ORIGINAL ARTICLE

Correlation of Serum Alanine Aminotransferase and Aspartate Aminotransferase Levels to Liver Histology in Chronic Hepatitis C

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ABSTRACT

Objective: To assess the correlation of serum alanine aminotransferase and aspartate aminotransferase levels to severity of disease on liver biopsy in patients of chronic hepatitis C.

Study Design: Descriptive study.

Place and Duration of Study: Department of Gastroenterology at Military Hospital, Rawalpindi, from January 2006 to February 2007.

Methodology: One hundred and seven diagnosed non-cirrhotic chronic hepatitis C adult patients were included. Serum alanine aminotransferase and aspartate aminotransferase levels were determined. Knodell histopathological Index was determined on liver biopsy. The correlation and regression value between serum alanine aminotransferase levels and liver histology and serum aspartate aminotransferase and liver histology in chronic hepatitis C patients was determined using Pearson correlation analysis.

Results: Patients of chronic hepatitis C had raised serum alanine aminotransferase and levels with the mean baseline level of 93 International units per litre (IU/L) with a range of 13–383 IU/L. Serum aspartate aminotransferase levels were also elevated with mean baseline level of 59.65 IU/L ranging from 18–370 IU/L. On liver biopsy based on Knodell histopathological Index, 47.7% of patients had mild, 39.9% had moderate and 13.1% had severe disease. There was significant association between serum alanine aminotransferase levels severity of the disease on liver biopsy ($p < 0.03$) with weak positive correlation between the two ($r = 0.217$). There was also significant association between serum aspartate aminotransferase levels and severity of the disease on liver biopsy ($p < 0.001$) with weak positive correlation between the two ($r = 0.32$).

Conclusion: The serum alanine aminotransferase and serum aspartate aminotransferase levels do not indicate the severity of the disease on liver biopsy in chronic hepatitis C patients.

Key words: *Chronic hepatitis C. Liver biopsy. Serum alanine aminotransferase. Serum aspartate aminotransferase.*

INTRODUCTION

Chronic hepatitis C is one of the chronic infectious diseases of the liver. It may lead to cirrhosis of liver in 20-30% of the patients and hepatocellular carcinoma in 5-10% of cirrhotic patients. According to the report of World Health Organization (WHO), approximately 170 million individuals in the world population are suffering from this disease.[1] In Pakistan, the number of patients diagnosed to have chronic hepatitis C is on the increase. The prevalence rate of anti-hepatitis C virus (HCV) antibodies in Pakistani population, reported mostly in hospital based studies in patients, blood donors and in general population is 0.5-11.7%.[2-6]

Chronic hepatitis C is diagnosed by persistently raised serum alanine aminotransferase (S. ALT) and serum aminoaspartate (S. AST) levels, serological tests which detect anti-HCV in serum and molecular tests which detect HCV ribonucleic acid (RNA) genome and assess the qualitative and quantitative viral load.[7] Although raised S. ALT and S. AST levels indicate liver disease, in 25-30% of patients of chronic hepatitis C, the serum ALT and S. AST levels return back to normal after 12 weeks of infection despite progression of disease.[8] Some studies reveal that most of the patients with normal or near normal ALT levels show slow progression of the disease and milder liver lesions on histology.[8-12] Whereas, in some studies serum ALT and S. AST levels were not the reliable indicator of histological severity of the disease.[13-16] Liver biopsy though not necessary for the diagnosis of chronic hepatitis C but is considered the "gold standard" for assessing the severity of the disease.[13-19] Liver biopsies are scored by Knodell histopathological index (HPI) based on inflammatory, necrotic and fibrotic changes.[8] Liver biopsy has its own limitations and risks. In many countries, liver biopsy is replaced by authenticated non-invasive biochemical markers. A total of 14 validated serum biomarkers have been identified between 1991 and 2008.[10] In Pakistan, many health authorities still rely on persistently raised serum ALT and S. AST as indicator to commence the

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anti-viral therapy and liver biopsy is not done as a mandatory diagnostic tool. Moreover, serum ALT and S. AST are also used to follow-up the patients already treated to rule out relapse of the disease.

This study was designed to determine the co-relation of serum levels of alanine aminotransferase and aspartate aminotransferase to severity of the disease on liver biopsy in patients of chronic hepatitis C.

METHODOLOGY

This study was conducted in the Department of Physiology at Army Medical College and Military Hospital, Rawalpindi, Pakistan, from January 2006 to February 2007 to assess the correlation of S. ALT and AST levels to severity of the disease on liver biopsy in patients of chronic hepatitis C. Approval from Ethical Committee of Army Medical College, Rawalpindi was obtained before the commencement of the project. One hundred and seven (80 males and 27 females) non-cirrhotic chronic hepatitis C patients, aged between 18-48 years were included in this study by non-probability convenience sampling after written and informed consent. Criteria for non-cirrhotic chronic hepatitis C diagnosis was persistently raised S. ALT above normal (> 42 IU/L– International Units/Litre), positive anti–HCV anti-bodies by Fourth Generation ELISA (Enzyme Linked Immuno Sorbent Assay) Method, positive HCV RNA by polymerase chain reaction (PCR) and liver biopsy compatible with diagnosis of chronic hepatitis C on the basis of Knodell HPI. In Knodell histopathological iIndex (HPI) stage shows degree of fibrosis in liver tissue and grade shows inflammatory changes in liver induced by chronic hepatitis C. Cirrhosis was ruled out on the basis of physical examination, ultrasonography of abdomen and liver biopsy. Patients treated previously with interferon (IFN) – alpha-2b and/or ribavirin and pregnant female patients were excluded from the study on the basis of history, physical examination and laboratory tests including urine for pregnancy test. Patients were selected keeping in view the inclusion and exclusion criteria. All patients were briefed about the study and written and informed consent was taken. Blood samples were drawn under aseptic measures for baseline S. ALT and S. AST levels and qualitative HCV RNA by PCR. Liver biopsy was performed according to the procedure protocol and grading of the severity of the disease was determined by Knodell HPI in these patients. Mean and standard deviation of age, S. ALT and S. AST was determined. Percentage of severity of the disease on the basis of Knodell HPI was also determined. The association between S. ALT and S. AST levels and severity of disease on histopathology was assessed by chi-square test. Pearson correlation and regression value (r-value) between S. ALT and S. AST levels with severity of chronic hepatitis C on liver biopsy was determined. Statistical analysis was done on SPSS 15. Statistical significance was set at < 0.05.

RESULTS

A total of 118 patients were screened for the study. Out of them, 11 patients were excluded from the study due to presence of decompensated liver disease on the basis of history of upper gastrointestinal bleed, ultrasonographic evidence of cirrhosis of liver or presence of ascites. A total of 107 patients met the inclusion criteria and were included in the study.

The demographic and mean values of age, male to female ratio, baseline S. ALT and S. AST levels and histology at liver biopsy are shown in Table I. The age ranged from 18 -48 years with mean of 35 $\pm$ 7.12 years. Among 107 patients of chronic hepatitis C, 80 were males and 27 were females (Table I). All patients underwent liver biopsy to be assessed for the degree of necroinflammatory changes and stage of fibrosis because of HCV. These histopathological changes were further sub-grouped on Knodell histopathological index scoring system (HPI). Out of 107 patients, a total of 51 (47.7%) had mild disease on the basis of Knodell HPI while 42 patients (39.3%) had moderate and 14 (13.1%) had severe disease on liver biopsy (Table I). The mean baseline ALT level was 93 $\pm$ 62.83 IU/L with a range of 13–383 IU/L. Nine point three percent of the patients had normal S. ALT levels and 70% of them showed mild and 30% showed moderate disease on histological basis. Seventy one percent of the patients showed 2-3 folds increase in their ALT levels and histological severity was mild to moderate. Only 7.4% of the patients showed 4 folds increase in ALT and among them 62% had severe and 38% showed moderate disease on liver biopsy. Eleven percent of patients had ALT increase to 5 folds or more and among them 50% had moderate, 33% had mild and 17% had severe histological severity. There was significant association between S. ALT levels and severity of the disease on liver biopsy ($p < 0.03$) with weak positive correlation between the two ($r = 0.217$).

Table I: Demographic features of patients of chronic hepatitis C.

Characteristics	Values
Age Mean $\pm$ SD	35 $\pm$ 7.12 years
Sex Male/female ratio	80/27
S. ALT Mean $\pm$ SD (range)	93 $\pm$ 62.83 13-383 IU/L
S. AST Mean $\pm$ SD (range)	59.65 $\pm$ 42.47 18-370 IU/L
Knodell HPI on liver biopsy (percentage)	
Mild	47.7%
Moderate	39.3%
Severe	13.1%

Serum aspartate aminotransferase levels were also elevated with mean baseline level of 59.65 $\pm$ 42.47 IU/L with a range of 18–370 IU/L. Among 107 chronic hepatitis C patients, 31 patients (29%) had normal baseline S. AST levels. Among patients with normal

S. AST levels, 58% had mild; 32% had moderate and 10% had severe liver disease on Knodell HPI of liver biopsy. Among 107 patients, 26 (29%) patients had raised S. AST levels up to 2-3 folds; 42% had mild, 38% had moderate and 19% had severe disease on liver biopsy. Only 5% of patients had markedly 4-5 fold raised S. AST levels and majority of them (60%) had moderate disease on liver biopsy. There was significant association between S. AST levels and severity of the disease on liver biopsy ($p < 0.001$) with weak positive correlation between the two ($r = 0.32$).

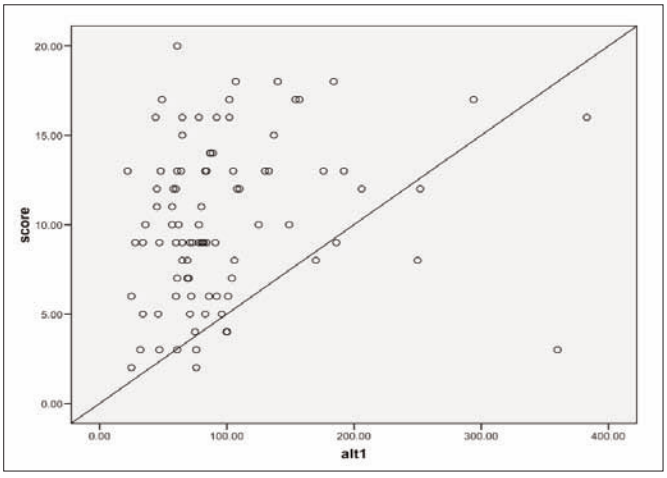

Figure 1: Serum ALT levels (Knodell HPI).

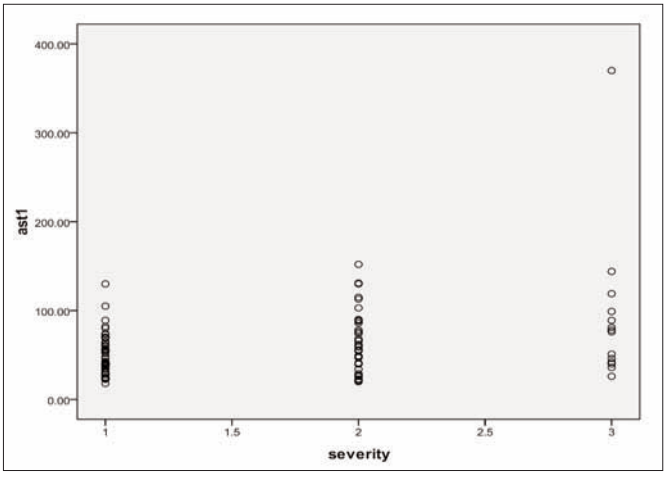

Figure 2: Serum AST levels (Knodell HPI).

DISCUSSION

There are varying results reported regarding the validity and reliability of S. ALT and S. AST levels as indicator of severity of hepatitis C.[8-12] Persistently raised S. ALT levels is usually taken as an indicator for commencement of the treatment for the disease or as indicator of relapse of the HCV disease from patients' perspective, although CHC patients may have normal S. ALT levels during disease or on relapse of the disease. This study was carried out to determine the correlation between S. ALT and S. AST with severity of the disease based on liver biopsy.

Liver biopsy in patients of chronic hepatitis C shows varying degrees of presence of inflammation, fibrosis and necrosis.[7] Histological picture comprises of lymphoid aggregates in hepatocytes and bile ducts, steatosis and fibrous tissue in liver parenchyma.[7] In Knodell histopathological index (HPI) stage shows degree of fibrosis and grade shows inflammation.[7] In this study, 47.7% of patients had mild liver disease, 39.9% had moderate and 13.1% had severe liver disease based on Knodell HPI.

In this study, most of the patients had S. ALT levels between 2-3 times normal although 9.3% of the patients had normal S.ALT levels as reported in literature.[11,16,18] Giannini *et al.* revealed that most of the patients with normal ALT levels have mild disease, slow progression and better response to anti-viral treatment. In this study only 9.3% of the patients had normal baseline S. ALT levels and 70% 0f them showed mild liver disease. This is in accordance to other studies reported in literature in which patients with normal ALT levels had mild disease.[8,10,11] Dor-Mohammadi *et al.* mentioned that normal ALT levels indicate milder liver disease but some patients with normal ALT may have advanced liver disease. In this study, 70% of the patients with normal ALT had mild, 30% of patients with normal ALT had moderate disease in accordance with Dor-Mohammadi's findings but none of the patient with normal S.ALT had severe histological picture on liver biopsy.

Few studies do not support the association of normal S.ALT levels with mild liver disease. Sanai *et al.* reported no statistically significant difference in necro-inflammatory scores, mean fibrosis grading and hepatic steatosis in patients with normal ALT levels and those with elevated S.ALT levels.[21] The only positive association in their study was increased frequency of normal S.ALT in females as compared to male patients of CHC. However, in this study among 9.3% of patients having normal S.ALT, the sample size of female patients was too small to draw a statistical conclusion. More elaborate study with large sample size of chronic hepatitis C patients with normal S. ALT comprising of both male and female patients is required to determine the correlation of normal serum ALT with severity of the disease and gender of the patient and its association with response to therapy.

Haber *et al.* discovered that ALT levels do not predict liver histological status in chronic hepatitis C although more than 10 fold rise in ALT suggest piecemeal necrosis.[13] In this study no correlation was found between ALT levels and liver histological severity ($r=0.217$). Only 11% of patients showed ALT more than 5 folds but among them only 17% had severe disease on histology in contrast to the Haber study.[13] Michealsen *et al.* reported that S. AST

is more useful than ALT as an indicator of histological severity of the disease.[14] Lee *et al.* also reported that serum ALT does not show positive co-relation with histological severity of the disease but shows a linear relationship with piecemeal necrosis.[17] Kobayashi *et al.* discovered that there is linear relationship in serum ALT and histological picture in treated patients of chronic hepatitis C,[9] which was also the case in this study as depicted by significant p-value (0.03). Toyoda *et al.* reported that age, gender and liver fibrosis independently influence serum ALT levels in patients with chronic hepatitis C. In younger patients, serum ALT levels were higher in males with milder disease than in females but when in older patients, ALT was higher with severe disease. In this study, no association was found between ALT and severity of the disease based on age group or gender of the patient. Vardar *et al.* compared S. ALT and Knodell HPI by liver biopsy in 156 patients of CHC but did not find any statistically significant difference in the mean value of ALT between patients with stage 0-1 and those with stage 3-4,[22] as found in this study.

S. AST levels however, were within normal range in 29% of the patients and majority of them had mild liver disease on biopsy. The wide range of S. AST indicates diverse biochemical response in different individuals. However, in this study, the lower value of S. AST was associated with milder disease based on histological picture as reported in literature.[10-11] Vardar *et al.* in their study found no association between S. AST levels and liver fibrosis indicating S.AST as poor indicator of severity of disease,[22] as found in this study. Similarly, Bartos *et al.* did not find positive association between aminotransferase levels and liver fibrosis in chronic hepatitis C patients,[23] in accordance with this study.

CONCLUSION

The serum alanine aminotransferase and amino-tranferase levels do not indicate the severity of the disease on liver biopsy in chronic hepatitis C patients.

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