Evaluation of Liver Chemistry Tests and Clinical Parameters in Patients with Periodontal Disease and Chronic Hepatitis C

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The concept of periodontal medicine has been created by taking into consideration the strong connection between the development of the periodontal disease and other general conditions. The presence in blood, saliva and gingival fluid of certain inflammatory markers that are common for the two conditions – periodontitis and chronic hepatitis C, that can generate the appearance of the periodontal inflammation, can be an explication for the probable interconnection of the two conditions. The purpose of this pilot study is to investigate whether chronic hepatitis C can be a worsening factor for the development of the periodontal disease, by setting correlations between the periodontal pathology and some metabolic markers of both hepatitis C and periodontitis patients in comparison to periodontitis-only ones. Positive correlations would justify the expansion of the study for a larger group of patients and the dosage of inflammatory markers for biologic fluids such as blood, saliva and gingival fluid.

Keywords: periodontal medicine, inflammatory markers, periodontal inflammation, periodontitis, chronic hepatitis C

The concept of periodontal medicine has been created by taking into consideration the strong connection between the development of the periodontal disease and other general conditions such as diabetes mellitus type 1 and 2, cardiovascular disease, obesity, rheumatoid arthritis, liver disease and premature child-birth [1]. The common pathological pathways of these diseases seem to be centered on alterations of the immune system but the topic is far from being completely understood.

The inflammation of the periodontal structures, such as gingivitis or periodontitis, causes a rise of the flow of the gingival fluid and frequent gingival bleeding. For patients suffering from chronic viral hepatitis C this causes the transfer of the virus from the blood stream into the gingival fluid and further down the saliva, as it is being carried by mononuclear peripheral blood cells. More elevated levels of HCV RNA have been found in the gingival fluid of infected patients than in their saliva, while in 78% of cases, viral RNA molecules were found in the gingival fluid even though they were absent in saliva samples [2 -4]. The presence in blood, saliva and gingival fluid of certain inflammatory markers that are common for the two conditions – periodontitis and chronic hepatitis C, that can generate the appearance of the periodontal inflammation, can be an explication for the probable interconnection of the two conditions. For example, the level of the aspartate aminotransferase enzyme is an indicator for both the degree of liver fibrosis [3] and the level of activity of the periodontal disease, which is modulated after periodontal treatment [5].

The purpose of this pilot study is to investigate whether chronic hepatitis C can be a worsening factor for the development of the periodontal disease, by setting correlations between the periodontal pathology and some metabolic markers of both hepatitis C and periodontitis patients in comparison to periodontitis-only ones. Positive correlations would justify the expansion of the study for a larger group of patients and the dosage of inflammatory markers for biologic fluids such as blood, saliva and gingival fluid.

Experimental part

Material and methods

The study was approved by the Ethics Committee of University of Medicine and Pharmacy of Craiova. The patients who accepted to sign the informed consent, from both medium urban and rural, were divided in two groups: the group P- 13 patients (6 men, 7 women) with periodontal disease age range 40-58 years and the group PH- 11 patients (8 men, 3 women) with periodontal disease and chronic hepatitis C age range 36-62 years. Patients in both groups had no other systemic disease: diabetes, cardiovascular, rheumatoid arthritis or hypertension. The patients who were included in the study were the non-smoking ones, those who hadn't taken any antibiotics or anti-inflammatory drugs in the previous 3 months and those who had ended the Interferone treatment at least one year prior to the study. No pregnant patients or those who had given birth in the last six months were included in the study.

The patients were examined periodontally, taking into consideration the following aspects: the probing depth (PD), the number of teeth with periodontal pockets deeper than 4mm, the gingival index (GI) Silness and Loe, the maximum probing depth and the number of remaining teeth.

For the patients diagnosed with hepatitis C the serum levels of ASL and ALT were determined and a FibroScan analysis was performed for the fibrosis stage of the liver. Abdominal ultrasonography was performed in order to exclude the cirrhosis possibility. The years from onset diagnostic of hepatitis C was also registered.

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The data was statistically analyzed for comparisons – t test ($p<0.05$ for statistically significance) and correlation – Pearson test, between the periodontal condition and the values of the chemical markers or liver-influenced parameters.

Results and discussions

The demographical characteristics of patients were shown in the table 1.

In the PH group, 9 patients (81.81%) had values of ALT over the normal limits and 6 patients (54.54%) had AST elevation but the average of these two markers was elevated (table 2).

In the group P, 4 patients (30.76%) had values of AST over the normal limits and 5 patients (38.46%) had ALT elevation but the average of these two markers was in normal limits. Between the two groups it was a statistically significant difference ($p<0.05$) between the values of AST and ALT, for the ALT the difference had a stronger statistical significance ($p<0.05$) (table 2).

Although the average number of teeth with periodontal pockets deeper than 4mms was the same, a statistically significant ($p<0.05$) difference of maximum pocket depth was found between the two groups (table 2).

The difference in remaining teeth between the PH and P groups was statistically significant ($p<0.05$). A moderate correlation between the number of remaining teeth and the age from the onset of the hepatitis diagnosis was found, as well as one between the age of the hepatitis diagnosis and the gingival bleeding index (GI) (table 2).

The gingival index (GI) had a statistically significant difference ($p<0.05$) between groups PH and P (table 2).

Our results show no correlations between the degree of liver fibrosis or ALT and AST levels and the clinical periodontal parameters.

Given the limited number of female patients in the two study groups, no gender-related comparisons or correlations could be made between the results of the study.

Morita et al.[6] assessed the associations between the presence of periodontal pockets and serum levels of liver biochemical parameters. They showed that alanine aminotransferase (ALT) and g-glutamyltransferase (GGT) levels were higher in subjects with than without periodontal pockets. The presence of periodontal pockets was associated with serum levels of GGT, a liver biochemical parameter, in Japanese adults with no drinking habit, suggesting that periodontal disease is associated with liver function, independent of alcohol ingestion.

After the statement that a relationship between levels of aspartate aminotransferase in gingival crevicular fluid and gingival inflammation exists, Persson [7], aiming to determine whether levels of the enzyme aspartate aminotransferase (AST) in gingival crevicular fluid (GCF) are associated with disease activity as assessed by the level of gingival inflammation and probing attachment loss, Persson et al [8] found that maximum enzyme level was significantly elevated at sites with confirmed disease activity as assessed by attachment loss, with maximum AST levels 725 units higher at these sites, on average, than at other sites ($p < 0.0001$). Maximum AST values were also associated with severe gingival inflammation ($p < 0.005$) where values were about 600 units higher than at sites with mild or with no gingival inflammation. The results support the idea that an objective diagnostic test, based on levels of AST in GCF that distinguishes between disease-active and disease-inactive sites may be possible. Elevated salivary aspartate aminotransferase levels were seen in generalized chronic gingivitis and chronic periodontitis patients, with higher values recorded in generalized chronic periodontitis correlating to the tissue destruction taking place in these conditions.

According to the American Association of Gastroenterology (AGA), patients with hepatitis C have 5 times higher serum levels of AST and ALT, the later predominant [9]. The PH group had both ALT and AST elevated levels, with ALT predominant, the increase being 5 fold, while for the P group both ALT and AST mean levels are in normal range even though there were patients within the group with small increases of these markers despite not having a liver condition diagnosed. This fact can be explained by the origin of the AST and ALT enzymes, the individual variations and by some physiologic parameters. Both these transaminase are released from damaged hepatocytes into the blood after hepatocellular injury. The AST is also abundantly expressed in some non-hepatic tissues including heart, skeletal muscle and blood tissues. The ALT is found in low concentrations in tissues other than the liver, so it is frequently considered specific for hepatocellular injury. ALT has diurnal variation, may vary

Patients (n)	Gender (n)		Age (y)	Medium	
	M	F		U	R
PH n=11	8	3	46.9±8.44	11	-
P n=13	6	7	47.5±5.36	8	3

Table 1
DEMOGRAPHIC CHARACTERISTICS OF THE TWO GROUPS (PH AND P) OF PATIENTS

n=number, y=year, M=male, F=female, U=urban, R=rural

Table 2
VALUES OF CHEMICAL LIVER AND CLINICAL LIVER AND PERIODONTAL PARAMETERS

Groups	AST (UI/ml)	ALT (UI/ml)	RT (n)	HCV Onset (y)	AT (n)	MD (mm)	GI
PH	45.42±25.04*	63.85±34.14**	12.9±3.89^,#	6±2.28^^,#	6±1.2	7.27±1.13 ##	3.2±0.6^^,&
P	32.28±11.2*	30.7±7.4**	17±4.1^	-	5.8±1.6	5.26±1.4 ##	1.7±0.2&

*AST=aspartate aminotransferase, ALT=alanine aminotransferase, RT=remaining teeth, AT=affected teeth by pockets >4mm, MD=maximum deep of pockets, GI=gingival index; * statistical significant differences between PH and P groups values of AST ($p<0.05$); ** statistical significant differences between PH and P groups values of ALT ($p<0.05$); ^ statistical significant differences between PH and P groups of RT ($p<0.05$); ^ ^positive correlation between the onset of hepatitis C and GI in PH group ($r=0.3$-0.5, $p<0.05$); # positive correlation between the onset of hepatitis C and RT in PH group ($r=0.3$-0.5, $p<0.05$); ## statistical significant differences between PH and P groups of MD ($p<0.05$); & statistical significant differences between PH and P groups of GI ($p<0.05$)*

day-to-day and may be affected by physic exercise. The serum AST levels may be higher in African-American males, varying day-to-day or with exercise [9].

In our study, the difference of remnant teeth between groups PH and P was statistically significant, as well as the maximum pocket depth even if the number of teeth with periodontal pockets deeper than 4mms was the same. In a study published by the Australian Dental Journal, Coates et al indicate that the number of missing teeth in patients with hepatitis C infection was also significantly higher than in the general patients and that periodontal health tended to be poor [10].

In some studies with large numbers of participants, designed for the connection between periodontal and cardiovascular diseases, it was concluded that this fairly large, prospective study with a long follow-up period presents for the first time a dose-dependent relationship between number of teeth and both all-cause and CVD mortality, indicating a link between oral health and CVD, and that the number of teeth is a proper indicator for oral health in this respect in patients with affected periodontium [11].

The gingival index was higher in the PH group than in the P one, probably due to the hepatic impairment or as a result of a more significant inflammatory reaction. Further studies will have to determine various biological markers in serum and gingival fluid for a larger group of patients in order to conclude if this clinical data is supported by statistically significant immunological or metabolic changes. Given the fact that the gingival fluid is a liquid which precisely shows alterations of the periodontal tissues, it has been successfully used for the assessment of various biomarkers independently or together with other determinations in gingival tissue, saliva or serum, before and after periodontal treatment [12, 13], for different connections between periodontal disease and systemic conditions [14-16] or during orthodontic movement of the teeth [17-19]. Due to the fact that the HCV is one of the most important risk factors of HCC and liver fibrosis [20, 21], in the regard of recent findings which show that the periodontal disease might be associated with progression of viral liver disease, controlling oral disease is important for prevention and management of liver damage [20].

Within the limitations of this study, it can be stated that hepatitis C can be an aggravating factor for the development of the periodontal pathology. Further studies will have to determine various biological markers in serum, gingival fluid and periodontal tissues for a larger group of patients to support these clinical findings.

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Manuscript received:11.01.2017