Low Viral Load Does Not Exclude Significant Liver Damage in Patients with Chronic HBV Infection in Bangladesh

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Abstract

Background: In general, it is assumed that patients with chronic hepatitis B virus (HBV) infection with high viral load exhibit increased liver damages. Accordingly, the treatment guidelines emphasize on reducing viral load in chronic HBV carriers. The ethical and scientific basis of these observations was mainly accumulated from investigations from developed countries of the world. More than 80% chronic HBV carriers live in the developing nations of the world, but little is known about relationship between HBV viral load and extent of liver damages in these countries. In this study, we addressed this issue to provide insights about this. **Methods:** In this retrospective study we reviewed the records of 210 chronic hepatitis B (CHB) patients from our pool of 561 Bangladeshi CHB patients. All of these 210 patients had low HBV DNA ($<10^5$ copies/ml by PCR). Of them 16 were HBeAg +ve and rest 194 HBeAg -ve. They have also been tested for other serologic markers of HBV (i.e. HBsAg, anti-HBe), HCV (i.e. anti-HCV) and serum alaninetransaminase (ALT) level. All patients also underwent per-cutaneous liver biopsy. **Results:** 37.5% (6/16) HBeAg +ve patients with low HBV DNA had significant hepatic necro-inflammation (HAI-NI $\geq$7), whereas this figure was 31.44% (61/194) in case of HBeAg -ve patients. On the other hand significant hepatic fibrosis (HAI-F $\geq$3) was observed in 31.25% (5/16) and 14.4% (28/194) in HBeAg +ve and -ve patients respectively. **Conclusion:** This study shows that a correlation could not be established between viral load and liver damage in patients with CHB in Bangladesh. A significant percentage of patients with low HBV DNA may have marked hepatic necro-inflammation and fibrosis, more so in case of HBeAg +ve CHB. Further study may be needed to find out the influence of other factors on liver damages in CHB patients in developing nations like Bangladesh, where about 8 million chronic HBV carriers are living. Most of these patients have not been characterized and treatment modalities have not been defined for them. Our study may suggest the research direction for management of these cases.

Key Words: Low HBV DNA, Chronic hepatitis B, Hepatic necro-inflammation, Hepatic fibrosis.

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Introduction

HBV infects nearly 350 million people worldwide. Of them 75-80% reside in Asia and Western Pacific. HBV is responsible for over 1 million deaths per year globally. The clinical manifestations vary widely with asymptomatic acute viral B hepatitis on one end and hepatocellular carcinoma (HCC) on the other end of the spectrum. It is a major cause of cirrhosis of liver and HCC worldwide.[1]

Bangladesh is in the intermediate prevalence region for HBV infection. The lifetime risk of acquiring this infection in Bangladesh is >40%. HBV results in a wide range of liver diseases with asymptomatic acute hepatitis in one end and hepatocellular carcinoma (HCC) on the other end of the spectrum. It has been estimated that this virus is responsible for 10-35% cases of acute viral hepatitis, 35.7% cases of fulminant hepatic failure, 33.3-40.5% cases of chronic hepatitis and 46.8% cases of HCC in Bangladesh[2] .

With PCR now days HBV DNA can be detected at levels as low as 500 copies/ml. It is important to know the pre-treatment HBV DNA level at baseline in order to monitor response to anti-virals and to look for drug resistance. The primary aim of anti-viral therapy is suppression of HBV DNA. In HBeAg +ve CHB patients, anti-viral therapy is indicated if HBV DNA is $\geq$100,000 copies/ml, subject to

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satisfaction of other criteria also. In case of HBeAg -ve CHB however, treatment has to be started if HBV DNA is >10,000 copies/ml. Pegylated interferon, interferon-alfa, lamivudine, adefovir, entecavir, talbivudine and tenofovir are the different first line anti-virals effective in CHB, all having their advantages and disadvantages. The points that are considered in choosing a particular anti-viral among others include, efficacy, safety, drug resistance, mode of administration and cost[3].

It is not uncommon in our practice to see patients with low HBV DNA load of $<10^5$ copies/ml. It remains a question whether such patients are likely to develop more severe liver disease. The aim of this study is to compare the correlation between low HBV DNA load and grade and stage of liver disease in patients with CHB.

Methods

It is a retrospective study. We reviewed the records of 210 chronic hepatitis B (CHB) patients from our pool of 561 Bangladeshi CHB patients. They were all HBsAg positive for at least 6 months) and attended our OPDs in Dhaka, Bangladesh between July 2005 and October 2008. Written informed consent was obtained from each patient. The patients had to be negative for anti-HCV antibody and positive for serum HBV DNA by quantitative analysis of HBV in human serum. First HBV DNA was extracted from the patient's serum. It was then amplified by polymerase chain reaction (PCR) and detected using fluorescent reporter dye probes specific for HBV in the Rotor Gene-3000 (Corbett Research). The patients were enrolled irrespective of their HBeAg status and liver enzyme levels. Patients with clinical evidence of liver cirrhosis were excluded.

All patients underwent percutaneous liver biopsy. Biopsies were done using trucut biopsy needle under local anaesthesia. Patient characteristics are shown in Table I. We checked prothrombin time and platelet count in every patient, within a week before the procedure. Liver biopsies were done if baseline prothrombin time was not prolonged more than 3 seconds beyond control value and platelet count was not less than 100,000/cmm. Biopsies were scored using histologic activity index (HAI) scoring system[4-5] .

All the 210 patients included in this study had low HBV DNA ($<10^5$ copies/ml by PCR). Of them 16 were HBeAg +ve and rest 194 HBeAg -ve.

Results

All the 210 patients included in this study had low HBV DNA ($<10^5$ copies/ml by PCR). Of them 7.6% (16/210) were HBeAg +ve and rest 92.4% (194/210) HBeAg -ve. HBV DNA load 10^5 copies/ml was considered to be low load.

It was observed that patients who have HBeAg positive HBV infection, tend to high levels of HBV DNA, while the reverse applies for thoise with HBeAg negative HBV infection.

37.5% (6/16) HBeAg +ve patients with low HBV DNA had significant hepatic necro-inflammation (HAI-NI $\geq$7), whereas this figure was 31.44% (61/194) in case of HBeAg -ve patients. On the other hand significant hepatic fibrosis (HAI-F $\geq$3) was observed in 31.25% (5/16) and 14.4% (28/194) in HBeAg +ve and -ve patients respectively.

The extent of hepatic of necro-inflammation was similar in both HBeAg [ositive and negative patients with low HBV DNA. However, patients with HBeAg negative HBV infection with low HBV DNA count tend to have advanced fibrosis more frequently than their HBeAg negative counterparts.

Table-I

Characteristics of study population

Parameter	Value
Total Patients	210
Age (years)	25 (18–55)
Gender (Male: Female)	119:40
HAI Score	1–18
Fibrosis Score	0 – 4

Discussion

The aim of this study was to asses whether patients with low HBV DNA load have negligible ongoing necro-inflammation or fibrosis in the liver in case of both HBeAg +ve and -ve CHB. Contrary to the usual belief, we observed that a significant percentage of patients with both HBeAg +ve and -ve CHB develop significant necro-inflammation and/or fibrosis. Similar reports are sparse in the world literature.

However there are several studies that have failed to show any correlation between HBV DNA load and severity of liver damage in CHB patients. These include study from Iran with a sample size of 200 patients[6]. There are at least two more papers in the literature having similar observations[7-8]. From Bangladesh also, our group as well as our colleagues have reported similar experience in the recent past[9-10]. Two more recent studies have rather reported that high HBV DNA load is associated with less severe histologic liver disease[11-12].

HBV DNA load in CHB patients may be influenced by host factors like immune response and alcohol consumption and viral factors like genotype and pre-core/ core promoter mutations[12]. CHB patients may have fluctuating HBV DNA level, which may also explain such observation. The pathogenesis of liver damage is immune-mediated where the role of cytokines is crucial. Several studies have failed to show correlation between HBV DNA and serum aminotransferases, which is additional evidence that HBV DNA does not correlate with severity of liver disease[13-14].

Conclusion

This study shows that a correlation could not be established between viral load and liver damage in patients with CHB in Bangladesh. A significant percentage of patients with low HBV DNA may have marked hepatic necro-inflammation and fibrosis, more so in case of HBeAg +ve CHB. Further study may be needed to find out the influence of other factors on liver damages in CHB patients in developing nations like Bangladesh, where about 8 million chronic HBV carriers are living[15]. Most of these patients have not been characterized and treatment modalities have not been defined for them. Our study may suggest the research direction for management of these cases.

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