BULLETIN OF STOMATOLOGY AND MAXILLOFACIAL SURGERY
Volume 22 N 3

DOI:10.58240/1829006X-2026.22.3-193

ORIGINAL RESEARCH

PERIODONTAL STATUS IN PATIENTS WITH CHRONIC HEPATITIS B: A CLINICAL AND HISTOPATHOLOGICAL STUDY

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Received: Mar 6. 2026; **Accepted:** Apr 27. 2026; **Published:** May 12. 2026

Abstract

Background: Periodontal diseases are highly prevalent and are increasingly associated with systemic conditions, including viral infections. Chronic hepatitis B virus (HBV) infection may influence the severity and progression of periodontal tissue damage.

Objective: To evaluate the condition of periodontal tissues in patients with HBV prior to complex treatment.

Methods: This study included 195 patients divided into two groups: HBV patients (n=95) and a control group (n=100). Clinical periodontal assessment included the Periodontal Index (PI) and Sulcus Bleeding Index (SBI). Histological examination of gingival biopsies was performed. Statistical analysis was conducted using non-parametric tests, with significance set at $p<0.05$.

Results: Patients with HBV demonstrated significantly worse periodontal status compared to controls. The mean PI was 4.08±0.41 versus 0.95±0.48 in controls ($p<0.001$), while SBI was 2.82±0.21 versus 1.68±1.66 ($p<0.001$). Clinically, gingival hyperemia, edema, and bleeding were significantly more frequent in the HBV group. Histopathological analysis revealed inflammatory infiltration in 100% of HBV patients, predominantly lymphoplasmacytic in nature, along with epithelial degeneration and micro-ulceration.

Conclusion: Chronic HBV infection is associated with significant periodontal tissue damage, confirmed by both clinical and morphological findings, highlighting the need for integrated dental and medical management.

Keywords: Periodontal disease, hepatitis B, inflammation, histopathology, SBI, PI

1.INTRODUCTION

Among the important problems of modern practical dentistry, the issues of improving the diagnosis, prevention, and treatment of periodontal tissue diseases, despite numerous studies conducted worldwide, remain highly relevant and of great social significance [1–3]. Currently, periodontal diseases represent a major problem in dentistry due to the widespread prevalence of lesions of the oral cavity and periodontium,

the diversity of nosological forms, and their relationship with systemic pathologies [4,5].

According to the World Health Organization (WHO), inflammatory periodontal diseases are among the most common dental diseases worldwide after dental caries [6].

Periodontal tissues constitute a complex structural and functional unit and participate in various bodily functions, including chewing, swallowing, speech, and breathing. In the structure of diseases affecting the organs and tissues of the oral cavity, inflammatory processes in the periodontium occupy one of the leading positions, causing significant functional disorders of the maxillofacial region. According to WHO conclusions, tooth loss due to periodontal diseases occurs five times more frequently than in complicated forms of dental caries [7,8]. According to modern concepts, the development and progression of inflammatory periodontal diseases are considered not only as local inflammation of periodontal tissues caused by dental plaque microflora, but also as a systemic response of the body to bacterial and viral infections [9].

Since the late twentieth century, there has been an increase in the incidence of viral hepatitis [10,11]. The global distribution and high epidemic potential of this group of diseases maintain their social and economic significance. The WHO *Global Hepatitis Report* (2017) indicates that approximately 325 million people worldwide suffer from viral liver diseases, and mortality associated with these diseases, unlike HIV infection, tuberculosis, and malaria, continues to increase [12]. According to WHO data, about one-third of the world's population may come into contact with the hepatitis B virus (HBV) during their lifetime, and approximately 257 million people are chronically infected with hepatitis B [13].

The etiology of many chronic liver diseases remains unclear; however, even liver cirrhosis of viral etiology, which should be regarded as the final (stage IV) stage of chronic viral hepatitis, is often mistakenly not considered a consequence of infectious pathology [14].

Among medical specialties, certain professions are at particularly high risk of HBV infection, including workers in hemodialysis centers and clinical laboratories, obstetricians-gynecologists, surgeons, and dentists. Among dentists, the incidence of HBV infection is reported to be 1.7 times higher than among other groups of healthcare workers [15].

Many authors have reported a high frequency and diverse clinical presentation of lesions of the oral cavity, particularly periodontal tissues, in diseases of the gastrointestinal tract [16–18]. As a result of diseases of the digestive system, the functional activity of the salivary glands, as well as the composition and properties of saliva, undergo changes. This leads to disruption of the dynamic balance between demineralization and remineralization processes and contributes to the development and progression of dental caries.

Comorbid conditions have become increasingly common in recent years and represent one of the factors that significantly complicate the management of patients with periodontitis due to the potentially mutually aggravating course of these diseases [19,20]. For example, inflammatory periodontal diseases may necessitate postponement of antiviral therapy for HBV, thereby accelerating the progression of liver damage [21-23].

When determining management strategies and selecting appropriate therapy in patients with mild to moderate periodontitis in the presence of chronic infections, it is essential to consider that more frequent and prolonged exacerbations of periodontitis in patients with comorbid pathology are mainly associated with the infectious component. At the same time, unfavorable features of the disease course are linked to endogenous intoxication, immune system disorders, imbalance in lipid peroxidation processes, excessive infectious load, activation of pro-inflammatory cytokines in periodontal pockets, and suppression of the local immune response. When developing a plan for long-term follow-up of patients with periodontitis associated with chronic infections, a differentiated approach is required. This approach should include the development of long-term treatment and rehabilitation programs, taking into account the severity of the pathology and the unfavorable nature of the pathological process in periodontal tissues. Monitoring of such patients should be carried out with the involvement of infectious disease specialists and include additional laboratory and instrumental diagnostic methods. The duration of follow-up in each case should be determined individually based on the course of periodontitis [18,20].

Thus, periodontal tissue diseases in the presence of concomitant systemic conditions represent one of the most complex problems in dentistry due to difficulties in diagnosis and treatment [24]. Lesions of the oral mucosa may aggravate the course of the underlying disease and determine the specifics of therapeutic measures [25,26]. Accurate and timely assessment of periodontal tissue condition, as well as the selection of modern and rational treatment approaches, remain highly relevant issues in contemporary dentistry [4].

The aim of this study was to assess the condition of periodontal tissues in patients with viral hepatitis B prior to complex treatment.

MATERIAL AND METHODS

Study Design and Population

This observational comparative study included 195 patients examined between 2022 and 2024. Participants were divided into two groups: HBV group (n = 95) and control group (n = 100).

Ethical Considerations

The study protocol was approved by the Ethics Committee of Yerevan State Medical University. Written informed consent was obtained from all participants.

Inclusion Criteria

- Confirmed HBV diagnosis
- Presence of periodontal lesions
- Age between 21 and 57 years

In addition to the underlying disease, patients with HBV had oral cavity lesions. The age of the patients ranged from 27 to 54 years, and they were hospitalized in the infectious diseases clinic of the "Mikaelyan Institute of Surgery" of Yerevan State Medical University (Yerevan, Armenia) during the period 2022–2024. The control group included 100 individuals without HBV who had periodontal tissue damage and who applied to the Stomatology Scientific and Educational Clinical Center No. 1 of Yerevan State Medical University and the "Orthodent" dental clinic during the same period. Their age ranged from 21 to 57 years.

Clinical and laboratory diagnostic methods

The final diagnosis of HBV was established based on the detection of hepatitis B virus surface antigen (HBsAg) in blood serum using enzyme-linked immunosorbent assay (ELISA) and detection of hepatitis B virus DNA using polymerase chain reaction (PCR). The patients underwent traditional clinical and laboratory examination methods, including general blood and urine tests, as well as biochemical blood tests: determination of total bilirubin and its fractions, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total protein and its fractions, and coagulogram. All patients underwent stomatological status assessment according to previously developed criteria, which included evaluation of the condition of the marginal and alveolar parts of the gingiva and the dento-periodontal complex. An index assessment of the condition of the periodontal tissues was also performed using the periodontal index (PI) according to Russell [27], and the gingival sulcus bleeding index (SBI) according to Mühlemann and Son was determined [28].

Morphological study: The material for morphological studies consisted of biopsy tissue samples excised from the mucous membrane in the area of direct localization of the pathological process in all patients with HBV infection. According to the standard histological protocol, the tissue samples were fixed in 10% neutral formalin, dehydrated, and embedded in paraffin. A series of sections with a thickness of 4 µm were stained with hematoxylin–eosin for general assessment of the condition of the examined tissues [29]. Histological micropreparations were studied using a ZEISS Primo Star trinocular microscope (ZEISS Microscopy, Germany) at magnifications of ×100 and ×400. Microphotographs were obtained using a ZEISS Axiocam ERc 5s (Carl ZEISS Microscopy, Germany). All features were examined in accordance with international standards, WHO recommendations, and recognized research methods [30].

Statistical analysis: Descriptive analysis (mean ± SD for continuous variables and frequencies/proportions for categorical variables) was performed for all variables of interest. Differences between the two groups were evaluated using the chi-square test or Fisher's exact test for categorical variables and the Wilcoxon signed-rank test for continuous variables. Spearman correlation analysis was performed to determine relationships between continuous variables. A p-value of < 0.05 was considered statistically significant, and < 0.001 was considered highly significant. Analyses were conducted using Excel 2013 and R software, as well as the VassarStats program to calculate odds ratios (OR) and 95% confidence intervals (CI).

RESULTS

The study included 95 patients with HBV, including 71 men (74.7%) and 24 women (25.3%). The control group consisted of 100 individuals without HBV with periodontal tissue damage: 62 men (62.0%) and 38 women (38.0%). The mean age in the group of patients with HBV was 40.17 ± 13.48 years, and in the control group it was 37.99 ± 16.66 years. During the assessment of stomatological status, patient complaints and data from clinical examination of the oral cavity were taken into account, including evaluation of the condition of the marginal and alveolar parts of the gingiva, the dento-periodontal complex, as well as periodontal indices PI and SBI before and after complex treatment. Table 1 presents the data of the clinical examination of the condition of the marginal and alveolar parts of the gingiva before complex treatment.

Table 1. Clinical examination of marginal and alveolar gingiva in HBV and control groups

Variable	Control group (n = 100)	HBV group (n = 95)	p-value
Hyperemia			
Absent	99 (99.0%)	32 (33.7%)	<0.001
Present	1 (1.0%)	63 (66.3%)	
Cyanosis			
Absent	75 (75.0%)	65 (68.4%)	>0.05
Present	25 (25.0%)	30 (31.6%)	
Edema			
Absent	87 (87.0%)	32 (33.7%)	<0.001
Present	13 (13.0%)	63 (66.3%)	
Bleeding			
Absent	89 (89.0%)	24 (25.3%)	<0.001
Present	11 (11.0%)	71 (74.7%)	
Epithelial desquamation			
Absent	100 (100%)	91 (95.8%)	>0.05
Present	0 (0%)	4 (4.2%)	

An objective examination of the oral cavity revealed a number of pathological changes in the gingiva. In patients with HBV, hyperemia and edema of the gingiva were detected in 66.3% (63) of cases, which is statistically significantly higher compared to the control group ($p < 0.001$), where these symptoms were observed in 1% and 13% of examined individuals, respectively. Cyanosis of the gingiva was observed in 31.6% of cases ($p > 0.308$). Gingival bleeding was observed in 74.7% of the examined patients with HBV, which is significantly higher-approximately 7 times-compared with the control group ($p < 0.001$). Desquamation of the gingival epithelium, resembling the clinical picture of desquamative gingivitis, was observed in 4.2% (4) of cases, which was not statistically different from the control group ($p > 0.454$), where this symptom was not observed. The condition of the dento-periodontal complex in patients with HBV is presented in Table 2.

Table 2. Condition of the dento-periodontal complex in HBV and control groups

Variable	Control group (n = 100)	HBV group (n = 95)	p-value
Subgingival dental plaque			
Absent	61 (61.0%)	28 (29.5%)	<0.001
Present	39 (39.0%)	67 (70.5%)	
Tooth mobility (Grade I)			
Absent	71 (71.0%)	73 (76.8%)	>0.05
Present	29 (29.0%)	22 (23.2%)	
Tooth mobility (Grade II)			
Absent	93 (93.0%)	46 (48.4%)	<0.001
Present	7 (7.0%)	49 (51.6%)	
Tooth mobility (Grade III)			
Absent	95 (95.0%)	92 (96.8%)	>0.05
Present	5 (5.0%)	3 (3.2%)	
Periodontal pockets >3.5 mm			
Absent	61 (61.0%)	12 (12.6%)	<0.001
Present	39 (39.0%)	83 (87.4%)	
Purulent discharge			
Absent	91 (91.0%)	55 (57.9%)	<0.001
Present	9 (9.0%)	40 (42.1%)	

Subgingival dental deposits, identified on the lingual and vestibular surfaces of the central incisors and canines of the lower jaw, as well as on the buccal surfaces of the upper premolars and molars, were detected in 70.5% (67) of cases in the HBV group, whereas in the control group they were detected in 39% (39) of patients, which is statistically significant ($p < 0.001$).

When analyzing the data on pathological tooth mobility of grades I and III in patients with HBV and in the control group, no statistically significant differences were found ($p > 1$). Grade II pathological tooth mobility in patients with HBV was detected in 51.6% (49) of cases, which is statistically significantly higher compared to the control group ($p < 0.001$), where this finding was observed in 7% (7) of patients. The presence of periodontal pockets (PP) > 3.5 mm was observed in 87.4% (83) of patients, and purulent discharge from PP was observed in 42.1% (40) of patients. Both indicators showed a high level of statistical significance ($p < 0.001$).

To assess the degree of periodontal damage in patients with HBV, periodontal indices were determined to evaluate inflammatory changes in the periodontium: the Periodontal Index (PI) according to Russell and the Sulcus Bleeding Index (SBI) according to Mühlemann and Son (Table 3).

Table 3. Periodontal indices (mean ± SD)

Index	Control group	HBV group	p-value
PI (Periodontal Index)	0.95 ± 0.48	4.08 ± 0.41	<0.001
SBI (Sulcus Bleeding Index)	1.68 ± 1.66	2.82 ± 0.21	<0.005

∗ p-value: comparison between HBV and control group

In patients with HBV, the periodontal index values differed significantly from those of the control group. The PI value averaged 4.08 ± 0.41 points, which is 4.3 times higher than in the control group (Fig. 1), and the SBI value averaged 2.82 ± 0.21 points, which is 1.68 times higher than in the control group (Fig. 2). The differences were statistically significant with a high degree of reliability ($p < 0.005$).

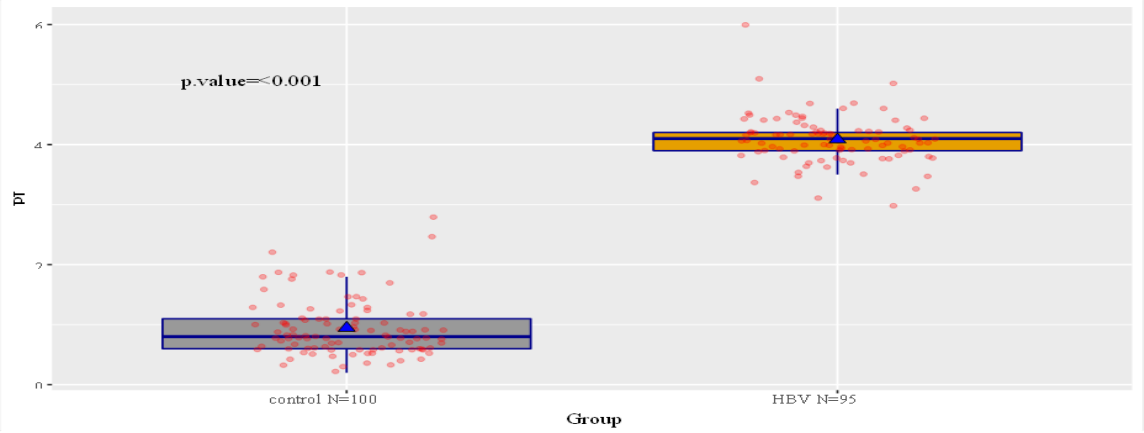

Figure 1. PI index value in patients with HBV and in the control group

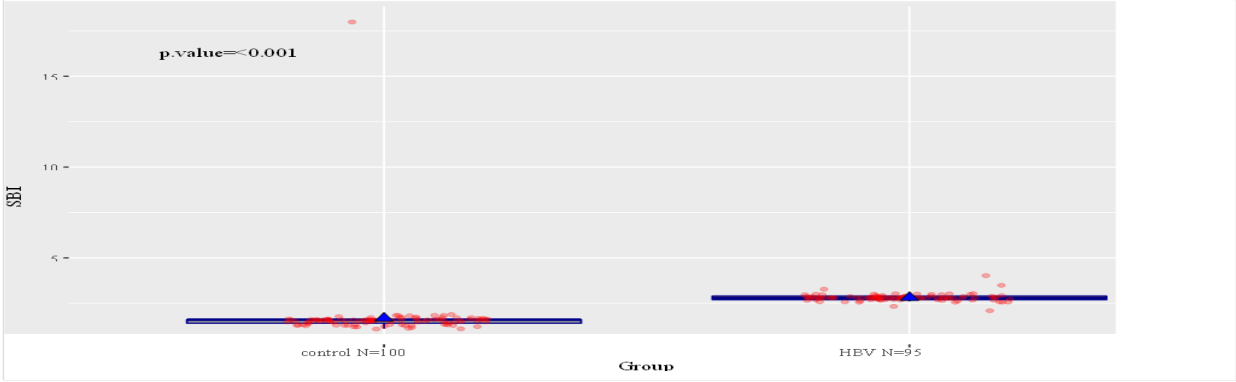

Figure 2. SBI index score in patients with HBV and in the control group

Pathohistological Study

Pathological changes in the oral cavity were localized in the alveolar bone region, namely in the area of the gingiva and the transitional fold. The results of the histological study showed that patients with HBV had combinations of pathohistological signs that manifested as inflammatory infiltration with circulatory disturbances, gingival ulceration with fibrinous deposits, dystrophic changes in the squamous epithelium, and, in isolated cases, sequestration of the jaw bone was observed. A comparative analysis of these pathomorphological changes demonstrated that lymphoplasmacytic infiltration of the gingival tissue was detected with a high degree of statistical significance ($p < 0.001$). Signs of inflammation of the gingival tissue were observed in biopsy samples in 100% of patients with HBV in the form of pronounced inflammatory cellular infiltration, which was predominantly productive in nature ($p < 0.001$). The inflammatory infiltrate was mainly represented by lymphocytes and plasma cells, reflecting pronounced chronic inflammation (Fig. 3).

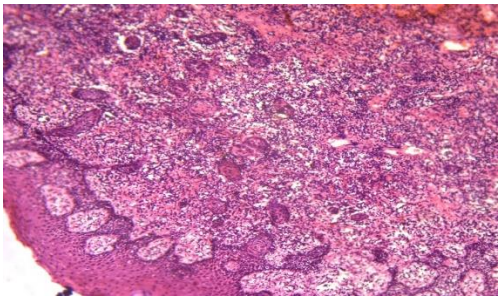

Figure 3. Lymphoplasmacytic infiltration of gingival tissue in a patient with HBV (hematoxylin–eosin staining, ×100)

Morphological examination of the gingiva revealed damage to epithelial cells, including the appearance of vacuoles in their cytoplasm, i.e., vacuolar degeneration progressing to ballooning dystrophy, as well as cell death and desquamation of the epithelium with the formation of micro-erosions. These changes were often detected only by microscopic examination and were observed in 75% of cases. Erosions or micro-ulcers were covered with fibrinous deposits in 25% of cases in patients with HBV (Fig. 4).

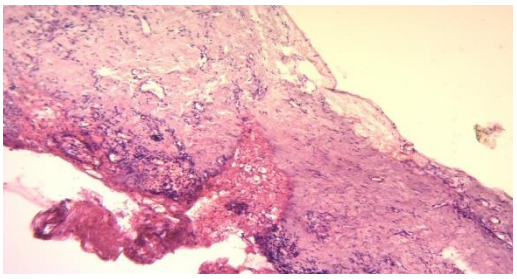

Figure 4. Micro-erosions of the gingival tissue covered with fibrin deposits. Superficial ulcers of the oral mucosa are covered with fibrin deposits (hematoxylin–eosin staining, ×100).

In isolated patients, fragments of necrotic bone tissue were identified, most likely due to sequestration of the jaw bone in HBV (Fig. 5).

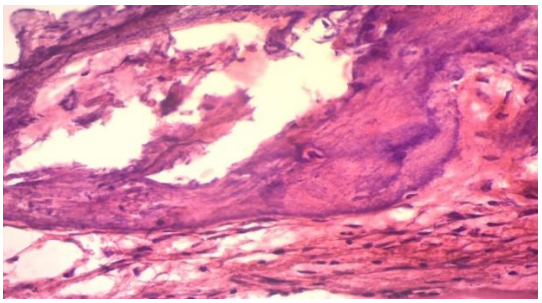

Figure 5. Fragments of necrotic bone tissue in HBV (hematoxylin–eosin staining, ×400).

Thus, numerous morphological signs can be conditionally divided into those that indicate the severity and activity of inflammation and those associated with a long-term chronic course of inflammation in periodontal tissues.

4. DISCUSSION

There is practically no pathology that does not affect the condition of the oral mucosa. At the same time, the similarity of clinical manifestations in the oral cavity among diseases of different etiology and pathogenesis contributes to difficulties in establishing a definitive diagnosis[31,32]. Many researchers consider the periodontium as an integral part of the whole organism and recognize the close pathogenetic relationship between periodontal diseases and somatic pathology. Patients with periodontitis who have concomitant and background diseases require special attention, both in the diagnosis of combined pathology and in treatment and prevention [21]. Lesions of the periodontal system aggravate the course of diseases and serve as an important addition to the overall clinical picture of hepatitis and HIV infection [33–35]. Viral liver lesions occupy an important place in assessing the dental health status of patients [36]. At the same time, dentists and physicians of other specialties do not pay sufficient attention to the condition of the oral cavity in liver diseases [37]. The experience of dentists working in infectious disease departments has shown that the effectiveness of diagnosis and treatment of oral mucosal lesions depends on the earliest possible examination of admitted patients [38]. Dental care for patients, even with an established diagnosis of viral hepatitis, is mainly provided upon request due to acute pain. There are very few developments in dental management strategies for patients with hepatitis. Even in countries with a high level of dental services, sufficient experience in this area has not yet been accumulated [39,40].

In a comparative study of the criteria selected to characterize the condition of various parts of the periodontium in viral hepatitis B compared with the control group, it was established that in the latter (except for isolated cases), periodontal lesions are practically not observed. According to the results of our study, pathognomonic symptoms of periodontal lesions in viral hepatitis B were reliably identified [41].

The data on the condition of the marginal and alveolar parts of the gingiva in patients with HBV are of particular interest. When comparing patients with viral hepatitis B to the control group, hyperemia, edema, and bleeding were more frequently observed in the HBV group. Based on the above, it can be reliably concluded that the marginal and alveolar parts of the gingiva are more frequently affected in HBV. It should be noted that, according to Fedeli U. et al. (2017), who studied the characteristics of periodontal damage in patients with chronic liver diseases of viral etiology, more severe dystrophic and inflammatory changes in periodontal tissues are observed in chronic hepatitis and liver cirrhosis caused by hepatitis B virus compared to those caused by hepatitis C virus [42]. Our data indicate that it is difficult to draw a definitive conclusion regarding the comparative severity of periodontal damage in HBV, since we did not conduct a comparative analysis with other viral hepatitis groups.

There are few studies in the available literature that have investigated and systematized the symptoms of periodontal damage in HBV, especially early manifestations of the disease. The reliability of the frequency of occurrence of specific symptoms has also not been sufficiently studied. Some authors even report contradictory findings regarding the relationship between periodontal tissue lesions and viral hepatitis. In our opinion, such discrepancies may be related to methodological limitations of previous studies. For example, Nagao Y. et al. (2014) investigated periodontal tissue lesions in patients with chronic hepatitis (HBV – 20 patients, HCV – 23 patients) and liver cirrhosis caused by HBV (15 patients) or HCV (16 patients). Based on descriptive analysis of a small sample size, the authors concluded that there was no association between chronic HBV or HCV and the frequency or nature of periodontal lesions [21]. However, given the limited sample size and the absence of robust statistical analysis, the reliability of these conclusions is questionable.

There are also isolated studies that describe only a few individual signs in small patient samples. No comprehensive comparative analysis of these signs in patients with viral hepatitis B has been conducted. In our opinion, this is important, as patient management protocols and treatment strategies may differ significantly. It should be noted that the literature contains several review articles addressing this issue, which describe in detail the epidemiological data and pathophysiological mechanisms of extrahepatic manifestations in viral hepatitis and HIV infection [43–46]. However, there is a lack of original research studies in this area. Therefore, we attempted to analyze and compare the available data reported in the literature.

Pakfetrat A. et al. (2015) examined 110 HIV-positive patients, some of whom also had HBV infection, to assess the prevalence of oral lesions. The authors identified severe periodontitis in 27.3% of patients [47]. As noted above, in our study, periodontitis was detected more frequently in patients with viral hepatitis B. In addition, we evaluated individual symptoms of periodontal damage, most of which demonstrated a high frequency of occurrence.

Azatyan V.Yu. et al. (2021) investigated pathomorphological changes in the oral mucosa in patients with HBV, HCV, and HIV infections; however, no detailed study of periodontal tissues was conducted to

allow comparison with our findings [48].

The problem of liver diseases of viral etiology remains highly relevant due to their widespread distribution. The global prevalence and high epidemic potential of these diseases maintain their significant social and economic burden. Pathologies caused by HBV are most commonly observed in young, working-age individuals, leading to disability and relatively high mortality rates. Therefore, the study of periodontal tissue condition in viral hepatitis B, including the features of pathomorphological changes and their comparative assessment with control group data, is highly relevant and justified the conduct of this study.

One limitation of this study is that patients were recruited from a single clinic in Yerevan, although this clinic is one of the largest in the Republic of Armenia.

Another limitation of the present study is the reduced sample size available for cytokine analysis in oral fluid, as only 18 patients in the HBV group and 30 individuals in the HBV-negative group consented to participate. This may limit the statistical power of immunological comparisons and should be taken into account when interpreting cytokine-related findings.

CONCLUSION

Thus, viral hepatitis B contributes to damage of the periodontal tissues. Pathomorphological examination indicates the nature of periodontal tissue damage, which manifests as inflammatory infiltration, circulatory disturbances, and ulceration of the gingival tissue.

List of Abbreviations and Designation

ALT - Alanine aminotransferase
ALP- Alkaline phosphatase
AST - Aspartate aminotransferase
CI - Confidence Intervals
DNA - Deoxyribonucleic acid
ELLISA - Enzyme-linked immunosorbent assay
GGT -ɤ-glutamyl transferase
HBsAg - Detection of hepatitis B virus surface antigen
HBV – Hepatit B Virus
OR - Odds Ratio
PCR - Polymerase chain reaction
PI - Periodontal index according to Russell
PP - Pathological pockets
RA – Republic of Armenia
SBI - Gingival sulcus bleeding index according to Miihlemann and Son
SD - Standard deviation
WHO - World Health Organization

DECLARATIONS

Conflict of Interest

The authors declare no conflict of interest.

Funding

No external funding was received for this study.

Ethical Approval

This work was approved by the Ethical Committee at Yerevan State Medical University, done in compliance with the Helsinki Declaration, and written informed consent was obtained from the patients.

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