ORIGINAL ARTICLE

Diagnostic Importance of Tumor Necrosis Factor Alphain Patients with Chronic Hepatitis C with and without Liver Cirrhosis

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ABSTRACT

AimObjective: To examine the diagnostic importance of tumor necrosis factor alphain chronic hepatitis C infection with or without liver cirrhosis.
Study Design: Prospective study.
Place and Duration of study: Department of Gastroenterology, Bolan Medical Complex Hospital, Quetta from 1st January 2019 to 30th June 2019.
Methodology: Total 90 Patients of chronic hepatitis C were divided into two groups, group I and II, Group I contains 45 patients with liver cirrhosis and group II consist of 45 patients without cirrhosis. The ageof these patients were between 30 to 50 years. The clinical history and examination were done while blood and liver biopsy samples were taken from all the patients and sent to the pathology department for diagnosis of chronic hepatitis C infection and liver cirrhosis.
Results: There were 50(55.56%) male patients and 40(44.44%) female patients. Mean age of patients 39.4±5.36. The serum TNF alpha was significantly higher in liver cirrhosis 71.96±18.35 than the patients without cirrhosis that was 42.72±13.5 with p-value <0.0001.
Conclusion: Application of TNF alpha is a good and accurate predictor of chronic hepatitis C with and without liver cirrhosis that would be essential to reduce the requirement of liver biopsy among chronic hepatitis C patients.
Keywords: Tumor necrosis factor alpha, Hepatitis C virus, Chronic hepatitis C, Liver disease

INTRODUCTION

About 3% of world's population is infected with hepatitis C virus, 170 million people throughout the world[1] and10-20% of chronically infected people progress to cirrhosis within 20 years.[2]Hepatitis C virus infection is a major health problem in Pakistan. It is an important reason behind the high morbidity and mortality rates with an incidence rate of about 25% according to a published report.[1]

Hepatitis C virus (HCV) is a key factor leading to chronic liver diseases (cirrhosis, hepatocellular carcinoma, etc.). The frequently targeted cells are hepatocytes which support HCV replication and the innate immune system gives response to the virus during HCV infection. The CD8 +T cells recognize viral peptides after 4 to 8 weeks that binds to human leukocyte antigen class I molecules in virus-infected hepatocytes.[1]

Among the cytokines, most attention was devoted to TNF-alpha (TNF-α). Serum TNF-α level elevates in chronic hepatitis C patients[3] and SVR has been found to be associated with the baseline increased production of TNF-α.[4] A positive correlation has been found between serum TNF-α levels and hepatic necro inflammatory score as well.[5]

It was demonstrated that HCV can directly induce the expression of TNF-α in hepatocytes.[6] Induction of TNF-α by HCV is dependent on Toll-like receptor (TLR) 7 and TLR8. Form recognition receptors seen in many cell types that participate in the innate immune response associated with viral infections and viral antigens are called TLRs.[7] TNF binds to two receptors, TNFR1 and TNFR2; the first is

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structurally expressed in most cells, the second is inducible and has a more limited expression pattern.[8] Upon receptor binding, TNF-α signals through a variety of cytosolic proteins, including TRADD (TNFR1-associated death domain protein)[9] and TNF receptor-associated factor 2[10], leading to I-B degradation and the subsequent release and nuclear translocation of nuclear factor (NF)-κB. Binding of NF-κB to gene promoters initiates transcription of numerous proinflammatory cytokines, including TNF-α, IL-6, IL-8, and CXCL-10 which suppresses HCV replication.[11,12]

TNF-α has been found to be higher in cirrhotic patients compared to CHC patients with r mild or no fibrosis.[13] Consistent with these results, our study also confirmed the association between TNF-α-308 GG polymorphism and fibrosis score (p=0.006). This may be explained by higher constitutive and inducible transcriptional activity of TNF. Nevertheless, in a meta-

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analysis of 11 different studies, no association was found between TNF-α-308G> A polymorphism and liver cirrhosis risk in both Caucasians and Asian populations.[14]

After circulating HCV particles reach the basolateral surfaces of hepatocytes, where the virus first binds to several receptors; the virus attaches to hepatocytes, it fuses the membrane, and enters the cytosol and starts to replicate.[15] Liver damage from HCV depends on both host's immune system-mediated reactions and viral cytopathic effects.[16] The CD95 frequency was significantly higher in HCV antigen-positive hepatocytes compared to uninfected cells.[17] TNF might play a role in hepatic necrosis and inflammation. Serum ALT level correlates with liver damage and we propose that elevated ALT levels are the hallmark of hepatocyte injury eventually leading to fibrosis as well as elimination of virus in CHC (the more inflammation, the more viral eradication).

This study was planned for detection TNF alpha among patients of chronic hepatitis C associated *with* and *without* liver cirrhosis. We also highlight the importance of predictive value of detection of liver fibrosis and cirrhosis by liver biopsy which is very expensive test as well as to causes many complications.

MATERIALS AND METHODS

This comparative/observational study was carried out at Department of Gastroenterology, Sandeman Provincial Hospital, Quetta from 1st January 2019 to 30th June 2019. A total of 90 patients of chronic hepatitis C were divided into two groups, group I and II. Group I included 45 patients with liver cirrhosis and group II had 45 patients without cirrhosis. The ages of these patients ranged between 30 to 50 years. These patients of CHC confirmed by the presence of hepatitis C virus (HCV) RNA. The biopsy reports of 45 chronic hepatitis C patients who went for liver biopsy were collected, and 45 patients of chronic hepatitis C without cirrhosis included along with 30 normal subjects in the study. Clinical information about these patients was obtained from medical records to assess inclusion criteria for this study. Laboratory tests were recorded. Statistical analysis was performed using SPSS-24.

RESULTS

In our study, 50 (55.56%) male patients while 40 (44.44%) were female. Mean age of patients 39.4±5.36 (Table 1). The serum TNF alpha was significantly higher in liver cirrhosis 71.96±18.35 than the patients without cirrhosis that was 42.72±13.5 with p-value <0.0001 (Table 2). Table 3 showed the parameters (ALT, AST, platelets,TNF-α and APRI)comparisons in two groups (patients with cirrhosis and without cirrhosis) ALT of patients with cirrhosis have mean (M=49.33) which is lower than group II mean (M=69.67) with p-value (<.001***).AST of patients with cirrhosis have mean (M=77.60) which is higher than group II with mean (M=57.77) with p-value (<.001***). Platelets count and APRI values were significantly lower in patients with cirrhosis with p-value <0.001.

Table 1: Age,sex and clinical finding among the patient of chronic hepatitis C infection (n=90)

Age	Sex	Clinical findings in patients with cirrhosis	Clinical findings of chronic HCV patients
39.4±5.36	Male 50 (55.56%) Female 40 (44.44%)	Ascites, splenomegaly,mild fever,bleeding tendency, loss of weight, indigestion, vomiting	Mild fever, bleeding tendency, Loss of weight, indigestion,vomiting

Table 2: Mean serum TNF-alpha value in both groups

Variables	Group I	Group II	P-value
TNF-alpha	71.96±18.35	42.72±13.5	0.002

Table 3: Comparison of ALT, AST, platelets, TNF-α and APRI in patients with and without cirrhosis and control groups

Variables	Group I	Group II	P-value
ALT (u/l)	49.33±20.38	69.67±35.02	<001***
AST(u/l)	77.60±19.96	57.77±21.45	<01**
PLT (10^9/l)	88.70±28.99	208.70±54.86	<01**
APRI	2.35±.69	732±.31	<.01**

**P<0.01 Significant, * **P<0.001 Significant, *P>0.05 = Non significant

DISCUSSION

Chronic hepatitis C is one of the commonest life threatening diseases found all over the world and associated with higher morbidity and mortality.[18] African and Asian countries report elevated infection rates compared to NorthAmerica and Northern and Western Europe.[19] Inflammatory cytokines including tumor necrosis factor-α (TNF-α) are an integral part of inflammation in chronic HCV infection. TNF-α mediates its effects by binding to two distinct cell surface receptors, namely, tumor necrosis factor receptor I (TNFR-I) and TNFR-II.[20] We conducted present study to examine the diagnostic importance of tumor necrosis factor alpha in patients of chronic hepatitis C and compare between liver cirrhosis and without cirrhosis. In this regard 90 patients of HCV infection were analyzed. In our study 50 (55.56%) female patients while 40 (44.44%) were male. Mean age of patients 39.4±5.36. These results showed similarity to many previous studies in which had a higher male versus female population (55% to 62%) and average age of patients with HCV infection was reported to be 40 years.[21,22]

In present study statistical analysis revealed highly significant increase in the mean value of serum TNF-α in patients with liver cirrhosis compared with healthy controls in this study. This result is in agreement with that of Tilg et al[23], who studied serum level of different cytokines (including TNF-α) in patients with chronic liver diseases. They found that serum levels of TNF-α increase significantly in chronic liver diseases and reached its maximum in decompensated cirrhosis. They suggested that this elevation in the cytokine levels represent a consequence of liver dysfunction rather than inflammatory disease.[24] Zhang et al[25] studied the serum level of TNF-α and interleukin (IL)-6 in patients with chronic liver diseases

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and reported that serum level of TNF-α was significantly elevated in patients compared with controls. They suggested that high serum level of TNF-α is an important mediator in the pathogenesis of liver necrosis and alterations in microcirculation[21]and similar results were reported by Yuan et al[26] and Lee et al.[27]

We found that ALT of patients with cirrhosis have mean (M=49.33) which is lower than group II mean (M=69.67) with p-value (<.001).AST of patients with cirrhosis have mean (M=77.60) which is higher than group II with mean (M=57.77) with p-value (<.001). Platelets count and APRI values were significantly lower in patients with cirrhosis with p-value <0.001. These results were comparable to many of previous studies.[28,29]

CONCLUSION

The application TNF alpha is a good and accurate predictor value of chronic hepatitis C with and without liver cirrhosis that would be essential to reduce the requirement of liver biopsy among CHC patients.

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