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Original Article

The Impact of Transient Elastography in the Assessment and Follow-up of Patients with HBeAg-Negative Chronic Hepatitis B Virus Infection

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ABSTRACT

Background:
Liver fibrosis is the main prognostic factor for chronic hepatitis B (CHB). Change of inactive hepatitis B to active one is usually done silently. In this setting accurate estimation of fibrosis is an important step in the management of affected patients. The aim of this study was to determine the impact of fibroscan to evaluate liver fibrosis in inactive chronic hepatitis B.

Materials and Methods:
In a prospective study between February 2016 and June 2018, we evaluated liver fibrosis among patients with inactive CHB by fibroscan assessment. The inclusion criteria were the presence of serum HBsAg more than 6 months, persistence normal liver enzymes during the last 6 months, and HBV–DNA viral load < 20000 IU/mL. All other liver diseases were excluded. All patients underwent liver fibroscan. The factors affecting fibroscan results such as severe obesity, cardiac and renal failure, decompensate cirrhosis, and ascites were excluded. The patients were visited every 6 months. The eligible patients were followed up for one year.

Results:
210 patients were enrolled in this study. The mean age was 37.49 ± 12.8 years and of them132 patients were male. Regarding the HBV DNA load, 48 (22.9%), 84 (40%), and 78 (37.1%) patient had viral load undetectable, under, and more than 2000 IU/mL, respectively. The mean transit elastography (TE) value among these patients was 5.8 ± 1.26 kPa. TE value more than 7.2 kp was seen in 25 (11.9%) patients with mean of 8.1 ± 1.4 kPa. There was no significant association between TE results and viral load levels in general. Moreover, we did not observe a significant association between age and viral load and TE.

Conclusion:
We showed that inactive hepatitis B is not a benign condition, which needed regular follow-up by evaluating liver enzymes, vial load, and TE. Hepatic fibrosis has prognostic significance because afflicted patients are at higher risk of developing cirrhosis; although liver biopsy is considered as the best available gold standard for assessing hepatic fibrosis.

Keywords: Elastography, Liver fibrosis, Cirrhosis, Hepatitis B virus

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INTRODUCTION

Hepatitis B virus (HBV) infection, despite many attempts for its prevention, remains as a worldwide public health issue with considerable morbidity and mortality (1), although, recently its epidemiological data has changed worldwide due to public education, global vaccination, and probably immigration (1-4). In this context, chronic HBV infection with negative hepatitis B e antigen (HBeAg) can be considered as the principal type of chronic HBV infection particularly in

endemic area. This status previously called "inactive carrier". This phase of HBV infection is defined as persistently normal alanine aminotransferase (ALT) values according to conventional cut-off values (ULN40 IU/L) along with undetectable or low HBV DNA levels (< 2,000 IU/mL). Indeed, some patients in this phase, may have HBV DNA levels > 2,000 IU/mL (usually < 20,000 IU/mL) accompanied by persistently normal ALT. The risk of progression in these patients is very low (5,6). In fact, despite serial monitoring of these patients by assessment of ALT, HBV load, and HBeAg status, some patients fall in to gray zone and need more evaluation individually. In this regard the status can progress to chronic active hepatitis (CHB) silently. In fact there are few cohort studies in this subject and other studies have been on patients that do not strictly follow the definition of HBV infection, so there are limited data in this regard. Furthermore, transforming different HBV infection phases may not follow a unique order (7,8). Hence distinguishing these phases may not be easy and may cause HBV related long-term complications (9). Monitoring of these patients is based on checking ALT, and HBV DNA levels regularly and liver fibrosis assessment via liver biopsy or non-invasive modalities (10,11). Liver fibrosis traditionally has a prognostic value for prediction of liver cirrhosis. Also liver biopsy is not useful for dynamic changes during the process of fibrogenesis. In fact, liver biopsy has its own important complications and limitations (12,13). Therefore many efforts were done to develop and standardized a non-invasive method for evaluation of liver fibrosis. Indeed liver biopsy may not be useful for screening and follow-up. Although in clinical practice either the progression, or the regression of liver fibrosis over time may be significant that need evaluation of liver stiffness (14,15). In this regard, transit elastography (TE) has been introduced and developed during the last decades. This modality is actually used for liver fibrosis assessment worldwide. Liver stiffness is evaluated by TE via measuring the velocity of shear waves in the liver parenchyma (16).This method is tolerated and can be repeated easily. TE as a non-invasive method was accepted by European association for the study of the liver as a reliable marker for assessment of liver stiffness in chronic liver diseases and during the last few years this modality has become the first choice of monitoring for patients with HBV infection (12). In patients with HBeAg-negative chronic HBV infection, TE can detect the possible progression of infection or the influence of other co-morbidities such as non-alcoholic steatohepatitis that lead to liver injury (7,17). Therefore, due to limited data in this regard we designed a study to assess the impact of TE in the evaluation and follow-up of such patients.

MATERIALS AND METHODS

In a cross-sectional study from February 2016 to June 2018, of the patients referred to hepatitis clinic of Firoozgar and Imam Khomeini Hospitals due to chronic HBe-Ag–negative HBV infection eligible subjects were recruited. For each patients a questionnaire including demographic and lab data was completed.

The inclusion criteria were presence of serum HBsAg for more than 6 months, persistence normal liver enzymes during the last 6 months, HBV–DNA viral load < 20000 IU/mL. Exclusion criteria were coinfection with hepatitis C virus, hepatitis D virus or HIV, auto immune hepatitis, or other liver diseases such as Wilson's disease, elevated total bilirubin level, high grade liver steatosis in transabdominal ultrasonography (Grade 3), cirrhosis, history of anti viral therapy, unsuccessful TE evaluation, alcoholic beverage abuse (more than 60 gr for men or more than 40 gr for women), body mass index more than 30, renal, cardiac or respiratory failure, presence of any cancer, or anti cancer treatment.

The enrolled patients were followed up for at least one year. They were visited every 6 months regularly. In each visit lab data including complete blood count, and liver enzymes (ALT and AST) were requested. The lab results of the first and the last visit were recorded. The patients with elevated liver enzymes were considered for more evaluation.

Liver transient Elastography

TE was performed by a physician with at least one thousand fibroscan performance experience in Firoozgar Hospital, using FibroScan (FibroScan; Echosens, Paris, France). The examination was performed as standard with the patient lying in dorsal decubitus with maximum abduction of right arm. For each patient, at least 10 successful shots were considered as a correct exam. The results of fibrosis were reported in kilopascals (kPa). According to

Table 1: Basic characteristics of the patients according to the result of transit elastography and age

Variables		TE ≤ 7.2	TE > 7.2	Age ≤ 40	Age > 40	Total
Age (Mean ± SD)		37.2 ± 24.5	39.4 ± 10	29.6 ± 6.1	51.6 ± 8.5	37.4 ± 12.7
Sex (male/Female)		117/68	15/10	82/49	50/29	132/78
BMI total (Mean ± SD)		24.5 3.1	25.4 ± 2.5	24.3 ± 2.9	25.1 ± 3.2	24.6 ± 3
BMI	< 18.5 (n)	5	0	4	1	5
	18.5-25 (n)	96	11	66	34	100
	25-30 (n)	84	14	65	40	105

TE: Transit elastography, BMI: Body mass index

Table 2: Laboratory results according to TE and age

Variables	TE ≤ 7.2	TE > 7.2	Age ≤ 40	Age > 40	Total
ALT	22.6 ± 7.40	24.44 ± 8.6	23.8 ± 7.6	21 ± 6.9	22.8 ± 7.5
AST	22.1 ± 5.9	25.3 ± 8.6	22.9 ± 5.9	24.5 ± 6.3	22.5 ± 6
Bilirubin total	0.80 ± 0.26	0.76 ± 0.30	0.79 ± 0.39	0.77 ± 0.33	0.78 ± 0.35
Platlet	226 ± 68	203 ± 61	224 ± 70	221 ± 65	223 ± 67
Triglyceride	127.8 ± 42.1	131.1 ± 36.6	124.2 ± 40.8	135.5 ± 42.7	128.2 ± 41.7
Cholesterol total	174.4 ± 37.1	169.4 ± 34.6	167 ± 33.4	186 ± 39.4	173.8 ± 36.7
HBV load (IU/ml)	3019 ± 4652	2456 ± 2965	2781 ± 2580	3261 ± 4313	2952 ± 4482
TE (Kp)	5.46 ± 0.83	8.1 ± 1.4	5.7 ± 1.0	5.94 ± 1.5	5.78 ± 1.3

AST: Aspartate aminotransferase; ALT: Alanin Transferase ; TE: Transit elastography

the manufacture's guideline, the median value of successful measurements was considered as the liver stiffness. The minimum cut-off point for significant fibrosis based on previous reports was 7.2 kPa.

Ethic:

The study was approved by Ethics Committee of Iran University of Medical Sciences according to Helsinki declaration. A written informed consent was obtained from each patient before enrollment.

Statistic:

The results were collected and analyzed using SPSS software (version 20.0 SPSS, Chicago, Illinois USA) for Windows. Descriptive analysis was used for reporting the prevalence of sex and age distributions. T test was used for assessment of the results. Chi-square test was used for qualitative variables. *P* values less than 0.05 was considered as statically significant.

RESULT

In this study 650 subject participated, of them 210 eligible patients were enrolled in this study. The mean age of the participants was 37.49 ± 12.8 years and of them 132 (62.9%) patients were male. Table 1 illustrated the basic characteristics of the patients. The mean body mass index (BMI) was 24.62 ± 3.1. The mean liver enzymes at the beginning and end of the follow-up for ALT were 22.8 ± 7 and 21.9 ± 6 (U/L), respectively and for AST were 22.49 ± 6 and 20.68 ± 2 (U/L)respectively.

Regarding the HBV DNA load, 48 (22.9%), 84 (40%), and 78 (37.1%) patient had viral load undetectable, under, and more than 2000IU/mL, respectively. The mean TE value among these patients was 5.8 ± 1.26 kPa. TE more than 7.2 kPa was seen in 25 (11.9%) patients with mean of 8.1 ± 1.4 kPa.

The mean TE level in patients with viral load undetectable, less, and more than 2000 IU/mL were 5.56 ± 1.31, 5.73 ± 1.16, and 5.98 ± 1.31 kPa, respectively. There was no association between TE level and viral load in general ($p = 0.9$).

Furthermore, regarding the age and sex, we did not observe a significant association between age and sex with viral load ($p = 0.2$ and 0.4, respectively) and TE level ($p = 0.4$ and 0.1, respectively) (table2). There was also no significant association between age less or

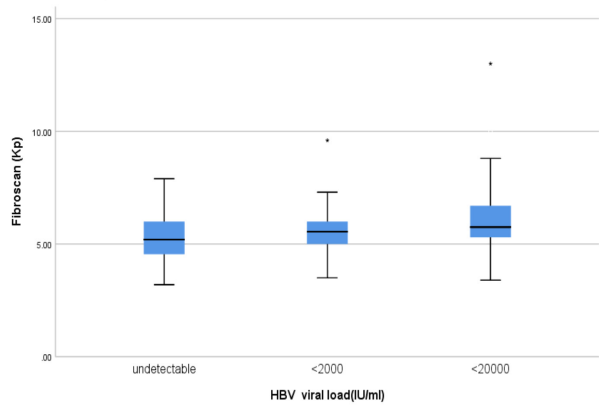

Fig. 1: Association between TE result (KP) with HBV viral load (p = 0.08)

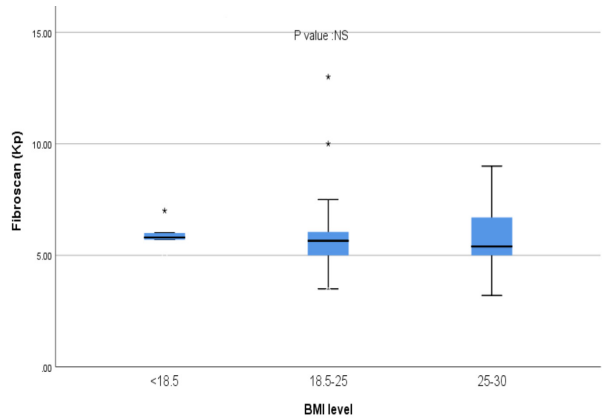

Fig. 2: Association between Fibroscan results and BMI levels

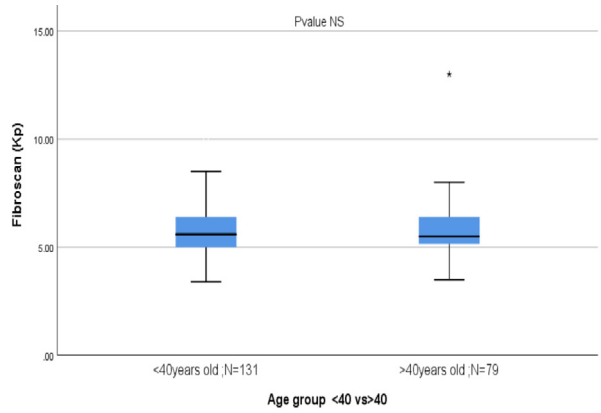

Fig. 3: Fibroscan result according to age (< 40 vs > 40)

more than 40 years with TE level ($p = 0.12$) (Figure 1). Also, as illustrated in figure 2 and 3, there was not an association between TE level and BMI ($p = 0.49$).

During this study three patients had increased liver enzymes who received treatment. Of them two patients had TE level more than 7 and viral load more than 2000 IU/mL. In next step the association between variables including TE level, liver enzymes, age, and viral load were assessed. We did not observe a significant association ($p > 0.05$).

DISCUSSION

The finding of this study indicated that TE evaluation in HBeAg–negative chronic hepatitis B infection is not significantly associated with liver enzymes, age, BMI, or viral load in general. In present study we tried to exclude the confounding factors such as congestive heart failure, or frank obesity in the evaluation of TE.

A recent meta-analysis, including 4,386 patients with HBV in 27 studies, demonstrated that TE had high diagnostic accuracy for the detection of liver fibrosis, particularly F > 1 (18). In this context, Huang and colleagues in a study on 263 patients with HBV and with ALT levels less than two times of upper limit of normal showed that TE was a useful modality for the diagnosis of fibrosis. In this study, it was revealed that liver stiffness value was correlated significantly with both liver fibrosis and necroinflammatory activity on biopsy (19). Kim and colleagues in their large scale research indicated that TE had a high value for prediction of HBV related long-term complications (20).

The mean liver stiffness in our study was 5.8 ± 1.26 kPa. Bazerbachi in a meta-analysis reported that the mean TE in healthy subject was 4.6 kPa that increased with steatosis and obesity (21). Furthermore, some researchers indicated that the level of ALT might not be associated with TE level particularly among patients with HBeAg negative (22). In the present study we did not reveal a significant association between TE value and ALT. Indeed, in patients with HBV infection or inactive carriers we do not expect elevated liver enzymes. Moreover, after one–year follow-up we observed that three patients needed treatment that two of them already had fibrosis more than 7 kPa. Hence we may advise to performed TE and strict follow-up for patients with fibrosis.

TE in the present study did not have a significant association with BMI. Previous studies indicated that overweight and high BMI had an impact on TE results (8,23,24). Petta and colleagues in a large community-

based study on 890 subject revealed that obesity had influence on TE result (24). Actually we cannot give an exact explanation for this disparity but it may be related to the number of participants.

Regarding the association between viral load and TE, there were not many studies in this regard and previous studies had different results. In fact, the TE value in inactive patients should be similar to healthy people and lower than CHB, although there is an overlap between these groups (10,25). Sporea and colleagues in 140 patients with inactive hepatitis B demonstrated that liver stiffness was 5.6 ± 2.1 kPa that was comparable with our study. They indicated that liver stiffness may be associated with viral load (26). Oliveri and co-workers revealed that the mean TE value of patients with inactive hepatitis B was 4.3 ± 1.0 that was almost near the healthy participants in this study (27). Moreover, Maimone and others assessed TE in 125 patients with inactive CHB. They defined that the mean TE level was 4.8 ± 1.2 kPa, which was significantly lower than that of patients with active CHB (28). Overall, different studies illustrate that median TE values are about 5 kPa. In fact, as far as we know, there is no published research about TE value for healthy persons in our country. In the present study we did not compare patients with healthy persons or active hepatitis.

The question that may be brought in mind in this step is that: what is the cut of point of TE in these patients? In our study, regarding previous reports we considered 7.2 kPa as a level of considerable fibrosis. Hence, of total patients, 25 patients had liver stiffness more than 7.2 kPa in whom two patients showed elevated liver enzymes and medical treatment was started for them. In a prospective study on 173 patients with HBV, TE was compared with liver histology. The researchers indicated that the optimal liver stiffness cutoff values were 7.2 kPa for liver stiffness and 11.0 kPa for severe liver stiffness (15). This was confirmed in a large meta-analysis on patients with chronic hepatitis B (29). Few studies evaluated the histological assessment of inactive HBV infection for its complications. Along with this fact, in present study, we did not perform histological assessment because liver biopsy was not required for these patients and also fibroscan evaluation was already validated for patients with HBV.

Regarding the sex and age, we did not reveal any association between these two items with stiffness and viral load. Furthermore, age is considered as a prognostic factor for HBV progression (21,30). Also Tokuhara and colleagues and Petta and co-workers indicated that age may influence on TE result (14,24). This result may be due to the number of enrolled patients as well as limited follow-up period. Actually it is accepted that age and sex may influence on changing the status of inactive to active chronic hepatitis B. In this regard, Chu and colleagues in a large scale study during 11.5 years follow-up, showed that 314 of 1965 inactive carriers developed elevated ALT twice as upper normal limit. They indicated that male sex as well as elderly was significantly associated with HBV reactivation (31). Additionally, in another prospective study on 414 Alaskan patients, 36 (9%) patients had reactivation during 10 years follow-up. In this study male sex and viral load were considered as risk factors (32). Furthermore, a longitudinal study reported liver fibrosis progression, detected by increased LS, in 2.9% of patients with inactive chronic hepatitis B (33).

This study has some limitations; first of all the number of patients who had all the inclusion and exclusion criteria was very few. Secondly follow-up period was not too long; although even in this short period we showed reactivation in three patients. Thirdly we did not compare the fibroscan results with histological evaluation.

CONCLUSION

Present study focused on simple but very important issue in the field of hepatology particularly in our region where HBV infection is common. Based on these results we believe that inactive hepatitis B is not a benign condition and needs regular follow-up by liver enzymes, viral load, and TE evaluations. In patients with elevated TE level with persistent normal ALT, tight follow-up or even liver biopsy may be considered.

CONFLICT OF INTEREST

The authors declare no conflict of interests related to this work.

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