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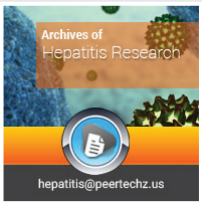

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Research Article

The association with histopathological findings and predictive significance of transforming growth factor beta 1 (TGF β1) in patients with chronic viral hepatitis

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Abstract

Background: Chronic Viral Hepatitis (CVH) is the most common cause of hepatocellular cancer and cirrhosis related to liver fibrosis. The gold standard in the diagnosis of fibrosis is liver biopsy. TGF β1 is a pleiotropic cytokine that plays a pivotal role in carcinogenesis and fibrosis. The results of studies investigating the relationship between TGF β1 and histopathological findings are controversial. We aimed to investigate the relationship between TGF β1 and histopathological findings.

Methods: Patients with Chronic Hepatitis B (CHB) and C (CHC), Non-Alcoholic Steatohepatitis (NASH), inactive HBsAg carriers, patients with cirrhosis and healthy control cases presenting to the Gastroenterology Clinic of Sisli Etfal Training and Research Hospital between 2009-2010 were included in the study. Laboratory tests, HCV RNA, HBV DNA, viral load, and viral markers (such as HBsAg, anti-HCV) were determined. Biopsies were performed on patients with hepatitis B and C, and non-alcoholic steatohepatitis (NASH). Histologic features were defined as Histologic Activity Index (HAI) and fibrosis stage (Knodell's scoring). TGF β1 was evaluated by the ELISA method.

Results: 267 cases including 44 non-alcoholic steatohepatitis cases [27 female (57%)], 38 inactive HBsAg carriers [23 female (60%)], 48 patients with chronic hepatitis B [17 female (35%)], 27 chronic hepatitis C [14 female (60%)], 15 decompensated cirrhosis [3 female (20%)] and 94 healthy control cases were included in the study. Compared with healthy controls, all other subgroups had significantly elevated TGF β1 levels. TGF β1 was found to have a specificity of 93.6% and a sensitivity of 88.9% (AUC: 0.948, 95% CI: 0.916-0.981) in determining liver diseases. TGF β1 had a positive correlation with fibrosis and histological activity index in patients with CHB and CHC. There was a negative correlation between TGF β1 and HBV DNA and HCV RNA. TGF β1 had a significant correlation with LDL and total cholesterol in cases with CHB and CHC.

Conclusion: TGF β1 is correlated with both HAI and fibrosis in patients with CHB and CHC. TGF β1 might have a role in the prognostic significance of elevated LDL levels and low viral load in patients with CHC.

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Introduction

Chronic Viral Hepatitis (CVH) due to hepatitis B and C is the leading cause of chronic hepatitis, cirrhosis, and hepatocellular cancer. Therefore, CVH has increased morbidity and mortality rates [1,2].

The basic histopathological finding in the liver of patients with CVH is necroinflammation with its pathologic definition of histologic activity index (HAI) and fibrosis. Necroinflammation is the major criterion for the initiation of therapy in CVH cases [3]. Moreover, hepatic fibrosis, caused by necroinflammation and leading to cirrhosis, has been demonstrated to be reversible [4,5]. An improvement in the fibrosis stage has been reported to prevent the development of cirrhosis and hepatocarcinogenesis [6]. Therefore, pre-and post-treatment assessment of the fibrosis and the other histopathological findings are important with respect to the efficacy of the treatment and the disease progression. However, the current gold standard diagnostic method is liver biopsy, which carries a high morbidity and mortality risk and also has limitations such as inter-observer variability, sampling errors, and contraindication in patients with bleeding diathesis [7,8].

Tests used in the diagnosis and follow-up of CVH such as transaminase levels, viral markers (e.g., HBsAg, anti-HCV), and viral load are not correlated with liver necroinflammation and fibrosis [9-11]. Therefore, it is clear that diagnostic and follow-up tests correlated to the hepatic histopathological findings are required in patients with CVH.

TGF β1 is the major component with significant functions among the TGF β isomers in the human liver [12]. TGF β1 is a pleiotropic, multifunctional marker that is pivotal in hepatic fibrogenesis through the production of excessive extracellular matrix by the activation of hepatic stellate cells and carcinogenesis [7,13]. It has also been reported to have a critical role in the termination of hepatocellular proliferation and apoptosis [14]. Therefore, TGF β1 may be related to liver fibrosis and necroinflammation.

The results from the trials investigating the correlation of TGF β1 with the histopathological findings are controversial. [15,16]. In this study, we aimed to investigate the importance of TGF β1 in liver disease, and its relationship with histopathology and laboratory parameters (lipid panel and viral load) in patients with CVH.

Methods

Patients

Patients with chronic hepatitis B and C presenting to the Gastroenterology Clinic of Sisli Etfal Training and Research Hospital in 2009-2010 were included in the study. Chronic Hepatitis C (CHC) infection was defined as HCV RNA positivity for more than 6 months. All patients with hepatitis B included in the study were HBeAg negative. Chronic Hepatitis B (CHB) was defined as persistent or intermittent transaminase elevation and serum HBV DNA levels over 2000 IU/mL in patients with HBsAg positivity for more than 6 months. Inactive HBsAg carriers were defined as persistently normal transaminase levels and serum HBV DNA levels below 2000 IU/mL in patients with HBsAg positivity for more than 6 months. Nonalcoholic Fatty Liver Disease (NAFLD) was defined as hepatosteatosis by biopsy and/or sonography with transaminase levels above the normal range. A diagnosis of cirrhosis was established using histologic criteria or by clinical and Doppler sonographic findings.

Exclusion criteria

Patients with acute inflammation (elevated CRP and sedimentation), use of angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists, coronary artery disease, essential and secondary thrombocytosis, history of thrombasthenia, hepatocellular carcinoma, portal vein thrombosis, alcoholism, viral co-infections (such as hepatitis D, human immunodeficiency virus, B plus C hepatitis) and systemic diseases (chronic renal failure, nephrotic and nephritic syndrome), and acute renal failure were excluded from the study.

HBV DNA and HCV RNA viral load assay and evaluation of other tests

Sera for the complement assay were collected from patients before commencing treatment. HBV DNA quantitation was made with the COBAS TaqMan HBV Monitor test (Roche Molecular Systems) in accordance with the manufacturer's instructions. The dynamic interval for HBV DNA detection was 6- 110.000.000 IU/ml. HBsAg, AntiHIV, AntiHCV, and Anti delta were assayed using ETI-MAK-4, ETI-AB-HCVK-4, and ETI-AB-DELTAK-2 kits respectively with a TİMAX (DiaSorin, Italy) device. AntiHBc IgG, AntiHBc IgM, and HBeAg tests were carried out with a DiaSorin LIAISON system. As all the genotype studies in Turkey show a predominance of genotype D HBV, we did not perform a genotype analysis [17-19]. Patients gave blood samples for HCV RNA testing to determine viral load before the initiation of treatment. HCV-RNA quantitation was done using COBAS Taqman HCV test v2.0 (Roche Molecular Systems) in accordance with the manufacturer's instructions. The dynamic range for HCV-RNA quantitation was 6-110,000,000 copies/ml. All patients with chronic hepatitis C were genotype 1b. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), albumin, C-reactive protein (CRP), erythrocyte sedimentation rate, complete blood count, urine analysis and urinary protein quantification were performed for all patients. ALT cut-offs were 30 IU/ L and 19 IU/L in males and females, respectively [20].

Evaluation of TGF β1 by Enzyme-Linked Immunosorbent Assay (ELISA)

Human TGF-β1 Enzyme-Linked Immunosorbent Assay (ELISA) (Bender MedSystems, GmbH, Vienna, Austria, Europe) was used for the detection and quantification of TGF-β1 according to the manufacturer's instructions. Briefly, serum samples were diluted 1:10 and incubated with 1N HCL for 1 hour at room temperature, and then neutralized with 1N NaOH. 1:2 serial dilutions of human TGF-β1 standard ranging

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between 30.00 and 0.47 ng/ml were prepared for the standard curve. ELISA was performed in 96-well plates that were pre-coated with a polyclonal antibody specific for human TGF-β1. Pretreated serum samples and serial dilutions of human TGF-β1 standard were added to the microplate; then the conjugate was added to each well and the plate was incubated for 4 hours at room temperature. The rest of the reaction steps were carried out on an automated ELISA analyzer (ETIMAX, Diasorin) which includes washing, pipetting substrate, incubation, stopping the reaction, and reading the absorbance of each microwell on spectro-photometer using 450 nm as the primary wavelength and 620 nm as a reference. The cytokine protein concentration of each sample was determined on a standard curve generated by performing parallel assays using known amounts of TGF-β1 standards by using absorbance values of samples. TGF β1 content in the liver tissue was not evaluated as previous studies have demonstrated a strong correlation between hepatic and plasma TGF β1 [21].

Evaluation of liver histology

A liver biopsy was performed using a liver biopsy needle after obtaining informed consent from the patients (length of specimen > 2 cm). Biopsy samples were fixed in buffered formaldehyde for 24 hours and then processed by routine procedures. Liver biopsy samples were evaluated by a pathologist blind to clinical and virological findings with hematoxylin and eosin stained sections and periodic acid-Schiff stain with diastase for necroinflammatory activity. Masson's trichrome and Sweet's reticulin stains were reviewed for fibrosis and structural change. Histologic features were defined as histologic activity index (HAI, grade) and fibrosis (stage) according to the scoring method described by Knodell, et al. [22].

Ethics

The study protocol was approved by the local ethics committee and written consent was obtained from all patients prior to inclusion in the study.

Statistics

Scale variables were presented as mean ± standard deviation (mean ± SD). Categorical data were evaluated using Chi-square analysis or with Spearman's correlation as appropriate. Parametric quantitative data were compared by Student's t-test or Pearson's correlation as appropriate. One-way analysis of variance (ANOVA) was used for comparisons between the 5 main groups. Post-hoc analyses of significant differences were performed using Tamhane's test. A group of healthy controls was tested to determine a diagnostic cut-off in liver diseases for TGF β1 using Receiver Operating Characteristics (ROC) analysis. The Mann-Whitney U test was used for inter-group comparisons (a corrected p-value of 0.008 was considered significant because multiple comparisons were performed). A p - value of < 0.05 was considered statistically significant. SPSS (Statistical Package for Social Sciences, for Windows, release 12.0.0 standard version) software was used for statistical evaluations. Medcalc 11.3.0.0 for Windows was used for the depiction of TGF β1 changes on a box-and-whiskers plot.

Results

A total of 267 patients including 44 nonalcoholic steatohepatitis [27 female (57%)] of mean age 37 ± 11 years, 38 inactive HBsAg carriers [23 female (60%)] of mean age 42 ± 12 years, 48 chronic hepatitis B patients [17 female (35%)] of mean age 43.5 ± 47 years, 27 chronic hepatitis C patients [14 female (60%)] of mean age 56 ± 6.7 years, 15 decompensated cirrhosis patients [3 female (20%)] of mean age 62 ± 9 years and 94 healthy control cases were included in the study.

Serum TGF β1 levels were 15.5 ± 21 ng/ml in NAFLD cases, 13.3 ± 34.25 ng/ml in inactive HBsAg carriers, 43.5 ± 47 ng/ml in CHB cases, 17.88 ± 13.3 ng/ml in CHC cases, 6.6 ± 8.74 ng/ml in patients with cirrhosis and 0.82 ± 2.83 ng/ml in healthy controls (Figure 1).

When compared with the control group, serum TGF β1 levels were significantly higher in patient groups with NAFLD ($p < 0.001$), inactive HBsAg carriers ($p < 0.001$), CHB ($p < 0.001$), CHC ($p < 0.001$) and cirrhosis ($p < 0.001$). Serum TGF β1 levels were significantly elevated in CHB cases, NAFLD ($p = 0.004$), inactive HBsAg carriers ($p < 0.001$), and cirrhosis cases ($p = 0.001$), but there was no difference among CHC cases ($p = 0.219$).

When compared with the control group, in cases where TGF β1 levels were above the upper normal limit of 3.46 ng/ml, the specificity of TGF β1 for the determination of liver disease was 93.6%, and its sensitivity was 88.9% (AUC: 0.948, 95% CI: 0.916-0.981) (Figure 2).

Upon comparison of mean lipid levels in patients with CHB and CHC, there was no statistically significant difference in terms of total cholesterol ($P = 0.483$), HDL ($p = 0.133$), LDL ($p = 0.678$), and triglyceride ($p = 0.567$) levels.

Demographic and laboratory data pertaining to patients with CHB and CHC included in the study are summarized in Tables 1,2.

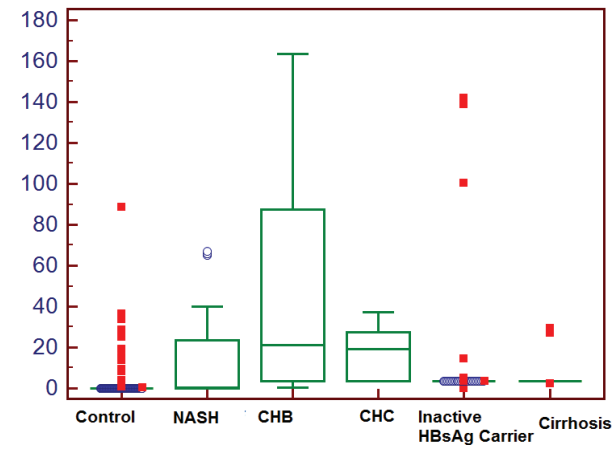

Figure 1: Serum levels of TGF β1 (ng/mL) in patient groups included in the study. The box represents the interquartile range. The whiskers indicate the highest and lowest values. The line across the box indicates the median value.

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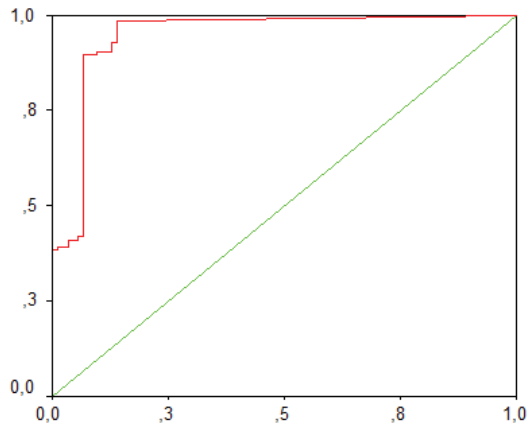

Figure 2: ROC (receiving operating curve) analysis. The x-axis shows 1-specificity (false positive fraction) and the y-axis shows sensitivity (true positive fraction) of TGF β1 for determination of liver disease. The green line is the chance diagonal (area under the curve, AUC:0.5) and the red line indicates the quality of the study test. The closer the AUC reaches 1.0 is better the diagnostic test.

Table 1: The relationship between serum TGF β1 and demographic and laboratory parameters in cases with CHB.

	CHB (*n* = 48)	r	*p*
ALT (IU/L)	106 ± 108	0.326*	0.024**
AST (IU/L)	66 ± 54	0.248*	0.089
Triglyceride (mg/dL)	114 ± 53	0.202	0.421
Total cholesterol (mg/dL)	173 ± 43	0.615*	0.009**
LDL (mg/dL)	182 ± 105	0.689*	0.002**
HDL (mg/dL)	47.8 ± 11	0.192	0.445
HAI	7.6 ± 2.78	0.344*	0.017**
Fibrosis	1.93 ± 0.9	0.350*	0.015**
HBV DNA (/10^7 IU/mL)	20.5 ± 50.7	-0.223	0.128

Abbreviations: ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; HAI: Histologic Activity Index

* Significant correlation coefficient values

** Significant *p* values

Table 2: Demographic and laboratory data and relationship with serum TGF β1 in cases with CHB.

	CHC (*n* = 27)	r	p
ALT (IU/L)	48 ± 22	0.164	0.49
AST (IU/L)	39.5 ± 16	0.264	0.26
Triglyceride (mg/dL)	132 ± 92	-0.272	0.245
Total cholesterol (mg/dL)	172 ± 46	0.681	< 0.001
LDL (mg/dL)	102.7 ± 12	0.522*	0.001**
HDL (mg/dL)	55 ± 4.8	0.335*	0.287
HAI	7.2 ± 2.3	0.463*	0.04**
Fibrosis	1.6 ± 0.7	0.698*	0.001**
HBV DNA (/10^7 IU/mL)	0.2 ± 0.16	-0.589*	0.006**

Abbreviations: ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; HAI: Histologic Activity Index

* Significant correlation coefficient values

** Significant *p* values

Discussion

High serum TGF β1 levels in patients with chronic viral hepatitis have been reported by the vast majority of authors [23-25]. In this study, we compared liver-related pathologies with high TGF β1 levels (NAFLD, CHC, CHB, cirrhosis, inactive HBsAg carriers) with the control group. According to this, we found serum TGF β1 levels higher than the upper normal range of 3.46 ng/ml established by the manufacturer to have a specificity of 93.6% and sensitivity of 88.9% in determining liver disease. Hence, the assessment of the TGF β1 level as well as the measurement of the transaminases, which clinically represent nonspecific hepatic tests, may provide further benefit.

In the present study, we demonstrated a correlation between TGF β1 and the stage of fibrosis in patients with CHC and CHB. Several authors have reported a correlation between TGF β1 and fibrosis [16,23,26]. While the exact mechanism underlying the increase in TGF β1 in cases with CVH is not known, the HCV core protein was reported to potentially promote hepatic fibrogenesis by the upregulation of the TGF β1 [27]. Although mean serum TGF β1 levels were lower in patients with HCV, there was no statistically significant difference compared to patients with CHB. The lower levels of TGF β1 in patients with CHC may be due to the lower average stage of fibrosis in these patients. This result also corroborates the significant correlation between TGF β1 and fibrosis.

Our finding of a negative correlation with viral load in addition to a significant correlation with inflammatory grade suggests that besides the antifibrotic effect, there might also be anti-inflammatory and antiviral effects, especially in patients with CHC [28-30]. It has been reported that a positive correlation between TGF β1 and inflammatory grade [31,32] as well as opposite to this correlation [26]. The high TGF β1 levels in cases with acute viral hepatitis demonstrated by Flisiak, et al supports its association with the active hepatic inflammation and thus the grade of inflammation because the advanced stage of fibrosis is not an expected manifestation in acute viral hepatitis [33]. The detection of a correlation between TGF β1 and the scoring of the active inflammation grade is an expected finding, considering the fact that it stimulates the chemotaxis of the macrophages and the granulocytes and the release of the cytokines such as IL-1 and IL-6 [13].

In the current study, we found a significant negative correlation between TGF β1 and viral load (HBV DNA and HCV RNA). The exact reason for the negative correlation with the viral load is not known. This negative correlation may be associated with the fact that TGF β1 suppresses the proteins expressed by the HCV replicon and the viral RNA replication [34], stimulates apoptosis [35] and increases the vial clearance [36] in cases with CHC. This apoptotic effect of TGF β1, a pleiotropic cytokine, may be more pronounced in cells infected by the virus.

We found a significant positive correlation between TGF β1 and LDL and total cholesterol levels. LDL elevation has been reported as a good prognostic indicator in patients with hepatitis

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C [37]. However, currently, the reason for this is not clearly established. Interferon alpha-2b was reported to increase the TGF β1 level [38,39] and the cases achieving a sustained virological response (SVR) were reported to experience an increase in LDL and total cholesterol levels during treatment [37]. Thus, TGF β1 may have a role in the increase of LDL and total cholesterol levels. The results from the current study suggest that this increase in the LDL and the total cholesterol levels observed in patients achieving an SVR response may be associated with the increased synthesis of TGF β1 induced by interferon.

The limitations of this study include the absence of an assessment of TGF β1's correlation with the therapeutical response during the course of chronic hepatitis, the absence of a determination of the TGF β1 receptors (particularly type II receptors) and the lack of an assessment of the correlation between the level of TGF β1 in the liver tissue and the serum TGF β1 level. However, since a highly significant correlation was demonstrated between the level of TGF β1 in the liver tissue and the serum TGF β1 level, such an association was not separately evaluated [21,40].

In conclusion, TGF β1 is highly sensitive and specific in determining liver diseases. In cases of CVH, the assessment of TGF β1 may provide additional benefits due to its significant correlation with the histopathological stage and grade, as opposed to the diagnostic and follow-up markers. TGF β1 might play an essential role in the increased serum LDL and low viral load previously reported as good prognostic factors in patients with CHC.

Acknowledgment

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