



Gastroenterology

TO COMPARE THE ROLE OF FIBROSCAN IN COMPARING FIBROSIS AMONG ASYMPTOMATIC HBsAG POSITIVE PATIENTS WITH NORMAL TRANSAMINASE TO NORMAL HEALTHY SUBJECTS AND TO COMPARE FIBROSIS BETWEEN HBeAg POSITIVE AND HBeAg NEGATIVE PATIENTS

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ABSTRACT Fibroscan is a non invasive test to detect fibrosis and degree of liver stiffness.. The present study evaluated role of Fibroscan in detecting fibrosis in study and control group. 8 out of 80 (10%) with hbsag positivity patients with normal transaminases had Liver stiffness (Fibroscan) >7 kPa, which shows that some fibrosis is going on despite no hepatitis. This shows that liver stiffness is high in HBsAg positive patients with normal transaminases as compared to normal subjects. Liver stiffness was statistically insignificant in HBeAg positive and HBeAg negative patients. HBsAg positive patients with normal transaminases with alarmingly high liver stiffness values require further examination, tight follow up including liver biopsy.

KEYWORDS :

INTRODUCTION:

Worldwide, more than 2,000 million people have been infected with hepatitis B virus (HBV) during their lifetime.¹ Of these, about 350 million remain chronically infected. Three-quarters of the world's population live in areas with high levels of infection. An estimated 1 million people die each year from HBV-related cirrhosis or primary liver cancer.¹ HBV has a very complex natural history, centered in the liver, where the interaction between immune system and the viral proteins leads to a hepatocyte damage and tissue repair.² Most of HBV treatment guidelines have reserved liver biopsy for cases that do not really meet clear cut-off values of treatment or where there is a discrepancy between high viral load ($\geq 2,000$ IU) and normal liver enzymes or vice versa. Most guidelines recommend treatment of chronic HBV for those with high HBV DNA $\geq 2,000$ and persistently elevated liver enzymes. HBV-infected patients with alanine aminotransferase (ALT) values close to the upper limit of normal were found to have abnormal histology and can be at increased risk of mortality from liver disease especially those above the age of 40 years. FibroScan is a non-invasive medical technology used to assess the level of liver fibrosis and the degree of liver stiffness.

The FibroScan device uses a technique called transient elastography to measure liver stiffness. During the procedure, the patient lies on their back while a probe is placed on the skin's surface, typically on the right side of the chest where the liver is located. The probe emits low-frequency sound waves that pass through the liver. The speed of these waves is influenced by the stiffness of the liver, with stiffer livers exhibiting faster wave propagation.

The FibroScan device measures the velocity of the sound waves and calculates the liver stiffness, providing a numerical value known as the liver stiffness measurement (LSM). The LSM is correlated with the degree of liver fibrosis, allowing healthcare professionals to assess the level of liver damage and monitor disease progression.

FibroScan is considered a non-invasive alternative to liver biopsy. Liver biopsy is an invasive and potentially risky procedure, whereas FibroScan offers a safer and more convenient method to assess liver fibrosis.

The results of a FibroScan test are often reported in kilopascals (kPa), with higher values indicating more severe liver fibrosis. The interpretation of the results typically follows a staging system that categorizes fibrosis levels from F0 (no fibrosis) to F4 (cirrhosis).

OBJECTIVES

Primary Outcome of the study was to compare role of fibroscan in detecting the fibrosis among asymptomatic patients having HBsAg positive with normal transaminases and normal healthy subjects and secondary Outcome was to compare fibrosis between HBeAg positive and HBeAg negative patients using fibro scan.

MATERIAL & METHODS

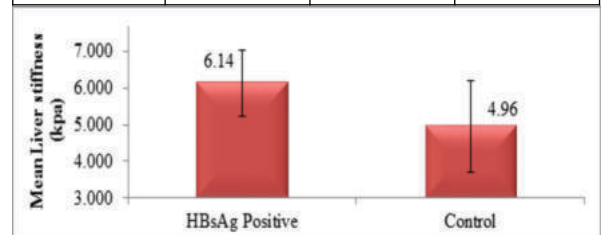
The present study was conducted at a tertiary care, super specialty hospital in the Department of Medical Gastroenterology, SVP Hospital, NHL Municipal medical college, Ahmedabad offering post graduate courses in broad as well as super specialties. Total of 80 patients were included in the study and was divided into 2 groups, Group A are HBsAg positive patients with normal transaminases patients and into Group B with normal healthy population. All patients with age > 15 years or any sex (M/F) were included in the study. Patient were excluded from study who were having Cirrhosis of liver or any liver disease, raised transaminases, patients positive for other chronic liver disease etiology including anti HCV, autoimmune markers and history of alcohol, DM, NASH, morbid obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$), fatty liver and who fail to provide informed consent. Liver stiffness measurements (LSMs) were taken by single operator by TE in all patients using a FibroScan® device (EchoSens - Paris, France). Statistical analysis was done by entering data in Microsoft Excel 2010 and analyzed with Epi info version 7.1.4.0.

Unpaired T test was used for analysis of continuous variables while chi square was used for nominal/ categorical variables. p value less than 0.05 was considered as significant.

RESULTS

The mean liver stiffness or Fibroscan value in study group was 6.14 ± 0.89 kPa and in control group was 4.96 ± 1.25 kPa. This difference in liver stiffness is statistically significant ($p < 0.0001$). Patients with HBsAg positive with normal transaminases have higher liver stiffness as compared to control population.

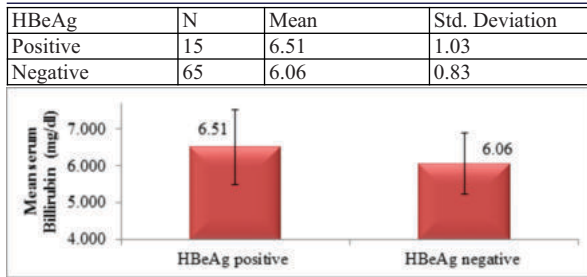
| Group | N | Mean | Std. Deviation |
|----------------|----|------|----------------|
| HBsAg Positive | 80 | 6.14 | 0.89 |
| Control | 80 | 4.96 | 1.25 |



Comparison of Mean Liver stiffness (kpa) between two groups

Mean value of Fibroscan in HBeAg positive patient was 6.51 ± 1.03 kPa and in HBeAg negative patients was 6.06 ± 0.83 kPa. This difference is statistically insignificant. ($p = 0.08$)

Comparison of mean Liver stiffness (kpa) in relation to HBeAg among HBsAg positive



DISCUSSION

In our study, total of 80 subjects were divided in 2 groups, one was the study group with HBsAg positive patients with normal transaminases and other was control group. The mean \pm SD liver stiffness or Fibroscan value in our study group was 6.14 ± 0.89 kPa and in control group was 4.96 ± 1.25 kPa. This difference in liver stiffness is clinically significant ($p < 0.0001$). Patients with HBsAg positive with normal transaminases have higher liver stiffness as compared to control population.

In our study, the mean liver stiffness in inactive carriers was 6.14 kPa, that is comparable with 5.6 kPa in the Sporea study, 5.8 kPa in Sohrabi study and 6.3 ± 5.8 kPa in Cristina study. In control subjects liver stiffness was 4.96 kPa in our study compared with 4.8 kPa in sporea study. Similar to our study, Sporea⁷ and Sohrabi⁸ studies suggest that the patients of chronic hepatitis B with normal transaminases have statistically significant higher liver stiffness value. Sporea and Sohrabi studies included patients of CHB with normal transaminases with negative HBeAg while Cristina¹⁰ Study included CHB patients with HBeAg positive and negative as well. Several studies have been published regarding the upper limit of normal liver stiffness values. In Chu et al⁹ values under a cutoff of 6 kPa were highly predictive of insignificant fibrosis in patients with normal ALT levels. The cutoff was higher, 7.5 kPa, when ALT was elevated (up to 5 times the upper limit of normal [ULN]).

In our study, 8 out of 80 cases patients had a liver stiffness (Fibroscan) value of >7 Kpa (10%), but had no biological, endoscopic and ultrasonographic evidence of cirrhosis. Liver biopsy was performed in 3 patients in our study, all suggest F2 stage. Sporea et al⁷ showed that in 16.6% of cases (20 inactive HBsAg carriers), the LS exceeded 7 kPa (the cutoff for significant fibrosis), while in Sohrabi MR study LS exceeded 7 kPa in 11.9% of cases (25 inactive HBsAg carriers), Cristina and group had 14% of patients (Inactive HBsAg carriers and Immunotolerant) have significant liver fibrosis taking as a cutoff value 7.9 kPa, requiring further investigation to determine the cause. All these studies suggest that some patients with inactive carrier stage may have significant fibrosis and further workup is needed in these patients. In the present study, there was no significant difference in liver stiffness in patients with either HBeAg positive or HBeAg negative (6.51 ± 1.03 kPa vs 6.06 ± 0.83 kPa, $p = 0.08$). We could not find any study to compare the result of our study. Further studies are required to directly compare the LSM difference in HBsAg positive patients with regard to HBeAg status.

D T Chao et al¹¹ in a systemic review among nine studies aimed to determine the proportion of CHB patients with normal transaminases ($ALT \leq 40$ IU/L) and liver fibrosis stage ≥ 2 . Secondary goals included subgroup analysis by hepatitis B e antigen (HBeAg) status, high hepatitis B virus (HBV) DNA levels, asian ethnicity, lower ULN of ≤ 30 IU/L (males) and 19 IU/L (females) and advanced age. Among nine studies ($N = 830$ patients), a significant proportion (20.7%; 95% CI: 16.2-26.0%) of CHB patients with ALT levels ≤ 40 IU/L had significant fibrosis irrespective of HBeAg status, high HBV DNA levels, ethnicity or age, although this proportion was higher in patients older than 30-40 years old. The corresponding proportion was 27.8% even when the newer ULN of 30 IU/L (males) and 19 IU/L (females) was applied. They concluded that approximately one fifth of CHB patients with $ALT \leq 40$ IU/L may have significant hepatic fibrosis.

The approach to such patients should be individualised, as further evaluation and treatment may be appropriate in these patients. But liver biopsy was performed only in 3 patients with high liver stiffness in this study, which is a limitation of the study.

CONCLUSION

The present study evaluated role of Fibroscan in detecting fibrosis in

study and control group. Both the groups had 80 subjects in each group. The study group had patients with HBsAg positive with normal transaminases and control group had apparently normal subjects. Out of these in study group 32 were female and 48 were male patients while in control group 34 were female and 46 were male patients. Patient underwent Fibroscan to measure liver stiffness. HBsAg positive patients underwent some other investigations e.g. HBeAg, Anti HBe antibody, HBV DNA. Liver stiffness (Fibroscan) was significantly high in study group as compared to control group (6.14 ± 0.89 kPa vs 4.96 ± 1.25 kPa) ($p < 0.0001$). 8 out of 80 (10%) patients had Liver stiffness (Fibroscan) >7 kPa in spite of normal transaminases, which shows that some fibrosis is going on despite no hepatitis. This shows that liver stiffness is high in HBsAg positive patients with normal transaminases as compared to normal subjects. So these patients should be on regular follow up to look for reactivation of HBV infection. In HBsAg positive patients liver stiffness was statistically insignificant in HBeAg positive and HBeAg negative patients ($p = 0.08$). In conclusion, present study focuses on simple but very important issue particularly in our country where HBV infection is common. HBsAg positive patients with normal transaminases with alarmingly high liver stiffness values require further examination, tight follow up including liver biopsy. TE (FibroScan) is a good, noninvasive method that can be used to follow up these patients to assess the progression of fibrosis. Large population based studies are required to assess the role of Fibroscan as a non-invasive tool to assess fibrosis in HBsAg positive patients with normal transaminases, so that it can be used as an alternative to liver biopsy.

REFERENCES

- Hepatitis B. 2002(WHO/CDC/CSR/LYO/2002.2:Hepatitis B). Available online: http://apps.who.int/iris/bitstream/10665/67746/1/WHO_CDS_CSR_LYO_2002.2_HEPATITIS_B.pdf. Accessed on May 18, 2019.
- McMahon BJ. The natural history of chronic hepatitis B virus infection. *Hepatology* 2009; 49:S45-55.
- Talwalkar JA, Kurtz DM, Schoenleber SJ, West CP, Montori VM. Ultrasound-based transient elastography for the detection of hepatic fibrosis: systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2007; 5:1214-20.
- Oliveri F, Coco B, Ciccorossi P, Colombatto P, Romagnoli V, Cherubini B, et al. Liver stiffness in the hepatitis B virus carrier: a non-invasive marker of liver disease influenced by the pattern of transaminases. *World J Gastroenterol* 2008; 14:6154-62.
- Verveer C, de Knecht RJ. Non-invasive measurement of liver fibrosis: application of the FibroScan in hepatology. *Scand J Gastroenterol* 2006; 41:85-8.
- Coco B, Oliveri F, Maina AM, Ciccorossi P, Sacco R, Colombatto P, et al. Transient elastography: a new surrogate marker of liver fibrosis influenced by major changes of transaminases. *J Viral Hepat* 2007; 14:360-9.
- Sporea I, Nicolita D, Sirli R, Deleanu A, Tudora A, Bota S: Assessment of noninvasive liver stiffness in inactive HBsAg carriers by transient elastography. *Hepat Mon* 2011; 11:182-5.
- The Impact of Transient Elastography in the Assessment and Follow-up of Patients with HBeAg-Negative Chronic Hepatitis B Virus Infection
- Masoudreza Sohrabi, Mohsen Nasiri Tosi, Parvin Azar, Mehdi NikKah, Zhaleh Bayani, Masoumeh Zarei, Hossein Ajdarkosh
- Chu CM, Liaw YF. Incidence and risk factors of progression to cirrhosis in inactive carriers of hepatitis B virus. *Am J Gastroenterol*. 2009; 104(7):1693-9.
- Cristina SJL, Marta CM, Mercedes GS, Almudena PM, Alvaro HM, Luis VSJ, Tesifon PC: Characterization and evaluation of liver fibrosis grade in patients with Chronic hepatitis B infection and normal transaminases. *Clin Mol Hepatol*. 2018Dec;384-391
- Chao DT, Lim JK, Ayoub WS, Nguyen LH, Nguyen MH. Systemic analysis: the proportion of chronic hepatitis B with normal transaminases ≤ 40 IU/ml and significant hepatic fibrosis. *Aliment pharmacol Ther*. 2014Feb;39(4):349-58.