



The relation between liver histopathology and GGT levels in viral hepatitis: More important in hepatitis B

LIVER

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ABSTRACT

Background/Aims: To investigate the relationship between gamma-glutamyl transpeptidase (GGT) levels and histopathological status determined by biopsy in patients with chronic hepatitis B and C.

Materials and Methods: Patients with chronic hepatitis B and C who were referred to the Uludağ University Faculty of Medicine Gastroenterology outpatient clinic between January 2005-January 2011 and underwent liver biopsy were included in the study. Overall, 246 patients with hepatitis B and 151 patients with hepatitis C were enrolled. According to the evaluation based on the Ishak score, patients with a histological activity index (HAI) between 0-12 were defined as low activity, and those with an HAI between 13-18 were defined as high activity. In addition, patients with a fibrosis score of 0-2 were defined as low fibrosis, and those with a score between 3-6 were defined as high fibrosis; comparisons were made accordingly.

Results: In patients with hepatitis B, the mean GGT level was 38.86 ± 42.4 (IU/L) in the low activity group and 60.44 ± 44.4 (IU/L) in the high activity group ($p < 0.05$). In hepatitis B patients, the mean GGT level was 26.89 ± 14.83 (IU/L) in the low fibrosis group, whereas it was 65.60 ± 59.7 (IU/L) in the high fibrosis group ($p < 0.001$). There was no significant difference between HAI and fibrosis group with regard to GGT levels in the hepatitis C patients.

Conclusion: In conclusion, it is proposed that in patients with chronic viral hepatitis, GGT levels can be taken into consideration to predict advanced histological liver damage, especially in patients with hepatitis B.

Keywords: GGT, viral hepatitis, liver pathology

INTRODUCTION

Histopathological examination of the liver with percutaneous needle biopsy is currently the most valuable test performed to determine the degree of liver injury in chronic hepatitis and is important for guiding and monitoring treatment, as well as recognizing pathology in the liver. However, such an examination is an invasive procedure, cannot be carried out in some patients with bleeding and clotting abnormalities, and may lead to some complications, albeit rarely; furthermore, there is lack of patient compliance. All of these elements can be considered as drawbacks of biopsy. Thus, efforts, especially with regard to obtaining information on the histology of the liver during treatment monitoring, have long been exerted to find methods or direct or indirect mark-

ers that can replace liver biopsy or reflect histological changes.

In previous studies, histological abnormalities were detected in the liver in the majority of patients found to be HBsAg positive during screening. Additionally, histopathological damage was observed in the liver in all anti-HCV-positive blood donors, though histological damage was not observed in some patients with abnormal transaminase values, findings that have caused this subject to be considered controversial over the years. However, it is important to know to what extent biochemical changes are related to histological changes, both for accurately interpreting biochemical changes and understanding whether it is possible to evaluate histology without biopsy (1).

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Table 1. The mean age and laboratory results for chronic hepatitis B patients according to their HAI scores

Parameter	Age (year)**	GGT (IU/L)*	ALT (IU/L)	AST (IU/L)**	ALP (IU/L)	Thrombocyte (x10 ³ /mL)*	INR**	HBV DNA (IU/mL)
Low activity (Ishak score HAI=0-12)	40.82±12.81	38.86±42.4	76.58±72.1	47.77±42.5	79.36±23.2	225.37±60.8	1.04±.09	1.94x10 ⁷ ±9.88x10 ⁸
High activity (Ishak score HAI=13-18)	49.77±9.72	60.44±44.4	101.50±84.4	72.03±53.5	86.36±31.1	185.49±83.8	1.15±.15	2.82x10 ⁷ ±4.54x10 ⁸

GGT: gamma glutamyl transpeptidase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; INR: international normalized ratio; HAI: histological activity index
*p<0.05; **p<0.001

Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values are frequently used to predict the stage of chronic hepatitis histologically, but their ideal cutoff values and accuracy are unclear (2,3). Among some biochemical markers thought to be indicators of liver fibrosis, procollagen type III, hyaluronate, matrix metalloproteinase-1, and plasma transforming growth factor-beta 1 have been investigated, and it was proposed that their analysis may be beneficial in indicating an advanced stage of fibrosis (4-7).

Gamma-glutamyl transpeptidase (GGT) is a microsomal enzyme that can be isolated from hepatocytes and gall bladder epithelium, and increases in GGT values occur in various liver, gall bladder, and pancreatic diseases. It has also been shown that high serum GGT levels are observed in metabolic syndrome, cardiovascular diseases, and type-2 diabetes mellitus (8).

The aim of the present study was to investigate the relationship between GGT levels and histopathological status determined by biopsy in patients with chronic hepatitis B and C who were followed in the Gastroenterology Department of Uludağ University, Faculty of Medicine.

MATERIALS AND METHODS

Patients with chronic hepatitis B and C who were referred to the Uludağ University Faculty of Medicine Gastroenterology outpatient clinic between January 2005 and January 2011 and underwent liver biopsy were included in the study. The liver biopsy results of these patients and their laboratory results, obtained at most 1 week before biopsy, were evaluated retrospectively as biochemical parameters. ALT, AST, GGT, alkaline phosphatase (ALP) thrombocyte, international normalized ratio (INR), HBV DNA, and HCV RNA values were recorded.

The patients were divided into two groups, chronic hepatitis B and C, and were additionally divided into groups of according to histological activity index (HAI) and fibrosis scores obtained by the liver biopsy results. According to an evaluation based on their Ishak score, the patients with an HAI between 0-12 were defined as low activity, and those with an HAI between 13-18 were defined as high activity. In addition, patients with a fibrosis score of 0-2 were defined as low fibrosis, and those with a score between 3-6 were defined as high fibrosis; comparisons were made accordingly.

The study was retrospective and based on file records; therefore, it did not need approval by the institutional review board or local ethics committee.

The data were analyzed using SPSS 16.0 software (IBM Corp., NY, USA). To determine whether the data were distributed normally, a Kolmogorov-Smirnov test was used. Comparisons between groups were analyzed with Student's t-test or the Mann-Whitney U-test. The relationship between liver histopathology and the clinical and laboratory parameters was determined with a Pearson or Spearman correlation analysis, and a p value of <0.05 was considered statistically significant.

RESULTS

Chronic hepatitis B

Overall, 246 patients who underwent liver biopsy due to chronic hepatitis B were included in the study; 170 patients were male (69.1%), and 76 were female (30.9%). Their mean age was 41.9±12.75, with an age range of 18-71. In the classification made according to their HAI, 215 patients were in the low activity group (87.3%), and 31 were in the high activity group (12.7%). In the evaluation made according to their fibrosis score, 137 patients were found to have low fibrosis (63.8%), and 89 had high fibrosis (36.2%).

No significant difference was found between the HAI groups in terms of ALT, ALP, and HBV DNA levels. However, in the patient group with a high activity score, significant increases in age, AST, GGT, and INR were found, whereas the thrombocyte values were significantly low. In the low activity group, the mean GGT level was 38.86±42.4 (IU/L), whereas it was 60.44±44.4 (IU/L) in the high fibrosis group (p<0.05) (Table 1). No difference was found between the two groups with regard to sex.

No significant difference was found between the fibrosis groups in terms of HBV DNA levels. However, the patient group with a high fibrosis score showed a significantly older age and higher ALT, AST, GGT, ALP, and INR values, though thrombocyte values were found to be significantly lower. The mean GGT level was 26.89±14.83 (IU/L) in the low fibrosis group and was 65.60±59.7 (IU/L) in the high fibrosis group (p<0.001) (Table 2). There was no difference between the two groups in terms of sex.

Table 2. The mean age and laboratory results for chronic hepatitis B patients according to their fibrosis scores

Parameter	Age (year)**	GGT (IU/L)**	ALT (IU/L)*	AST (IU/L)**	ALP (IU/L)*	Thrombocyte (x10 ³ /mL) **	INR**	HBV DNA (IU/mL)
Low fibrosis (Ishak score=0-2)	38.18±12.16	26.89±14.93	68.37±57.97	41.59±28.84	75.63±22.17	231.45±57.1	1.04±0.08	2.40x10 ⁷ ±1.17x10 ⁸
High fibrosis (Ishak score=3-6)	48.47±11.05	65.60±59.70	97.98±93.06	66.15±60.28	87.05±26.40	198.97±73.8	1.10±.13	1.35x10 ⁷ ±2.9x10 ⁸

GGT: gamma glutamyl transpeptidase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; INR: international normalized ratio; HAI: histological activity index
*p<0.05; **p<0.001

Table 3. The mean age and laboratory results for chronic hepatitis C patients according to their HAI scores

Parameter	Age (year)**	GGT (IU/L)	ALT (IU/L)	AST (IU/L)*	ALP (IU/L)*	Thrombocyte (x10 ³ /mL) **	INR**	HCV RNA (IU/mL)
Low activity (Ishak score HAI=0-12)	48.95±13.42	48.43±41.11	64.84±60.91	47.04±39.6	78.08±25.7	245.50±71.5	1.02±.11	2.20x10 ⁶ ±4.02x10 ⁸
High activity (Ishak score HAI=13-18)	55.54±7.18	73.80±64.60	89.00±67.31	71.88±36.5	93.67±35.3	172.82±71.3	1.10±.30	2.05x10 ⁷ ±3.06x10 ⁸

GGT: gamma glutamyl transpeptidase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; INR: international normalized ratio; HAI: histological activity index
*p<0.05; **p<0.001

Table 4. The mean age and laboratory results for chronic hepatitis C patients according to their fibrosis scores

Parameter	Age (year)**	GGT (IU/L)	ALT (IU/L)**	AST (IU/L)**	ALP (IU/L)*	Thrombocyte (x10 ³ /mL) **	INR*	HCV RNA (IU/mL)
Low fibrosis (Ishak score=0-2)	47.12±14.25	47.74±43.57	55.10±44.48	40.27±24.71	75.97±24.18	255.59±63.3	1.01±.11	2.28x10 ⁶ ±4.50x10 ⁸
High fibrosis (Ishak score=3-6)	53.83±9.39	58.79±48.82	85.39±75.79	65.55±50.25	87.18±31.28	199.79±83.0	1.07±.21	2.02x10 ⁷ ±2.70x10 ⁸

GGT: gamma glutamyl transpeptidase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; INR: international normalized ratio
*p<0.05; **p<0.001

Chronic hepatitis C

In the present study, 151 patients who underwent liver biopsy due to chronic hepatitis C were investigated; 72 patients were male (47.7%), and 79 were female (52.3%). The mean age of the patients was 50.2±12.66, with an age range of 19-75. In the classification made according to their HAI, 122 patients had low activity (80.8%), and 29 had high activity (19.2%). In the evaluation made according to their fibrosis score, 81 had low fibrosis scores (53.6%), and 70 had high fibrosis scores (46.4%).

There was no significant difference between the HAI groups with regard to ALT and HCV RNA levels, though a near-significant difference was found for GGT levels (p=0.052). However, a significantly older age and higher AST, ALP, and INR levels were found in the patient group with a high activity score, whereas thrombocyte values were significantly low (Table 3). No difference was found between the two groups in terms of sex.

No statistically significant difference was found between the fibrosis groups in terms of HCV RNA and GGT levels. In the low fibrosis group, the mean GGT level was 47.74±43.57; in the high fibrosis group, the mean GGT level was 58.79±48.82 (p: 0.11). In

addition, a significantly older age and increased ALT, AST, ALP, and INR values were found in the patient group with high fibrosis; thrombocyte values were significantly low (Table 4). No difference was found between the two groups in terms of sex.

The correlation analyses of the clinical and laboratory parameters with activity and fibrosis in both viral hepatitis groups are given in Table 5 and Table 6.

DISCUSSION

In chronic viral hepatitis cases, liver biopsy is currently used as the standard to determine histological activity and the level of fibrosis. However, an increased diagnosis and treatment capability with rapidly developing technology, which may be needed even after transplantation, makes it necessary to search for noninvasive tests. Although their superiority over biopsy has not been confirmed yet, the usefulness of many probable fibrosis markers in serum is being investigated in clinical studies of cases with chronic viral hepatitis (8).

Gamma-glutamyl transpeptidase, a membrane enzyme found in the ductal and canalicular cells of the liver, has been investi-

Table 5. The correlation analyses of clinical and laboratory parameters with activity in viral hepatitis groups

	Hepatitis B		Hepatitis C	
	r	p	r	p
Age	0.233	<0.001	0.17	0.03
GGT	0.223	0.01	0.20	0.052
ALT	0.114	0.08	0.14	0.08
AST	0.208	<0.001	0.23	0.005
ALP	0.100	0.21	0.20	0.02
Thrombocyte	-0.234	0.002	-0.370	<0.001
INR	0.235	<0.001	0.300	<0.001
HBV DNA	0.027	0.74		
HCV RNA			-0.140	0.88

GGT: gamma glutamyl transpeptidase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; INR: international normalized ratio

Table 6. The correlation analyses of clinical and laboratory parameters with fibrosis in viral hepatitis groups

	Hepatitis B		Hepatitis C	
	r	p	r	p
Age	0.388	<0.001	0.229	<0.001
GGT	0.440	<0.001	0.116	0.11
ALT	0.193	0.003	0.283	<0.001
AST	0.266	<0.001	0.396	<0.001
ALP	0.228	0.004	0.202	0.02
Thrombocyte	-0.239	<0.001	-0.397	<0.001
INR	0.267	<0.001	0.226	0.01
HBV DNA	-0.054	0.516		
HCV RNA			-0.024	0.79

GGT: gamma glutamyl transpeptidase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; INR: international normalized ratio

gated and used since the 1960s. The extracellular metabolism of glutathione, which is the main antioxidant molecule in cells, is controlled by GGT. Irrespective of the cause, abnormal levels of GGT are present in many patients with liver injury, constituting a sensitive test, especially in cholestasis conditions. Nonetheless, GGT levels can increase in many diseases and conditions (e.g., diabetes, pancreatitis, obesity, alcohol, or drug use), which decreases its specificity. For example, GGT may frequently be high in non-alcoholic steatohepatitis (NASH) patients in association with obesity and diabetes, but it is not used diagnostically (9).

In a study carried out in our country investigating the predictive value and benefit of noninvasive markers in the determination of significant fibrosis in chronic viral hepatitis, age, GGT, and thrombocyte values were found to be significantly associated with the degree of fibrosis. However, it was stated that these non-invasive markers cannot replace biopsy (10). In another study published in our country, although no relation was found in patients with chronic hepatitis C between ALT, AST, and GGT values and the overall HAI and the parameters making up this index, a significant relationship was found between HAI and these biochemical markers in patients with hepatitis B (1). After logistic regression analysis in a study involving 328 patients overall with hepatitis B, it was concluded that thrombocyte, ALT, AST, and GGT levels were the best markers of the level of fibrosis (11).

Many studies have been carried out to investigate easily accessible laboratory tests that can indicate marked fibrosis and cirrhosis in patients with chronic hepatitis C. However, the sensitivity of the results obtained in these studies is low, and the results of many studies have not been corroborated in different patient groups.

According to the multivariate analysis results of a retrospective study measuring the diagnostic value of several parameters

and scores in the determination of significant fibrosis in patients with chronic hepatitis C, AST, GGT, and α -2 macroglobulin were found to have independent predictive value (12). In another study investigating the predictive value of some basic biochemical marker combinations in the determination of clinically significant fibrosis in hepatitis C, the following markers were established as the most important: α -2 macroglobulin, α -2 globulin (or haptoglobin), γ -globulin, apolipoprotein A1, GGT, and total bilirubin. Accordingly, a non-invasive method measuring activation and fibrosis in the liver of patients with chronic hepatitis using these markers was developed (13). In a similar study carried out on patients with chronic hepatitis C, a model using age, cholesterol, thrombocyte number, and prothrombin time, along with GGT, was developed, and it was stated that this method can be used to indicate a lack of significant fibrosis (14).

In studies on patients treated for chronic hepatitis C, it was established that the success rate of interferon treatment was low in patients with high GGT levels, which was related to advanced fibrosis; hence, it was thought that serum GGT levels may be an important parameter in estimating the degree of fibrosis in patients with viral hepatitis (15,16).

In the present study, unlike previous studies, no significant relationship was found between the degree of fibrosis and GGT levels in patients with chronic hepatitis C. Regardless, GGT levels were found to be higher in patients with a high activity score than in patients with a low activity score, with a difference approaching statistical significance ($p=0.052$).

Significant results have usually been obtained in studies measuring the diagnostic value of non-invasive markers in patients with chronic hepatitis B. In one such study, a model was developed with five biochemical markers, including aminotransferases and GGT, and this model was stated to be a valuable

marker of hepatitis B-related activity and fibrosis (17). Another study developing a simple model including routine laboratory markers showed that a model involving GGT, thrombocyte, and albumin yielded significant results in determining the degree of fibrosis in patients with chronic hepatitis B (18). In a study with 70 chronic hepatitis B patients, it was concluded that GGT reflected inflammation in the liver better than ALT and AST and that GGT may have an important role in the clinical evaluation of chronic hepatitis B (19).

Evaluating the relationship between serum GGT levels and fibrosis score, Aygün et al. demonstrated by liver biopsy in patients with chronic hepatitis B that an increase in serum GGT was associated with advanced age, high AST and ALT levels, low albumin levels, and high fibrosis. Therefore, it was thought that high serum GGT levels may be considered an indicator of an advanced stage of fibrosis in patients diagnosed with chronic viral hepatitis B (8).

In the present study, compatible with previous studies, an increase in GGT levels in patients with hepatitis B was found to be significantly related to the activity and degree of fibrosis in the liver. Although there was no significant difference between HAI groups in terms of ALT, AST, and ALP levels, a significant difference was found between fibrosis groups.

In conclusion, it is thought that in patients with chronic viral hepatitis, GGT levels can be taken into consideration to predict advanced histological liver damage, especially in patients with hepatitis B. It is evident that some experimental models, including GGT, play an important role in the determination of the degree of liver fibrosis. Unlike other studies, in our study, no significant difference was found in hepatitis C patients between activity and fibrosis groups in terms of GGT levels. This study, which was carried out to determine noninvasive indicators of liver damage caused by two viruses leading to chronic viral hepatitis, reports results different from those previously reported, especially regarding GGT. These results should be corroborated with further studies including larger patient series.

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