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ASSOCIATION OF PRETREATMENT LIVER HISTOLOGY WITH SERUM ALANINE AMINOTRANSFERASE LEVEL AND BODY MASS INDEX IN HCV-RNA POSITIVE PATIENTS

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ABSTRACT

Objective: To assess association of pretreatment liver histology with serum Alanine aminotrasferase (ALT) level and Body Mass Index (BMI) in HCV positive patients.

Material and Methods: A prospective study conducted at Pathology and Gastroenterology Departments of CMH Peshawar from June 2007 to December 2008 included 100 adult HCV RNA positive patients. Percutaneous liver biopsy was performed and analyzed for necroinflammation, fibrosis and steatosis. The observations were recorded and analyzed by using SPSS 13.

Results: Fifty-four male and 46 female subjects between ages of 13-70 years were included in the study. 66% patients had ALT levels of 42-89 IU/L, 74.2% had grade II disease, 12.1% grade III disease. 34% patients had ALT levels of > 90 IU/L. 56% had grade II & 38.2% grade III disease. Correlation of ALT with disease grade was significant, P value 0.029. Association of ALT with disease stage was not significant, P value 0.139. Fifty-six percent of obese patients had elevated serum ALT. Association of BMI with ALT was significant P value 0.034.

Conclusion: Assessment of pretreatment liver histology and its association with ALT & BMI is helpful to determine the extent of hepatic damage and presence of steatosis.

Key Words: Alanine aminotransferase, Body Mass Index, Chronic Hepatitis C.

INTRODUCTION

Hepatitis C virus (HCV) infection is a tremendous global problem and remains the major cause of significant morbidity and mortality worldwide especially in developing countries[1]. In Pakistan, it is estimated that 10 million people i.e. 6% of the population, are infected with HCV[2]. Elevated serum Alanine aminotransferase (ALT) was considered as criterion for liver biopsy and treating patients of chronic hepatitis C (CHC)[3]. Half of the untreated patients show normal or minimally elevated serum ALT levels[4]. But in recent years 20% of CHC patients have normal ALT levels which may not reflect the course of the disease accurately[5,6]. In various studies significant correlation of elevated ALT levels to the disease grade and stage of fibrosis was found[7]. Almost all the patients with elevated ALT levels show some degree of fibrosis[8].

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According to the World Health Organization (WHO), there are now over 1 billion overweight adults worldwide, including at least 300 million obese individuals[9].

The relationship between obesity and liver disease was largely unrecognized until the recognition of nonalcoholic fatty liver disease (NAFLD) as a distinct clinical entity[10]. An elevated body mass index (BMI) is also associated with increased steatosis in patients with CHC, affecting the sustained virological response (SVR)[11]. Histological evaluation of liver biopsies in a number of studies showed that steatosis was present in 50% of cases[12]. No laboratory test can definitely establish the diagnosis of necroinflammation, steatosis and fibrosis. The only abnormality may be elevated serum ALT level but not in all patients[13]. Studies from Pakistan have indicated a high prevalence rate of steatosis as high as 65.7%[14]. Regardless of etiology, elevated ALT levels and increased BMI contributes to hepatic damage in terms of necroinflammation, fibrosis and steatosis and is also a risk factor for development of CHC[15]. BMI also influences serum ALT levels in patients with CHC[16]. ALT is still commonly used serum marker of liver cell injury, a reliable para-meter to monitor fluctuation in

liver inflammation as there is no current alternative method to monitor it. Interpretation of ALT levels in follow up of patients with CHC is important by correlating various clinical parameters like age and sex of patient and histological evaluation[17]. Based on these facts, liver biopsy is important in patients with chronic hepatitis C infection. It helps in evaluating the grade, stage of disease, grade of steatosis. The primary aim of this study was to assess the association of serum ALT levels and BMI with disease grade and stage and grade of steatosis in pretreatment liver biopsy for better management of the patients in terms of antiviral treatment.

MATERIAL AND METHODS

A prospective study was conducted at Gastroenterology ward and Pathology department of CMH Peshawar from June 2007 to December 2008 by randomly sampling 100 consecutive adult patients including males and females between age of 13-70 years. The patients were admitted for liver biopsy after fulfilling the pre-requisites. Biopsy material was processed appropriately, H&E and reticulin stains were used for evaluation by an experienced histopathologist using various scoring systems i.e. Modified Histological Activity Index for necroinflammation, Ishak scoring for fibrosis, Brunt's classification for grading steatosis. BMI was calculated and expressed as kg/m^2. Relevant investigations including blood complete, serum ALT, serum Bilirubin, Prothrombin time, screening test for Anti HCV Antibodies and HbsAg, HCV RNA confirmation by PCR and ultrasonography of liver were also carried out. Subjects excluded from the study were less than 13 years and more than 70 years, decompensated cirrhosis, diabetes mellitus, hemophilic, HbsAg Positive, alcoholic and patients with other co-morbid illness. The clinical, biochemical and histological variables were categorized, analyzed by using SPSS 13.0 and correlated by applying Pearson's test. Statistical significance was taken at the 5% level i.e. P value < 0.05.

RESULT

The study included 54 males and 46 females with age range of 13-70 years. Serum ALT level ranged from 42 to 237 IU/L. Not a single patient had normal ALT level. ALT levels were categorized as less or greater than twice upper normal limit (TUNL) i.e. <90 IU/L or >90 U/L respectively. Association of serum ALT levels with disease grade is summarized in Table 1. A significant correlation was seen between ALT levels and disease grade; Pearson correlation coefficient (r) 0.58, P value =0.029, suggesting that ALT levels increase with an increase in disease grade.

Disease stage i.e. fibrosis, was assessed with serum ALT levels. Out of 66 patients with <TUNL of ALT, 6 patients (9.1%) were in stage 0, 46 (69.7%) were in stage I, 12 (18.2%) were in stage II and 2 (3.0%) were in stage III of the disease. Out of 34 patients in >TUNL of ALT level group, none (0%) was in stage 0, 21 (61.8%) in stage I, 12 (35.3%) in stage II and 1 (2.9%) in stage III of the disease. Association of ALT level with disease stage is non- significant; P value = 0.139. Association of BMI with ALT & its impact on liver histology was also evaluated. 56.25% of obese patients had elevated levels of serum ALT (TUNL). This association of BMI with ALT was significant; r = 0.63, P value = 0.034. The correlation of BMI with steatosis is highly significant; r =0.67, P value= 0.0001, suggesting higher BMI is associated with increasing grade of steatosis. Association of serum ALT levels with steatosis was also studied. (Higher grades of steatosis were observed in 100% of patients with higher ALT levels i.e. >TUNL; r = 0.52, P value = 0.001 (Table 2).

Table1: Association of raised serum ALT levels with disease grade

Histological Grade	ALT < 90IU/L n (%)	ALT > 90IU/L n (%)	P value	R value
Grade 0	1 (1.5)	0 (0)	0.029	0.58
Grade I	7 (10.6)	1 (2.9)		
Grade II	49 (74.3)	19 (56)		
Grade III	8 (12.1)	13 (38.2)		
Grade IV	1 (1.5)	1 (2.9)		

n= number of patients; r= Pearson's correlation coefficient

Table 2: Association of serum ALT levels with Steatosis

Steatosis (n)	ALT < 90IU/L n (%)	ALT > 90IU/L n (%)	P value	R value
Grade 0 (59)	46 (78)	13 (22)	0.001	0.52
Grade I (29)	15 (51.7)	14 (48.3)		
Grade II (8)	4 (50)	4 (50)		
Grade III (4)	0 (0)	4 (100)		

n = number of patients

DISCUSSION

The HCV infection causes wide clinical spectrum of hepatic diseases ranging from acute hepatitis to chronic hepatitis, cirrhosis and HCC. Histological assessment of liver biopsy remains the 'gold standard' for assessment of necroinflammation, fibrosis and steatosis and is the only way to determine the extent

of fibrosis and steatosis in the liver[3]. The present study was conducted to see the association of serum ALT levels and BMI with liver histology in CHC patients before the start of antiviral therapy.

The majority of those defined as PNALT subsequently have an abnormal serum ALT[20]. They have a similar risk of disease progression to other HCV infected patients and therefore warrant the same consideration with regard to treatment. Higher grades of inflammation were seen with elevated ALT levels i.e.56% in grade II and 38.2% in grade III disease. An Iranian study by Dor Mohammadi showed that patients with normal ALT (mean ALT 33 IU/L) had milder liver damage than those with abnormal ALT levels (mean 85 IU/L) [21].

The ALT levels were set at a cut- off value of twice the upper limit of normal (TULN) i.e. 90 U/L. This cut-off value of TULN of ALT was mentioned in study by Zeuzem who analyzed prospective data indicating flare up of ALT levels in 20% of patient which was TULN considered as baseline[22]. Most of these flare ups were there either as single episode or lasted for > 3 months[22]. Several studies to define normal ALT levels have been conducted. Data of these studies showed ULN of ALT levels ranged from 30 IU/L by Okanou et al[23] and 72 IU/L by Jamal[23]. Another study by Sjogren concluded that correlation between serum ALT level & degree of hepatic injury is weak favoring histological evaluation for clinical assessment of these patients[24]. Some of the studies showed that serum ALT levels do not reflect the level of necroinflammation and/or the presence of fibrosis in chronic hepatitis C[25]. Another study by McCormick presented weak association between ALT levels and necroinflammatory activity[26]. These studies suggest that extent of liver injury in patients with chronic hepatitis C infection is evaluated accurately by liver biopsy.

Slight ALT elevation (1.5 times the upper limits of normal) does not necessarily indicate liver disease. It does not follow the normal bell shaped distribution in the population. It has different distribution in different population group. Similarly, the ALT values are high in obese patient as they commonly have fatty liver. ALT levels should be set higher for more obese patient[27]. Elevated ALT levels had significant correlation with BMI and steatosis in present study i.e. ALT and BMI (P value =0.034); ALT and steatosis (P value =0.001). Elevated level of ALT was observed in 49 (36.7%) patients in overweight category, 9 of 16 (56.2%) in obese category. Elevated BMI in hepatitis C is also a predominant factor for elevated ALT levels [28] which was similar to the results of present study.

Correlation of ALT levels with disease stage i.e. fibrosis was non significant (P value =0.139) in present study. Similar results were shown by Liu concluding that serum ALT levels did not correlate with stage of fibrosis (P value = 0.06) but correlated with necroinflammatory activity statistically (P value =0.01)[29].

In a Serbian study, it was found that ALT levels in patients with CHC without fibrosis were lower than those with fibrosis. Histological activity index correlated well to the degree of fibrosis in this study. Serum ALT levels also correlated to fibrosis stage and was concluded that it should always be considered to monitor the disease progression[7]. Correlation of BMI with different grades of steatosis was highly significant (P value =0.0001) as in 41% of the patients steatosis was observed. The result matched with the study conducted by Negro[30] who reported prevalence of steatosis between 40-80%. It has been suggested that modest weight reduction showed improvement in serum ALT level & steatosis.

The correlation of ALT with steatosis was also significant (P value =0.001) in the present study suggesting higher grades of steatosis was associated with elevated ALT levels. These results were similar to the study results by Perumalswami who concluded that steatosis was associated with higher BMI & abnormal serum ALT levels[32]. In another study by [33]Rinella et.al. suggested that subjects with normal BMI & in absence of risk factors did not develop steatosis.

The correlation of steatosis with fibrosis was also evaluated in the study and was found non-significant (P value =0.116) which was similar to study results by Westin et al.[34] They however, found significant correlation between steatosis and necroinflammation in all HCV patients. The present study showed association of BMI with age and gender of the patient which was significant. Higher percentage of patients was in overweight category. The trend of elevated BMI was seen as the age advanced. A similar result were shown by Soresi et al who suggested that increasing age was associated with higher BMI & was a negative predictor of therapeutic response[35]. Females present in the study were mostly in overweight and obese category and presented in higher grades of steatosis. This matched with the study results by Codes et al suggesting that steatosis was more frequent in females with evaluated BMI who were menopausal[36].

CONCLUSION

Assessment of ALT and BMI and its association with pretreatment liver histology is helpful to determine the extent of hepatic damage and presence of steatosis as natural history of HCV infection in asymptomatic patients remains poorly characterized. Hepatic histological evaluation continues to be required for clinical assessment of patients with CHC. Larger studies are needed to evaluate these parameters by regular follow up of these patients. Pretreatment histological evaluation becomes mandatory by taking into account various clinical and

biochemical parameters to decide for better management of CHC patients.

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