivalis* and *A. actinomyctemcomitans* in ascites

Periodontitis in cirrhotic patients with ascitic decompensation

Abstract

BACKGROUND

Periodontitis has been linked to numerous liver diseases. However, the relevance of periodontitis for the further course of decompensated cirrhosis has not yet been conclusively studied. In particular, it is unclear whether the typical periodontitis pathogens, *Porphyromonas gingivalis* and *Actinobacillus actinomyctemcomitans*, can be found not only in the oral mucosa but also in the ascites and stool.

AIM

This study investigates the relevance of periodontitis, *P. gingivalis* and *A. actinomyctemcomitans* in cirrhosis patients with ascitic decompensation

METHODS

This prospective study has been performed at the University Hospital Hamburg Eppendorf, a tertiary center at Northern Germany. A cohort of 27 patients with ascitic decompensated liver cirrhosis was examined dentally and the association of periodontitis with different clinical parameters of cirrhosis, as well as the outcome, was investigated. Gingival samples ascites, and stool were tested by PCR for the presence of

P. gingivalis and *A. actinomyctemcomitans*. Gingival samples were collected by probing into the deepest gum pocket of a sextant and wiping on a cotton swab.

RESULTS

In 22/27 (82%) of ascites patients periodontitis was diagnosed. This is significantly more frequent than in a control cohort of 100 unselected patients (59%, $P = 0.04$). *P. gingivalis* was detected in the gingiva of 6 patients, and simultaneously in the stool of one of them. *P. gingivalis* was not detected in the ascites of any patient. Five of six patients with *P. gingivalis* suffered from Periodontitis (83%). *A. actinomyctemcomitans* could not be found in any sample. Significantly more patients without periodontitis than with periodontitis died and the survival (Kaplan Meier analysis) was longer in patients with periodontitis in comparison to those without ($P = 0.02$). Transplant-free survival occurred more frequently in patients with periodontitis than in patients without 63% *vs* 0%, $P = 0.02$).

CONCLUSION

Decompensated cirrhotic patients suffer frequently from periodontitis. Neither translocation of *P. gingivalis* nor *A. actinomyctemcomitans* into ascites was observed. Survival of cirrhotic patients with periodontitis was not reduced.

Key Words: cirrhosis; ascites; decompensation; periodontitis; survival; gingiva

Pischke S, Ashouri MM, Peters U, Shiprov A, Schulze zur Wiesch J, Sterneck M, Fischer F, Huebener P, Mader M, Fischer L, Fründt T, Aarabi G, Beikler T. High incidence of periodontitis in patients with ascitic decompensated cirrhosis, but lack of detectable P. gingivalis and A. actinomyctemcomitans in ascites. *World J Hepatol* 2023; In press

Core Tip: Decompensated cirrhotic patients suffer frequently from periodontitis. Neither translocation of P. gingivalis nor A. actinomyctemcomitans into ascites was observed. Survival of cirrhotic patients with periodontitis was not reduced.

INTRODUCTION

Cirrhosis the final stage of chronic liver disease is a very serious condition with a significantly reduced life expectancy (1). One of the most threatening complications is spontaneous bacterial peritonitis (SBP) (1, 2). It is assumed that bacteria from the intestinal flora migrate into the abdominal cavity and multiply in the ascites. By contrast, secondary bacterial peritonitis in patients with patients with portal hypertension is a bacterial peritonitis due to an abdominal source of infection (e.g., abscess, perforation). Secondary bacterial peritonitis is much less common than spontaneous bacterial peritonitis, accounting for approximately 15% of all peritonitis cases. Secondary bacterial peritonitis causes a risk of mortality of 20% (3).

SBP is defined as the detection of > 250 polymorphonuclear cells, i.e. neutrophil granulocytes, per mm^3 in ascites (4). Gram-negative germs, as often found in the intestine, are the main pathogens of SBP. To what extent the colonization of the oral flora plays a role in the occurrence of SBP and whether germs from the oral cavity can enter the ascites *via* the intestinal tract and migration is still unclear.

Periodontitis an inflammation of the gingiva has become increasingly interesting in the last 20 years. The presence of periodontitis has been associated with systemic inflammation. In mice, it was possible to show in animal experiments that there is a link between periodontitis and the development of liver fibrosis (5).

P. gingivalis, one of the most relevant periodontal pathogens, is thought to enter the bloodstream through the oral mucosa and may cause the release of various cytokines. In addition to translocation of *P. gingivalis* directly to the blood stream by a damaged gingiva with reduced barrier function this bacterium can be easily translocated from oral cavity to the intestine and it can be easily imagined that disruption of the intestine

microbiota composition by orally derived P. gingivalis may contribute to the gut-liver axis and the pathogenesis of the development of spontaneous bacterial peritonitis (6, 7). However, this has never been studied in detail. The relevance of periodontitis in various cohorts of patients with liver disease has already been studied, including patients with cirrhosis. A 1995 Vienna study of 97 cirrhotic patients, 64 with alcoholic cirrhosis, 33 non-alcoholic, showed that alcohol dependend cirrhosis, but not cirrhosis in general, is associated with reduced oral hygiene ($p < 0.01$), reduced dental care ($p < 0.001$), presence of periodontitis and the number of teeth requiring treatment ($p < 0.001$) (8). A study from the USA investigated prospectively if treatment of periodontitis influences the oral-gut-hepatic axis in cirrhosis patients (9). In this study the effect of periodontal therapy has been studied in 26 cirrhotic patients receiving this therapy in comparison to 24 cirrhotic patients without periodontitis therapy. In an observational period of 30 days the cirrhosis group of treated patients experienced improved dysbiosis in stool and saliva, and improved endotoxin, LBP, and salivary and serum inflammatory mediators. Particularly the subgroup of patients with hepatic encephalopathy seem to benefit.

Furthermore, periodontitis as well as cirrhosis have the ability to induce an inflammatory response and lead to the creation of inflammatory mediators through which they may influence each other. In various patient cohorts patients with cirrhosis have been described to have poorer periodontal clinical parameters than those without cirrhosis (6).

There are some studies that suggest a link between periodontitis and liver diseases such as cirrhosis. It is believed that the inflammatory responses that occur in periodontitis can promote the development of liver diseases such as cirrhosis. Chronic inflammation in the body can lead to damage to liver cells and accelerate the progression of liver diseases.

However, it is important to note that further research is needed to understand and clarify the relationship between periodontitis and liver diseases such as cirrhosis.

These observations lead directly to the question of whether *P. gingivalis* also plays a role in the development of SBP and whether this pathogen can be found in ascites.

To study if *P. gingivalis* and *Actinobacillus actinomyctemcomitans*, typical bacteria associated with periodontitis can be found in ascites, we tested oral mucosal samples, ascites specimens, and stool specimens for the presence of *P. gingivalis* in a prospective study. Mucosal samples were probed by mucosal penetration into the deepest gum pocket of a sextant and wiped on a cotton swab, which was test by PCR. Furthermore, we analyzed whether the dental factors (detection of these bacteria, periodontitis, number of teeth, etc) were associated with the outcome of patients with end-stage liver cirrhosis

MATERIALS AND METHODS

Patients

In this prospective study, all adult cirrhosis patients who required paracentesis at the University Hospital Hamburg-Eppendorf, Hamburg Germany, between 03/2021 and 07/2021 have been asked to participate. This cohort includes both inpatients and outpatient with ascitic decompensation. Twenty-seven patients agreed to participate, gave written informed consent and were included in this study. Twenty-seven of them suffered from ascitic decompensation due to liver cirrhosis. Cirrhosis has been diagnosed previously based on clinical criteria, in association with liver elastography results and biopsies.

To investigate patient follow-up, medical records were evaluated in January 2023. There was no intervention by the investigators between study inclusion and this evaluation. Since all patients were reliably end-stage liver cirrhosis patients affiliated with our university hospital, good documentation was available from the treating physicians.

Intraoral examination (full mouth examination, including BOP/bleeding on probing) was done by an experienced student of dental medicine (M.A.) and has been supervised by the head of the Department of Periodontics, Preventive and Restorative Dentistry, (T.B.). The intraoral examination included dental status (number of teeth), mucosal status, mouth hygiene (sulcus bleeding index). Periodontal disease has been graded according to the EFP/ORCA guidelines/recommendations (10).

All patients underwent a standardized interview and responded to a questionnaire regarding the frequency of their dentist visits and smoking behaviour, among other parameters.

To evaluate the frequency of periodontitis in an unselected control cohort without cirrhosis, 100 unselected patients from a standard dental practice served as controls. These patients were studied retrospectively and anonymized. These controls were 100 unselected patients undergoing standardized periodontitis screening at a usual dentist practice at Hamburg. Basic data like age, sex and periodontal status were analysed retrospectively for these anonymized patients in line with our local regulations and the rules of our ethical court. This control cohort has been mentioned within a previous publication (11).

Examinations

P. gingivalis was identified by species-specific PCR as described previously (12). A probe was inserted into the deepest gum pocket of a sextant and wiped on a cotton swab, which was test by PCR. Laboratory data and baseline patient characteristics, such as ALT, AST, bilirubin, as well as age, clinical attachment loss (CAL, i.e., the most important parameter to assess periodontal tissue loss due to periodontal disease), number of teeth, smoking status, and interest of the patients in dental medicine were recorded.

Statistical analysis

Continuous variables with a non-normal distribution were expressed as the median and interquartile range (IQR). Distribution of such parameters in various groups were compared using the Mann–Whitney U-test. Categorical variables were expressed as numbers (%) and compared with Fisher's exact test. P values less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS, version 21.0 (IBM Corp., Armonk, NY, USA).

Ethical statement

This prospective study was reviewed and approved by the Ethics Committee of the Medical Council of Hamburg (PV-4081 and MC-368/18). The study was performed according to the recommendations of the Declaration of Helsinki. The retrospective analysis of the control cohort was completely anonymized and therefore did not require any clarification or formal ethics committee approval according to local laws and regulations.

RESULTS

In 22/27 (82%) of ascites patients a periodontitis was diagnosed. Characteristics of patients with periodontitis in comparison with patients without are depicted in table 1.

Age in the total cohort ranged from 37 to 76 years (median 57 years). 15 (56%) were male. 9 patients suffered from diabetes (33%). 4 patients (15%) took anticoagulants. 16 (59%) patients suffered from alcoholic cirrhosis, 5 from NASH-cirrhosis (19%), 3 (11%) from re-cirrhosis after liver transplantation, and each 1 (4%) from PBC, HBV or HCV. 6 patients had a TIPSS and 2 patients a hepatocellular carcinoma (2 with alcoholic liver cirrhosis, 1 with HBV, 1 with NASH). 1 of the patients with re-cirrhosis after transplantation had NASH as underlying disease, 1 PSC and 1 alcoholic cirrhosis.

1

To compare the incidence of periodontitis in the cirrhosis cohort with the basic incidence in the general population, a retrospective cohort (n = 100) of patients from a Hamburg dental practice was analysed. This cohort has been described previously.

Forty-seven of these subjects were male (47%), with ages ranging from 17 to 89 years (median 51 years). Fifty-nine patients (59%) had periodontitis, which was significantly less than in the cirrhosis cohort, with an incidence of 82% (P = 0.04).

Significantly more patients without periodontitis than with periodontitis died and the survival (Kaplan Meier analysis) was longer in patients with periodontitis in comparison to those without (P = 0.02, figure 1). Transplant-free survival occurred more frequently in patients with periodontitis than in patients without (table 1).

In 2 patients no tooth was missing (0/32), in 1 patient 1 tooth, in 2 patients 3 teeth, in 1 patient 5 teeth, in 6 patients 6 teeth, in each 1 patient 7 and 8 teeth, in 3 patients 10 teeth in 2 patients 12 teeth and in each 1 patient 13, 14 or 16 teeth, 4 patients had a partial prosthesis and 5 patients were toothless and ha a total prosthesis. There was no associaton between number of teeth and survival.

Neither AST, ALT, bilirubin nor MELD score differed significantly between patients with and without periodontitis (table). However, there was a trend for a higher MELD score in patients without periodontitis (figure 2).

DISCUSSION

This study showed a surprisingly high rate of periodontitis in cirrhotic patients (82%) in comparison to healthy controls (59%, P = 0.04). This illustrates how important it is for patients with cirrhosis to see their dentist regularly. Hepatologists should specifically ask their cirrhotic patients if they see a dentist regularly when taking their medical history and, if not, encourage them to do so.

This observation of a high frequency of periodontitis is in line with a Danish study on 262 cirrhotic patients. In this study 46% (n = 66) had severe periodontitis, 39% (n = 55) had moderate periodontitis, and only 15% (n = 22) had no-or-mild periodontitis (13). Thus, it is undisputed that cirrhotic patients are a risk group for periodontitis.

But the much more important question is certainly whether periodontitis is associated with poorer survival or transplant-free survival. In this regard, our study showed that

63% of patients with periodontitis (12/22) survived without transplantation, compared to 0% (0/5) of patients without periodontitis (table 1, P = 0.02). In addition overall survival was better in patients with periodontitis in comparison to patients without (table 1, $p<0.05$, figure 1). Furthermore there was a trend for higher MELD-score values in the 5 patients without periodontitis in comparison to the 22 patients with periodontitis (figure 2). Thus, our pilot study does not show a worsened graft-free survival or a trend for a more severe liver damage (MELD score) for patients with periodontitis, but even slightly better values. These data contrast with a paper previously published from Denmark (14). In this study of 184 cirrhotic patients, 44% had severe periodontitis and there was in contrast to our study a poorer survival associated with the presence of severe periodontitis. It is unclear why our study did not confirm this and tended to show better survival and lower MELD scores in cirrhotic patients with periodontitis. However, this aspect resulting from our small pilot study containing 5 patients without periodontitis should not be overinterpreted. Since less than 20% of the cirrhotic patients in our study did not have periodontitis, much larger cohorts are needed to validate this finding.

A previous study showed an association between the severity of NASH and the presence of periodontitis (11). This finding is relevant in this context. Pathophysiologically, one can well imagine that the gingiva entry portal in periodontitis patients allows bacteria to enter the bloodstream and this leads to cytokine release and inflammation. The fact that this inflammation did not have a negative effect on survival in our end-stage cirrhosis patients with ascites, but that the patients without periodontitis actually survived worse in our study, requires further clarification in larger studies.

Our pilot study is very valid, as it is based on 27 well-defined and well-characterized patients, but larger cohorts are essential to further investigate the question.

The limitations of our study are not only the small size of the patient cohort, but also the monocentric study design and the different questions we investigated. We investigated both how often decompensated cirrhosis patients have periodontitis and whether *P.*

gingivivalis and *A. actinomyctemcomitans* translocate into the ascites, as well as whether periodontitis is associated with survival in decompensated cirrhotic patients. We were able to clarify two of these 3 questions, namely the frequency of periodontitis in decompensated cirrhotic patients and the conceivable bacterial transfer into the ascites. However, larger cohorts are needed to clarify the third question about the influence of periodontitis on survival. Furthermore, future studies should also prospectively investigate whether gingival status and bacterial colonization change over time.

In particular, it is relevant in this context whether periodontal therapy can also improve the survival of these end-stage liver cirrhosis patients. Recently, a review article clearly showed that periodontal therapy may have a positive effect on the course of NASH (15). The extent to which this may also be possible in cirrhotic patients should be investigated. Furthermore in a recently published study from the USA investigating 442 cirrhosis patients poor oral health was significantly associated with 3-month hospitalizations independent of portal hypertensive complications, MHE, or frailty (16).

However, the main reason why we conducted our study was to find out whether *P. gingivalis* and *A. actinomyctemcomitans*, classical periodontitis pathogens, can be found in decompensated cirrhotic patients *via* translocation in the ascites. However, this was not the case.

CONCLUSION

Basing on our small pilot study these two bacteria seem to be no relevant factors in the occurrence of ascites or possibly the occurrence of spontaneous bacterial peritonitis. This question has never been investigated before. And even if the hypothesis that these germs could enter the ascites from the reservoir of the gingiva in decompensated cirrhotic patients was not confirmed, this is still an important finding. Because it has now been conclusively clarified.

ARTICLE HIGHLIGHTS

Research background

This is a pilot study investigating the frequency of periodontitis in cirrotic patients with ascites decompensation.

Research motivation

It has not been studied previously if baceria of the oral mucosa associated with periodontitis can be translocated into ascites in cirrhotic patients.

Research objectives

To study he relevance of periodontitis in cirrhotic patients with ascites.

Research methods

Prospective cohort study.

Research results

In 22/27 (82%) of ascites patients periodontitis was diagnosed. This is significantly more frequent than in a control cohort of 100 unselected patients (59%, $P = 0.04$). *P. gingivalis* was detected in the gingiva of 6 patients, and simultaneously in the stool of one of them. *P. gingivalis* was not detected in the ascites of any patient. Five of six patients with *P. gingivalis* suffered from Periodontitis (83%). *A. actinomyctemcomitans* could not be found in any sample. Significantly more patients without periodontitis than with periodontitis died and the survival (Kaplan Meier analysis) was longer in patients with periodontitis in comparison to those without ($P = 0.02$). Transplant-free survival occurred more frequently in patients with periodontitis than in patients without 63% *vs* 0%, $P = 0.02$).

Research conclusions

Periodontitis is frequent in cirrhotic patients with ascites.

Research perspectives

Hepatologists should advice cirrhotic patients to go regularly to dentists. Future studies should evaluate if this improves dental status and periodontitis.

87809_Auto_Edited.docx

ORIGINALITY REPORT

5%
SIMILARITY INDEX

PRIMARY SOURCES

1	multimedia.elsevier.es Internet	86 words — 3%
2	www.ncbi.nlm.nih.gov Internet	39 words — 1%
3	pubmed.ncbi.nlm.nih.gov Internet	16 words — 1%
4	Shivani N, Jayachitra J. "An EEG-based Brain-Computer Interface for Stress Analysis", 2023 Second International Conference on Electronics and Renewable Systems (ICEARS), 2023 Crossref	14 words — < 1%
5	Tamara Rinstad, Birgitta Bergqvist, Ulf Mattsson. "Follow-up of need for dental treatment in 126 patients who have received radiation treatment to the head and neck region", International Journal of Dental Hygiene, 2019 Crossref	14 words — < 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 12 WORDS
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS