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Review of Interleukin-6 and Interleukin-18 Levels in Patients Diagnosed with Chronic Hepatitis B

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Objective: The hepatitis B virus (HBV) is a DNA virus of the Hepadnaviridae family. The course of infection depends on the patient's immune response. Interleukin 6 (IL-6) and Interleukin-18 are significant cytokines for immune response. Chronic hepatitis B patients may exhibit insufficient immune response against the hepatitis B virus. There may be differences in interleukin 6 and interleukin 18 (IL-8) levels between patients and healthy controls. In this study, we aimed to assess the relationship between the level of IL-6 and IL-18, and chronicity of the disease in patients diagnosed with chronic Hepatitis B virus infection.

Materials and Methods: Sixty-three treatments-naive patients diagnosed with chronic active hepatitis B infection who applied to our clinic between June 2010 and May 2011 were enrolled in the study. 5 mL of blood was collected from each patient and IL-6 and IL-18 levels were examined by the ELISA method.

Results: The IL-6 and IL-18 levels of the control group were compared with those of the subjects in the patient group. The Mann-Whitney U test was used to evaluate the control group and the patient group, and it was found that the IL- 6 level was statistically higher in the patient group (p 0.011). There was no significance for IL-18 levels between the control group and the patient group with low viral load. However, we detected a statistically significant elevation in IL-18 levels of patient groups with high viral load compared to the control group.

Conclusion: The response to IL-6 and IL-18 can be lower in patients, and the receptor resistance against IL-6 and IL-18 may have developed. This may be the reason for chronicity.

Key Words: *Chronic hepatitis B, proinflammatory cytokine, interleukin 6, interleukin 18.*

Kronik Hepatit B Hastalarında İnterlökin-6 ve İnterlökin-18 Düzeylerinin Araştırılması

Amaç: Hepatit B virüsü Hepadnaviridae ailesinden bir DNA virüsüdür. Hastalığın seyri hastanın immün cevabına bağlıdır. IL-6 ve IL-18 immün yanıt için önemli sitokinlerdir. Kronik hepatit B hastalarında hepatit B virüsüne karşı yetersiz immün yanıt oluşabilmektedir. Hastalar ve sağlıklı kontroller arasında IL-6 ve IL-18 düzeyleri arasında farklılıklar olabilir. Bu çalışmada, kronik hepatit B hastalarında IL-6 ve IL-18 ile kronisite arasındaki ilişkinin değerlendirmeyi amaçlandı.

Gereç ve Yöntem: Haziran 2010 ile Mayıs 2011 tarihleri arasında kliniğimize başvuran Kronik hepatitli 63 naif hasta çalışmaya alındı. Her hastadan 5 mL kan alındı ve IL-6 ve IL-18 düzeyleri ELISA yöntemi ile çalışıldı.

Bulgular: Hasta ve kontrol grupları IL-6 ve IL-18 düzeyleri açısından karşılaştırıldı. IL-6 düzeyinin hasta grubunda istatistiksel olarak anlamlı olarak yüksek olduğu saptandı (p=0.011). Kontrol grubu ile düşük viremi grubunda IL-18 için istatistiksel anlamlılık saptanmadı. Ancak yüksek viral yüklü hasta grubunda IL-18 düzeyi kontrol grubuna oranla istatistiksel olarak daha yüksek idi.

Sonuç: Hastalarda IL-6 ve IL-18 yanıtı daha düşük olabilir. IL-6 ve IL-18 reseptör direnci gelişmiş olabilir. Kronikleşmenin nedeni bu olabilir.

Anahtar Kelimeler: *Kronik hepatit B, pronflamatuar sitokin, interlökin-6, interlökin-18.*

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Introduction

The hepatitis B virus (HBV) is a hepatotropic, non-cytopathic, partially double-stranded DNA virus of the Hepadnaviridae family. The outcome of the infection after exposure to the hepatitis B virus depends on the patient's immune response. A primary immune response is rapidly activated after the infectious agent is contracted, and an efficient adaptive immune response is formed which tries to limit the pathogen (1).

Infection begins after the virus enters the liver cell, triggering a host response. The adaptive immune response, which develops against the hepatitis B virus plays a key role in the control of the infection (1, 2). After entering the liver cell, the virus is processed by the dendritic cells and is presented to cells of the immune system as an antigen. The normal cellular response, which develops against the HBV infection leads to liver damage, and to the development of hepatocellular carcinoma (HCC) and

cirrhosis in future (3). Proinflammatory T-helper 1 (Th1) cells and anti-inflammatory T-helper 2 (Th2) cells regulate this cellular response (1-3).

Dendritic cells (DCs) in the liver identify viral particles with Toll-like receptors (TLRs). DCs process viral antigens and present them to cells of the immune system via the class 1 and class 2 Major Histocompatibility Complex (MHC). With the activation of these cells, various cytokines are released, and the immune response is consequently created (4).

Cytokines are small soluble proteins secreted by the immune system and other cells of the body. They play a role as part of intercellular communication in the immune system. These proteins bind to their own specific cell receptors, and serve with autocrine or paracrine effect, and inhibit or induce cytokine-regulating genes. Until now, 100 different cytokines have been reported and grouped according to their roles. These proteins play a key role in the promotion, polarization and regulation of immune response. With the combination of cytokines, an antigenic signal occurs, which determines how the immune response will develop (4).

Interleukin 6 (IL-6) is a multifunctional proinflammatory cytokine, which has a significant role in the regulation of the immune response. IL-6 is a small polypeptide with a 4-alpha-helix structure, and with a molecular weight of 20 kilodaltons. Its structural stability binds with intermolecular disulfide bonds. IL-6 is a cytokine formed by multiple genes as a response to acute inflammation. IL-6 has differentiation and promoting effects on the growth of various target cells. IL-6 molecules are released from T cells, and induce B cell proliferation, differentiation and antibody production. IL-6 cytokines are induced by various signals such as viral infections, bacterial endotoxins, serum and double-stranded polyribonucleotides. This means that the IL-6 gene expression is regulated by many products, which trigger inflammation. IL-6 regulates the synthesis of broad-spectrum acute phase proteins in the liver. IL-6 is also involved in the pathogenesis of many fibrogenic diseases. It has been shown that IL-6 is generated to a greater extent during the course of autoimmune diseases, chronic inflammatory diseases and many cancers (5, 6).

The effects of IL-6 begin when it binds to the cell surface receptor. During HBV infection, IL-6 receptors bind to the HBV surface antigen and can enter the liver cell by this way. The HBV envelope protein pre-S (21-47) zone contains the IL-6 binding zone (7).

IL-18 is a proinflammatory cytokine, which is a member of the IL-1 family. It was first defined in 1989 as IFN-γ-inducing factor. IL-18 has a molecular weight of 18,300 DA (8). Interleukin (IL) -18 plays a critical role for Th1 response. It has been demonstrated that liver destruction was prevented when given antibodies against IL-18. IL-18 occurs very early in T cell activation and triggers the early steps of the cytokine cascade (9).

IL-18 is synthesized from Kupffer cells, activated macrophages, monocytic and dendritic cells, keratinocytes, osteoblastocytes, and astrocytes. It also triggers macrophages for the production of TNF α and NO which are important molecules of apoptosis. It also causes a positive effect on viral infection. It affects antitumor activity with NK cell activation. The IL-18 receptor complex (IL-18R) is composed of two chains and a heterodimer structure. It is a member of the IL-1R family. They are both required for initiating the signalization process. The α chain of IL-18R is responsible for ligand binding while the β chain of IL-18 is necessary for signal transduction (9).

IL-18 levels improve normal and induced immunity. TNF-α, IL-6, and INF-γ release can be depressed when IL-18 is neutralized in vitro, In Addition, IL-18 plays an important role in the natural course of HBV infections and HBV clearance (10).

In this study, we aim to investigate IL-6 and IL-18 levels in chronic hepatitis B patients, and to evaluate the relationship between the IL-6, IL-18 levels and chronicity.

Materials and Methods

Sixty-three antiviral treatment-naive patients diagnosed with chronic active hepatitis B infection, who applied to the Fırat University, Faculty of Medicine, Infectious Diseases Clinic, Department of Clinical Microbiology between June 2010 and May 2011 were enrolled in this study.

Five milliliters of blood was collected from each eligible patient, and the blood samples were put into biochemistry tubes, which were then centrifuged at 3000 rpm for 5 minutes. The serum samples obtained were stored at -80°C until the day of the study. The IL-6 and 18 levels in the blood samples were examined.

In addition, the age of all the subjects, aspartate amino transferase (AST) and alanine amino transferase (ALT) levels, HBeAg and anti-HBe status, HBVDNA level, histological activity indexes in liver biopsy and fibrosis scores, and USG findings were recorded. All biochemistry and serological tests, and HBV DNA level analysis were performed at the Fırat University Hospital Central Laboratory. Blood biochemistry tests were performed using an Olympus AU2700 device with the enzymatic kinetic method, while HBeAg and anti-HBe levels were evaluated with an Architect 2000 device (Architect System Abbott Diagnostics, Germany).

HBV DNA levels were investigated with the Roche Cobas Taqman (The COBAS® AmpliPrep/COBAS® TaqMan® HBV Test, v2. 0, Roche Diagnostics, Basel, Switzerland) while the High Pure PCR Template Preparation Kit was used for hepatitis B virus DNA extraction (Roche, Germany).

Serum IL-6 and IL-18 levels were measured by the enzyme-linked immunosorbent assay (ELISA) method using ELISA kits (BOSTER, Wuhan, CHINA), BIOTEK washer (ELX 50™ Microplate, 40710000, Winooski, USA) and BIOTEK reader (ELX 800™ 733310000, Winooski, USA).

Statistical Analysis: Differences in the distributions of demographic characteristics and selected variables between the groups were analyzed. Descriptive statistical analyses are presented as percentage for categorical variables, as mean with one standard deviation for normally distributed continuous variables or as median with range for non-normally distributed continuous variables. Results were compared using the Student's t-test for non-paired data, if distribution of variables was normal or the Mann– Whitney U-test for other than normal distributions. The data were evaluated using the Mann-Whitney U test and the Kruskal-Willis test, with the SPSS 15 program.

Results

Sixty three antiviral treatment-naive patients were enrolled in this study. A control group consisting of 25 healthy subjects of the same age range was also formed. The sixty-three patients were divided into two groups consisting of 25 patients with known HAI and fibrosis scores, and 38 patients with high HBV DNA levels, and these two groups were evaluated separately. The mean age of the patients was 39. The mean age of the control group was 38, the mean age of the group with moderate and severe inflammation of the liver was 38, and the mean age of the group with high HBV DNA levels was 42. Liver biopsy was performed in 25 of the patients enrolled in the study, and included patients with moderate and severe fibrosis of the liver. Pathological examination of the patients showed their ISHAK scores as follows: HAI with minimum of 5 and maximum of 12; and fibrosis with minimum of 1, and maximum of 3. The remaining 38 patients had high HBV DNA levels, and consisted of patients on whom no pathological evaluation was performed. The demographic, clinical and laboratory data of groups shown in Table 1.

The IL-6 levels of the control group subjects were compared with those of the patient group. The second group consisted of 25 patients whose HBV DNA levels were between 2000 IU/mL and 20000 IU/mL. The third group consisted of patients whose HBV DNA levels were >20000. The Mann-Whitney U test was used to evaluate the control group and the second group, and the IL-6 level was found to be statistically higher (P= 0.011) in the second group. Likewise, a statistical difference was found between the third group and the control group with regards to IL-6 levels (P<0.05). A comparison of the two groups with high levels of HBV DNA statistically proved that the IL-6 levels in the third group were higher (P= 0.018). No statistically significant difference was found between the HBeAg-positive and HBeAg-negative patients in all the groups (P= 0.899).

Patients with high levels of ALT and normal levels of ALT in all the groups were evaluated with the Kruskal-Wallis test; however, no statistically significant difference was found with regards to the IL-6 levels (P= 0.427). Similarly, it was found that patients with high levels of HAI and fibrosis had IL-6 levels higher than patients with low levels of HAI and fibrosis, but not statistically higher (P= 0.124). IL-6 titres for all groups presented at table 2 and figure 1.

Table 1. The demographic, clinical and laboratory data of groups

Parameters	Group 1	Group 2	Group 3
Mean age	39±12	38±13	41±13
Mean HBV DNA	-	2800	209820
HBeAg positivity/negativity	-	7/18	13/25
Mean ALT		90	95
IL-6 Mean±SD	9.85 ±25.54	123.3 ±469.7	1184.1±5636.06
IL-18 Mean±SD	1199± 696.36	1463±5636	1869.2±1095.4

Table 2. IL-6 and IL-18 levels for all groups

	IL-6 (Mean ±SD)	Confidence Interval 95% IL-6		IL-6 (Mean±SD)	Confidence Interval 95% IL-6	
		Lower	**Upper**		**Lower**	**Upper**
Group 1	9.85 ±25.54	-0.68	20,40	1199± 696.36	911.87	1468.76
Group 2	123.3 ±469.7	-70.54	317.30	1463±5636	1123	1804.06
Group 3	1184.1±5636.06	-668.34	3036.71	1869.2±1095.4	1509.15	2229.25

Table 3 Comparison of p values for IL-6 and IL-18 between the groups by Mann Whitney U test

COMPARATION GROUPS	***P* VALUE *for IL-6***	***P* VALUE *For IL-18***
Comparison of first and second groups	0.011	0.48
Comparison of first and third groups	0.008	0.009
Comparison of second and third groups	0.89	0.87
Comparison of normal ALT and High ALT groups	0.42	0.43
Comparison of High HAI and Grade of Fibrosis and Low HAI and Grade of Fibrosis groups	0.124	0.68

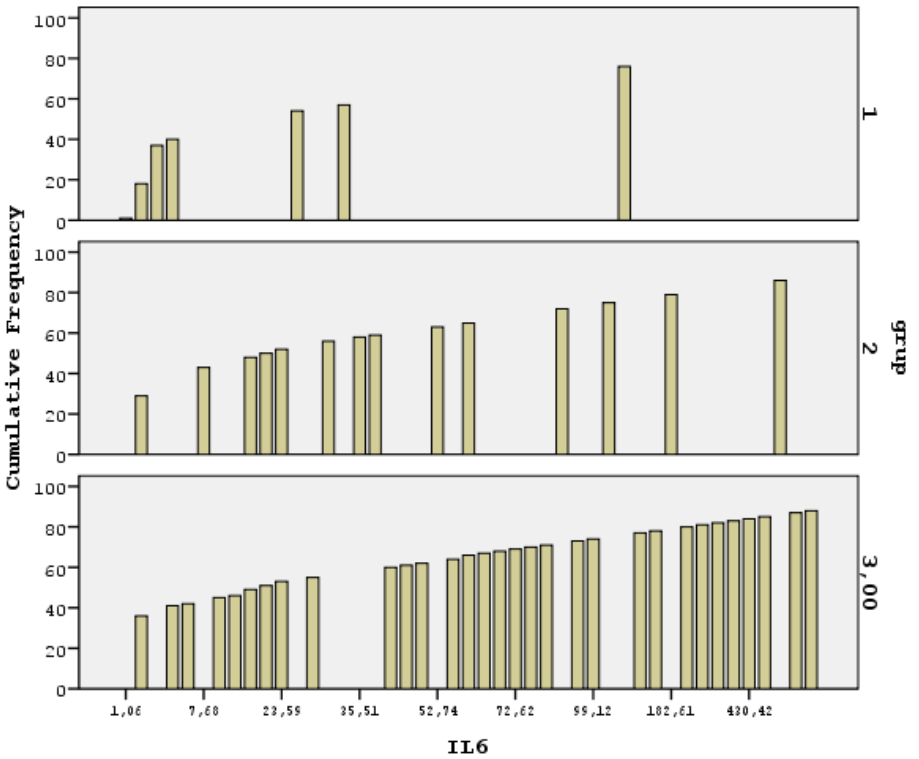

Figure 1. IL-6 levels for all groups

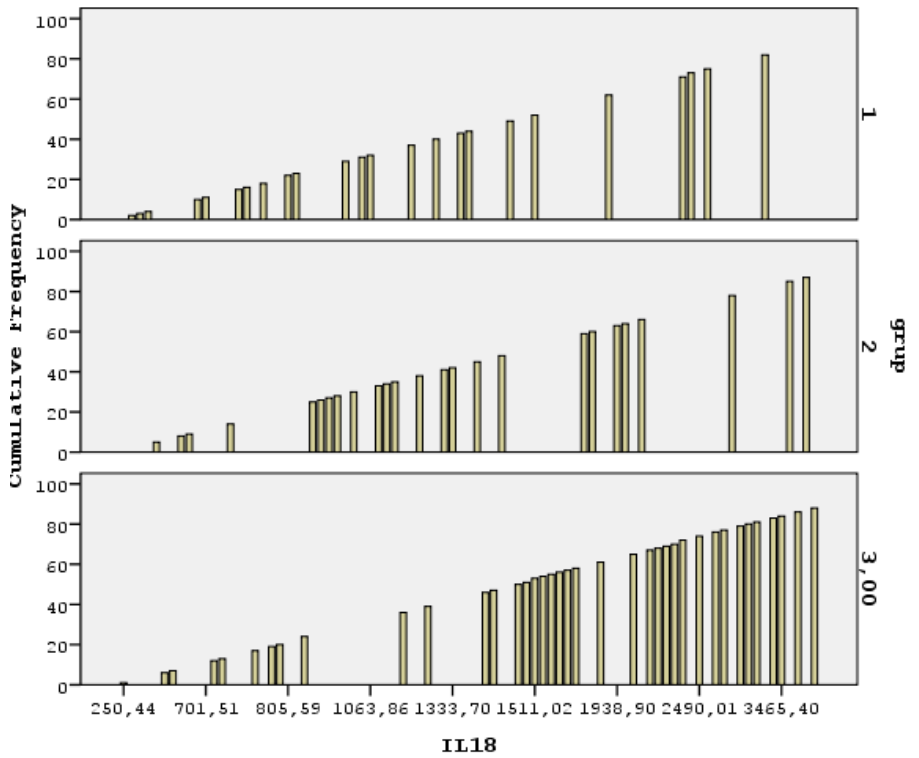

Figure 2. IL-18 levels for all groups

Comparison of *p* values for IL-6 between the groups by Mann Whitney U test presented at Table 3. Similarly, IL-18 levels evaluated were statistically. Mann-Whitney U test was used to evaluate the control group and the second group, and it was found that the IL-18 level was higher in the second group although there was no statistical significance (P= 0.48). However, higher IL-18 levels in the third group was founded to be statistically significant when compared to the third group and control group (P= 0.009). IL-18 levels were found to be higher in the third group than in the second group, but there was no statistical significance (P= 0.87). IL-18 levels were found to be lower in HBeAg positive group than in the HBeAg negative group, but there was no statistical significance (P= 0.337). Similarly, IL-18 levels were found to be high in the group with high ALT level when it compared to the group with a low ALT level. However, there was no statistical significance (P= 0.43). In addition, there was no statistical significance between the high fibrosis group and low fibrosis group. Nevertheless, in the group with high fibrosis IL-18 levels were found to be higher than in the group with low fibrosis. IL-18 levels for all groups presented at table 2 and figure 2.

Comparison of p values for IL-18 between the groups by Mann Whitney U test are shown in Table 3.

Discussion

Chronic viral hepatitis B is a disease with an incidence of 5-10% during adult age, and in some cases can lead to fibrosis, cirrhosis and HCC. Chronic HBV carriers have a higher risk of HCC compared to those who are not infected. HCC is the most common known primary liver cancer, and one of the ten most common types of cancers worldwide (11).

In viral hepatitis, a diffuse inflammatory reaction occurs, which leads to liver cell damage and death. However, although no progression to any significant liver disease is seen in some patients of the same age, same gender and same ethnicity, some patients develop chronic hepatitis. Although the reason for this trend is not clear, the immune responses of patients to the virus is suggested to form the basis of the condition. Different immune responses influence the incidence, course, treatment response and prognosis of the disease. The difference between immune responses in different persons is thought to be due to differences in the production of cytokines that play an important role in immune response (12).

In viral infections, numerous mechanisms are involved in the interaction between the virus and the host. The host response begins as a result of the interaction of specific T cells with mediators such as antigens and inflammatory cytokines. Cytokines are mediators involved in many biological processes such as inflammation, apoptosis, necrosis and fibrosis. Basically, they are released from lymphocytes and monocytes, and play a role in intercellular communication and regulation of immune responses (12).

It has been shown that the HBV-x protein initiates the acute phase response and increases the IL-6 level during hepatic inflammation (13). Additionally, a direct relationship between IL-6 and the pre-S domain of the large envelope antigen of HBV has also been reported (14).

It has been proven that hepatic cells, extrahepatic cells and HBV envelope protein induce the production of IL-6 with their connection between the pre-S1 domain: (a) this interaction is inhibited by IL-6 or anti-IL-6 antibodies, (b) the production of IL-6 and the identification of zones of HBV envelope protein of the pre-S1 domain are said to be induced through stimulation of T cells and peripheral blood monocytic cells (PBMCs) with Con A and LPS respectively (c) following exposure of IL-6-producing cells to phosphatidylinositol-specific phospholipase C (PI-PLC) or to low pH, it leads to cell-mediated IL-6 release and reduction in binding to the pre-SI (21-47) domain. These results support the fact that the cell-mediated IL-6 is either a cell surface receptor against HBV or a part of a multi-part receptor component. These findings support the idea that IL-6R can be the new target in the immunotherapy of hepatitis caused by HBV (15).

Previous studies have reported that immunoregulatory cytokines released from T cells and macrophages in chronic hepatitis B infection affect the virus remaining in the liver chronically and the extent of liver damage. Proinflammatory cytokines in particular are known to play an active role in liver damage caused by HBV. Numerous studies have demonstrated that the serum levels of IL-6, which is one of the most significant proinflammatory cytokines, is increased in chronic liver diseases (16-22).

In one study conducted, serum IL-6 was found to be 6.7% in asymptomatic carriers, 13.3% in patients with chronic persistent disease, 20% in chronic active hepatitis patients, 33.3% in cirrhotic patients, and 66.7% in HCC patients. The results of this study support the fact that there is a positive correlation between IL-6 and severity of the disease (22). It was also observed in our study that IL-6 levels were higher in the group with a higher viral load.

Previous studies have demonstrated that IL-6 is critical for acute phase response. The release of various cytokines such as IL-6 induces the initiation of early stage reactions of the inflammatory process (23). Serum concentrations of IL-6 are especially higher in acute hepatitis compared to chronic hepatitis. The fact that IL-6 levels are different in the acute and chronic phases of the disease can be helpful in distinguishing these processes. However, there is currently no reliable IL-6 indicator for acute hepatitis (20).

Studies conducted on humans have demonstrated that the comparable serum concentration in healthy controls is 1 pg/ml. This very low reference value may suggest that IL-6 level increases in many acute and chronic diseases (24).

IL-6 levels have also been shown to increase in patients with primary liver disease. Although serum IL-6 level is found to be higher in HCC patients than in normal healthy controls, no difference in the IL-6 receptor level has been observed. Furthermore, it has been suggested that high levels of serum IL-6 can lead to HCC in HBV patients. Therefore, IL-6 can be regarded as a biomarker or a risk factor for HCC (25-26).

In another study, the IL-6 levels were found to be high in chronic hepatitis B, cirrhosis and HCC (18). It was also reported that the IL-6 level in the ascites fluid of cirrhotic patients was higher, and the high level of IL-6 suggested to be important in ascites formation (27). Likewise, in our study, the IL-6 levels were found to be significantly higher in patients diagnosed with chronic hepatitis B.

The major determinant for IL-6 signaling in the liver is the circulating sgp130 level. Therefore, high plasma levels of sgp130 support the resistance to high plasma IL-6 levels. Chronic high levels of serum IL-6 cause down-regulation of IL-6R levels in the liver, and an increase in the plasma sgp130 level. Additionally, an increase in plasma sgp130 level in particular explains to a great the extent of IL-6 resistance which means a defective acute phase response (28).

It has been demonstrated in studies conducted in Turkey that, mean IL-6 levels are significantly higher in chronic hepatitis B patients than in healthy controls. In a study where patients diagnosed with chronic hepatitis B were divided into two groups consisting of those with normal ALT levels and with elevated ALT levels, the highest IL-6 levels were found in chronic hepatitis B patients with normal ALT levels. This result was also in chronic hepatitis B patients with high ALT levels, while the lowest IL-6 levels were found in healthy controls. The difference between the two groups was found to be statistically significant. Additionally, a significant reverse correlation between IL-6 levels and the serum ALT levels was observed in the patient group. ALT levels were reported to decrease, whereas serum IL-6 levels increased. Serum IL-6 levels are found to be higher particularly in cases with normal ALT levels (29).

These findings were also supported by other studies conducted in Turkey. In the study by Yazmacı et al. (30), 71 patients with liver disease of viral etiology were evaluated, and the researchers found that the IL-6 levels in the group with 31 liver cirrhosis cases were significantly higher than in the control group.

In another study conducted in Turkey, the IL-6 levels were found to be significantly high in patients with liver cirrhosis and spontaneous ascites infection (31).

In another study by Yıldız et al. (32) on 57 subjects consisting of 25 chronic hepatitis B patients and 32 inactive carriers, researchers found the IL-6 levels in the patient group to be significantly higher than the levels in the control group. Our study also reported high levels, consistent with those of the other studies conducted in Turkey.

Interleukin-18 (IL-18), previously known as interferon-γ (IFN-γ) inducing factor, is a cytokine which provides multifunctional effect such as activation of immune reaction via cytotoxic T lymphocytes, natural killer T helper type 1, and also IL-18 provides affinity to pathogens. It also provides an activation relationship between cells during inflammation and causes target cell apoptosis (33)

Migita et al. (34) demonstrated a relationship between IL-18 production and specific CD4 and CD 8 T lymphocyte response to HBV. In other studies, Kimura et al. (35) and Wen et al. (36) studied the possible role of IL-18 in hepatitis patients. The production of IL-18 was shown to be consistent with the severity of disease. IL-18 levels and liver inflammation were also reported to be correlate in chronic stage of disease.

HBV replication was reported to be inhibited reversibly and in a non-cytopathic manner after injection of recombinant IL-18 in the liver of experimental mouse models. The antiviral activity of IL-18 occurs through IFN gamma secretion of intrahepatic T cells and NK cells and also through IFN alpha and beta production in the liver (37).

IL-18 gene polymorphism has been reported to have a negative effect on the development of chronic hepatitis B disease (38). Recent studies suggest that IL-18 plays an important role in liver injury. Accordingly, deficits in mice have been shown to be resistant to LPS-induced liver injury. Total prevention of liver damage was determined by the neutralization of IL-18 via IL-18 monoclonal antibody during liver failure in mouse models (39). IL-18 was found to be significantly upregulated in chronic HCV patients. These findings suggest that this cytokine plays an important role in cellular immune response against hepatocytes in chronic disease course.

Prevention of acute liver damage after administration of anti-IL-18 monoclonal antibody has led to a focus on the importance of this cytokine in the pathogenesis of liver damage. In a study, decline of IFN-y production was shown after administration of recombinant IL-18 BP and LPS in mice. An elevation of IL-18 levels in patients with chronic HCV has been reported when compared with individuals in the control group (38).

In a study conducted in Turkey, a statistically significant elevated IL-18 level was determined in acute and chronic Hepatitis B. IL-18 was identified as playing an important role in acute and fulminant liver damage, with a significant increase in the levels of this cytokine (39). There is no other study which was reported from Turkey.

In our study, we found a relationship between viral load and IL-18 levels. We also demonstrated a statistical significance in the group a high viral load when compared with the control group. However, no statistical significance was found in the group with a low viral load and control group. These findings suggest that IL- 18 is a cytokine with important high viral potency in the patient groups. Our results are similar with other studies

conducted in Turkey and all over the world. Based on these results IL- 18 can be useful when recombinant IL-18 is administered with antiviral treatment for the eradication chronic hepatitis B disease.

In conclusion, IL-6 and IL-18 play an important role in the pathogenesis of viral hepatitis. IL-6 levels are found to be higher especially in chronic hepatitis B cases when compared to healthy persons. This may be due to the resistance to IL-6 receptors that develops against IL-6. With high levels of IL-6, down-regulation occurs in IL-6 receptors and this causes IL-6 resistance. Therefore, the signal required for the inflammation to start is not received or is delayed. Consequently, the virus cannot be eradicated from hepatocytes, and the infection continues chronically. High IL-18 levels in chronic hepatitis B indicate that this cytokine is an important marker for the degree of liver inflammation and high viral load. Further research is needed to have a better understanding on this subject.

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