



# The Relationship Between Serum IL-17 Level and Viral Load in Chronic Hepatitis B

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## Abstract

**Background:** Chronic hepatitis B is a major public health problem, especially, in developing countries. T helper 17 (th17) cells produce cytokines that have been shown to mediate host defensive mechanisms in various infections, but their role in HBV infection has not been well characterized.

**Objectives:** The aim of this study is to determine the level of interleukin 17 (IL-17) in patients with chronic hepatitis B infection and assess the relationship between different titers of viremia with serum IL-17 and liver enzyme levels.

**Methods:** Patients with chronic hepatitis B virus infection (HBV) who were referred to Hepatitis Clinic at Boo-Ali Hospital, Zahedan, Iran, were divided into three major groups according to their viral load and subsequently IL-17 and serum alanine aminotransferase (ALT) levels were measured. The data analysis was examined by Kruskal-Wallis and Mann-Whitney tests.

**Results:** In this cross-sectional study, 143 untreated patients with chronic hepatitis B infection were divided into three main groups. Seventy-four patients with HBV DNA less than 2000 IU/mL; 53 patients with HBV DNA between 2000 - 10<sup>7</sup> IU/mL and 16 patients with HBV DNA more than 10<sup>7</sup> IU/mL. The mean of serum IL-17 levels in these three groups was 30.66, 26.87 and 24.42 pg/mL, respectively. There was no significant difference between different levels of HBV DNA with the serum level of IL-17 and ALT (P > 0.05).

**Conclusions:** Although IL-17 may contribute to disease progression and liver injury in chronic HBV infected patients, the association between serum levels of IL-17 with viral load was not detected in this study.

**Keywords:** Viral Load, Hepatitis B, IL-17

## 1. Background

Hepatitis B is one of the most important infectious diseases which can cause acute/chronic liver damage, cirrhosis and hepatocellular carcinoma (1). According to reports, more than 2 billion people in the world have shown serologic HBV infection and about 400 million of them suffer from chronic infection. Hepatitis B virus kills one million people annually in the world (2).

In 2016, the prevalence of hepatitis B in Iran was 3 percent in men and 1.7% in women in a systematic study (3). Risk factors for transmission of the infection include exposure to infected blood or body fluids, intravenous drug use, sexual intercourse, working in health-care settings, blood transfusion, hemodialysis, living with an infected person, traveling to countries where infection rates are

high, and living in a nursing home (4). Patients may be asymptomatic for years (chronic carriers) or have chronic hepatitis with variable clinical manifestations (5). Chronic hepatitis B infection has three main phases, which include: (1) immune tolerant phase with maximum HBV DNA and minimum hepatic damage, (2) immune active phase with high levels of HBV DNA, liver inflammation and necrosis, and (3) inactive phase with minimal liver inflammation and fibrosis with low HBV DNA level (6, 7).

Although the innate immune response does not play a main role in process of HBV infection, adaptive immune response mediated by T lymphocytes against invading viruses, plays the key role in immunopathology, hepatic dysfunction, and tissue damage of chronic hepatitis B. For efficient clearance of the virus, it is necessary for T cell-

mediated immune response to be effective. The production of the cytokines such as gamma interferon-specific cytotoxic T lymphocytes (CTLs) can reduce virus replication (7). In fact, CTLs are used to clear HBV from viable liver cells and eliminate HBV infection by killing infected cells and antiviral cytokine production (8).

On the other hand, during chronic hepatitis B, chronic inflammation due to the activity of T lymphocytes, leads to liver inflammation and necrosis which leads to disease progression and hepatocellular carcinoma. Therefore, the host immune response, as a double-edged sword, can not only cause viral clearance, but also liver damage (9, 10).

Interleukin 17 (IL-17) is a pro inflammatory cytokine which is secreted by th17 cells. Inflammatory cytokines including interleukin (IL)-23 and IL-6 produced by cells of the innate immune response facilitate the differentiation of th17 (11). Increased levels of IL-17 stimulate macrophages, endothelial cells, fibroblasts and epithelial cells, and by indirect effects causes the production of other pro-inflammatory cytokines such as IL-1, IL-6, IL-10, TNF, chemokines and metalloproteinases (12). Thus, by inducing the production of these factors, IL-17 creates and strengthens inflammation. In addition, these cytokines cause immune suppression and increase tumor cell growth (13, 14).

The increased expression of IL-17 in chronic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel disease and asthma have been reported recently (15-18). Studies in mouse models infected with schistosomiasis and candida albicans revealed that pathological inflammatory reactions can be reduced by injecting antibodies against IL-17 (19, 20).

Research in recent years, has shown that th17 cell cytokines and serum levels of IL-17 in patients with hepatitis B infection may have a direct correlation with progression to liver cirrhosis and even to the severity of fibrosis (21, 22).

## 2. Objectives

Therefore, considering the importance of the immunology of hepatitis B, the objective of this study is to evaluate the level of IL-17 in patients with chronic hepatitis B infection and investigate the relationship between different levels of viremia with serum IL-17 levels and the amount of liver enzymes.

## 3. Methods

In this study, 143 patients with chronic hepatitis B virus infection (HBV) who were referred to Hepatitis Clinic at Boo-Ali Hospital, Zahedan, Southeastern Iran, were recruited and classified into three groups according to viral

load. Three groups were as follows: the first group consisted of patients with viral load less than 2000 IU/mL, the second group included patients with viral load between 2000 and  $10^7$  IU/mL, and the third group had viral titer above  $10^7$  IU/mL.

Inclusion criteria were chronic HBV infection based on laboratory findings and exclusion criteria included the following: lack of consent to participate in the study, duration of HBV infection less than 6 months, co-morbidities (immunodeficiency, autoimmune disease, bacterial and other viral infections, acute heart disease, fatty liver disease, and malignancy), pregnant women, addiction and history of taking antiviral drugs for the treatment of hepatitis.

Five milliliters of blood was taken from each patient and sent to the laboratory for measuring ALT and IL-17 titer. The level of IL-17 was measured by ELISA method (Human IL-17 Elisa Kit, EASTBIOPHARMA, USA).

To measure viral load, real time PCR and extraction kits were used according to instructions. Extraction mini kit was utilized to extract DNA (Dynabio™ viral nucleic acid DNA/RNA) and to determine the viral load of HBV, Dynabio™ HBV quantitative real time PCR kit, was used.

Finally, all patients' information and test results were analyzed using SPSS V. 21 software. According to the non-normal distribution of data, to compare quantitative data between groups, the Kruskal-Wallis test was used. An alpha of 0.05 is used as the cut-off for significance.

## 4. Results

In this study, 74 patients with a viral load of less than 2000 IU/mL, 53 patients with viral titer between 2000 and  $10^7$  IU/mL and 16 patients with viral load levels above  $10^7$  IU/mL were evaluated.

In the first group, 20 patients (27%) were female and 54 (73%) were male, in the second group 22 patients (41.5%) were female and 31 (58.5%) were male and the in the third group 3 (18.8%) were female and 13 (81.3%) were male. The mean for the duration of HBV infection in these three groups were 99.6, 89.6 and 72 months, respectively.

The mean of serum IL-17 level in patients with HBV DNA less than 2000 IU/mL was 30.66 pg/mL. The mean for patients having HBV DNA between 2000- $10^7$  IU/mL was 26.87 pg/mL, and for those who had HBV DNA more than  $10^7$  IU/mL was reported 24.42 pg/mL. There was no significant difference between different levels of HBV DNA with serum levels of IL-17 ( $P = 0.327$ ).

The mean of ALT in the first, second, and third group was 31.39, 36.77 and 48.56 IU/L, respectively. Comparing ALT levels based on the viral load of patients by Kruskal-Wallis test, no significant difference among the three groups of patients was observed ( $P = 0.174$ ) (Table 1).

**Table 1.** The Serum Levels of ALT and IL-17 in the Three Groups of Chronic Hepatitis B Infection Based on Viral Load

Variable, Groups (Viral Load Level)	Mean $\pm$ SD	Median	P Value
<b>ALT serum level (IU/L)</b>			0.174
Less than 2000 IU/mL	31.39 $\pm$ 16.63	27.5	
2000 to 10 <sup>7</sup> IU/mL	36.77 $\pm$ 29.46	30	
More than 10 <sup>7</sup> IU/mL	48.56 $\pm$ 32.32	45	
<b>IL-17 serum level (pg/mL)</b>			0.327
Less than 2000 IU/mL	30.66 $\pm$ 103.65	8.15	
2000 to 10 <sup>7</sup> IU/mL	26.87 $\pm$ 91.68	4.52	
More than 10 <sup>7</sup> IU/mL	24.42 $\pm$ 75.50	4.66	

## 5. Discussion

Chronic hepatitis B infection can damage liver cells by inducing autoimmune reactions directly or by producing antibodies. Evidence suggests that liver damage caused by immune system activity plays an important role in the pathogenesis of chronic hepatitis (22).

IL-17 is a pro inflammatory cytokine that has been determined as an important mediator in autoimmune disease and immune reactions against some specific pathogens, although the mechanism is unclear (9-18).

Studies have shown that th17 cells and cytokine IL-17 levels in patients with hepatitis B have direct correlation with progression to liver cirrhosis (21-24). The role of IL-17 on the level of viremia is unknown. We investigated the relationship between IL-17 with viral load in patients with chronic hepatitis B, and did not find any correlation between different levels of viral load with the amount of ALT and IL-17 ( $P > 0.05$ ).

In our study, IL-17 level in the third group (highest load group) was lower than other groups which might be due to the low number of patients in this group compared to the two other groups which is considered one of the limitations of this study. Patients with chronic hepatitis B in phase immune tolerance are known with features such as low intensity inflammation and fibrosis, high levels of HBV DNA and normal or slightly elevated liver enzymes. Due to the low intensity of inflammation and fibrosis at this phase, reduction in the levels of IL-17, as an inflammatory factor was not unexpected. In other words, increased levels of IL-17 consistent with the reduction of viral load and increased inflammation, has been confirmed in previous studies. This idea could be proposed if the pathological findings of the liver samples were available to these patients.

Zhang et al. studied increasing th17 cells in peripheral blood of patients with chronic hepatitis B liver and observed that the large number of th17 cells can potentially cause liver damage and aggravation in chronic HBV infec-

tion (23). Furthermore, Shi et al. demonstrated that serum levels of IL-17 in patients with chronic hepatitis B were directly related to the level of total bilirubin, ALT and Child Pugh Grade (24).

In addition, other studies showed a direct correlation between serum level and IL-17 gene expression with liver damage in hepatitis B patients as well as the degree of fibrosis in liver cirrhosis (22, 25-29).

The findings of our study that shows the lack of correlation between HBV DNA levels and IL-17 was similar to the research done by Wu et al. (30). On the contrary, the results of Zhang et al. were inconsistent with the two previous researches, as it showed that serum and intracellular IL-17 and th17 cells increased in patients with high levels of HBV DNA (23).

Meng et al. compared serum levels and gene expression of IL-17 and liver enzymes to viral load in patients with chronic hepatitis C, but no significant relationship was found (31). The type of infecting virus in this study was different, but it was similar to our findings.

Differences in sample size, severity of inflammation, fibrosis and viremia in patients with chronic hepatitis B in previous studies can partly explain the difference in the results. Due to the limited sample size in our study, especially, in patients with viral load above 10<sup>7</sup> IU/mL, it seems that further studies with larger sample size are necessary.

In this study, any relationship between different levels of viral load and ALT levels was not observed. The findings of previous studies showed a positive correlation between increased levels of IL-17 and ALT levels in patients with chronic and severe hepatitis B (23, 24, 28, 30). It should be noted that the mentioned studies examined the relationship between ALT and IL-17 levels in patients with varying degrees of inflammation and none of the previous studies compared the level of ALT based on HBV viral load.

### 5.1. Conclusions

The results of our study showed that with the rise of viral load in patients with chronic hepatitis B, the average

level of IL-17 is reduced, but this difference was not significant. These results suggest that in chronic hepatitis B infection, IL-17 might be associated with the control of liver injury and infection.

Due to limited studies, which compared IL-17 and ALT with viral load in patients chronically infected with hepatitis B, it is recommended that similar studies be conducted to assess the reproducibility of the results considering the severity of the disease (based on liver pathology, HBeAg, liver enzyme levels and viral load).

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### Footnotes

**Authors' Contribution:** Study concept and design: Maliheh Metanat and Ebrahim Alijani; analysis and interpretation of data: Fatemeh Bahrehmand, Manijeh Khalili, and Narges Arbabi; drafting of the manuscript: Soheila Khosravi and Esmaeil Sanei Moghadam; critical revision of the manuscript for important intellectual content: Roya Alavi-Naini and Maliheh Metanat; statistical analysis: Alireza Ansari-Moghaddam.

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**Ethical Approval:** It should be noted that the results were published confidentially and with the approval of the authorities in order to observe research ethics. The information provided in this study is derived from the thesis approved by the Ethics Committee No. 1394-106.

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