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Increased liver stiffness measurement values using transient elastography in Egyptian patients with acute viral hepatitis

Abstract

Transient Elastography (TE) is one of the non-invasive and reproducible tools for assessment of liver fibrosis/ cirrhosis. However, it remains to be determined if ALT flare interferes with fibrosis assessment.

Aim: To determine the effect of increased serum ALT and AST on liver stiffness measurement in patients with acute viral hepatitis.

Methods: Thirty consecutive patients with acute hepatitis of viral etiology with elevated liver enzymes (>10 folds of ULN) were prospectively included. Blood samples were collected and TE was done initially and after resolution of hepatitis and after normalization of liver enzymes. Patients with high BMI which could affect TE (> 40 kg/m2) and patients with ascites or liver cirrhosis were excluded. For determination of the etiology of hepatitis, history taking, a detailed physical examination and laboratory tests were performed in all patients.

Results: The mean age of patients was 32.87±10.2 years old and males represented 46.7% (n=14). In all patients, the degree of liver stiffness at the time of the peak increase in aminotransferases exceeded the cutoff values proposed for the prediction of significant fibrosis or cirrhosis. The mean value of LSM at the time of inclusion in the study was 13.91±6.7 kPa and the mean value of LSM after resolution of hepatitis was 7.7±3.08 kPa. A progressive significant reduction in liver stiffness values was observed (P<0.01) in the follow-up period in parallel with the reduction of ALT levels (P <0.01). Moreover, a statistically significant, positive correlation between ALT and LSM at the onset of acute viral hepatitis was found (r =0.38, P <0.05). No significant correlation was found between increased total bilirubin level and LSM (r =0.3 and P> 0.05). Reduction of mean value of LSM to 6.21±1.14 kPa was observed in 10 patients after 1 year of ALT normalization.

Conclusion: TE has not demonstrated reliable diagnostic accuracy in patients with acute viral hepatitis.

Keywords: transient elastography, liver stiffness measurement, alanine aminotransferase

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Abbreviations: TE, transient elastography; LSM, liver stiffne measurement; ALT, alanine aminotransferase; AST, aspartate aminotransferase

Introduction

Transient elastography (TE) is one of the most widely used non-invasive techniques for the assessment of the stage of liver fibrosis. This technique is a rapid, painless, non-invasive, reproducible, can be used in different liver diseases, it takes information from a much larger portion of the tissue in comparison with liver biopsy. Increased liver stiffness (LS) is not always diagnostic of fibrosis as the presence of significant necroinflammation or extrahepatic cholestasis may increase LS values in the absence of fibrosis.[1,2] Different studies were suggested that TE results may be influenced by Alanine Aminotransferase (ALT) flares.[3,4] Normal ranges of LS are much harder to be established because histology from normal liver is rarely available. An earlier small-scaled study using normal liver tissues from subjects undergoing donation for liver transplantation have identified a normal cut-off LS of < 7.2 kilopascal (kPa).[5] where as cirrhosis is generally present at levels above 12-14 kPa.[6] Although cut-off values for advanced fibrosis and cirrhosis have been well established for different diseases, the normal reference range of liver stiffness measurement (LSM) in specific population groups have not been well defined, especially from large population studies.[7]

Patients and methods

This study was conducted on 34 adult patients with acute hepatitis of viral etiology with elevated liver enzymes >10 folds of upper limit of normal (ULN), they were recruited from either the outpatient clinic or the inpatient unit of clinical hepatology department, National Liver Institute hospital, Menoufiya University. A written informed consent was obtained from all patients participated in the study. Among the selected patients, four patients refused LSM follow up due to clinical improvement and normalization of their liver enzymes. Exclusion criteria were high BMI (more than 40 kg/m^2) that could affect TE results, patients with ascites or liver cirrhosis, co-infection with other viruses, intravenous drug use, alcohol abuse or the use of hepatotoxic drugs within the 6 months preceding the study, metabolic liver disease, autoimmune hepatitis, vascular diseases of the liver, and biliary tract disorders, cardiac failure or pregnancy. For determination of the etiology of acute hepatitis, a detailed history taking and physical examination were performed in all patients, including past

history of exposure to hepatotoxic drugs and alcohol intake. Viral markers (HCV Ab, HBs Ag, HBcIgG, HBcIgM and HAV IgM) were detected by means of a third generation ELISA. Quantitative PCR using Real Time PCR Assay with lower detection limit 15 IU/ml was done for determining HCV RNA level and HBV DNA level in acute HCV and acute HBV infections. Diagnosis of acute HAV infection was based on the detection of anti-HAV IgM antibodies or HAV RNA. The following tests were performed for each patient: autoimmune markers, serum copper, serum ceruloplasmin, 24 hour urinary copper, Complete blood count using Sysmex instrument KX-21, Sysmex Inc., Japan, Bilirubin (total and direct), albumin, ALT and AST. These tests were done using Cobas Integra 400, Hoffman La Roche Company, Switzerland. Prothrombin time and concentration were assessed using Thromborel S, Behring fibrin timer II, Behring Inc., Germany. Body mass index (BMI) (kg/m2) was calculated in all patients: BMI = Mass (kg)/ (Height (m))^2.

LSM was performed with TE, a medical device based on elastometry. Measurement was assessed twice: at the time of inclusion in the study and after resolution of hepatitis and reduction of transaminases level. To assess the influence of necro-inflammation on LSM, we designed to perform LSM during the course of acute viral hepatitis, from the clinical onset to resolution in patients without a previous clinical history of liver disease. Success rate was calculated as the number of valid measurements divided by the total number of measurements. The Inter Quartile Range (IQR) was defined as an index of intrinsic variability of LSM corresponding to the interval of LSM results containing 50% of the valid measurements. The median value was considered representative of the elastic modulus of the liver. Only procedures with at least 10 valid measurements, a success rate of at least 60%, and an IQR-to-median ratio <30% were considered reliable. Follow-up LSM was carried out on the same day when AST, ALT and total bilirubin had returned within the respective normal ranges. LSM was done for 10 patients a year later. LSM in the right lobe of the liver was performed by a trained hepatologist through the intercostal spaces with the patient lying in the dorsal decubitus position with the right arm in maximal abduction. TE fibrosis score.[8–11]

a. F0= 0-2.9 kPa
b. F1= 3-5.9 kPa
c. F2= 6-8.9 kPa
d. F3= 9-16.9 kPa
e. F4= 17-75 kP

Statistical analysis

Data were statistically analyzed using SPSS (statistical package for social science) program version 21 for windows and for all the analysis a p value < 0.05 was considered statistically significant:

Data were shown as mean, range or value and 95% confidence interval (95% CI) or frequency and percent. Student t- test: was done for normally distributed quantitative variables to measure mean and standard deviation. Mann-Whitney test: was done for quantitative variables which are not normally distributed and. Spearman rank correlation coefficient was used when appropriate. P values less than 0.05 were considered statistically significant.

Results

Although, acute hepatitis A is the commonest cause of acute viral hepatitis, Patients with acute hepatitis A represented 16.7% (5 patients) of the total number of studied patients (n=30), patients with acute hepatitis B represented 50% (15 patients) and patients with acute hepatitis C represented 33.3% (10 patients) this is due to the patients taken in the study were adult patients in whom the incidence of acute hepatitis A less commonly than in the young age patients. Patients were recruited from the inpatient unit and outpatient clinic of hepatology department; National Liver Institute, Menoufiya University and patients who were referred from fever hospitals all over Egypt. The mean age±SD was 32.87±10.2 years old in the range of 18-49 years old. Males represented 46.7% (14 patients). Descriptive data and patient's characteristics in all studied patients were shown in Table 1. The mean of TE 1 (in acute hepatitis phase)±SD was 13.91±6.7 kPa in the range of 5.7-27.7 kPa while the mean of TE 2 (after resolution of hepatitis)±SD was 7.7±3.08 kPa in the range of 3.4-14.3 kPa. Reduction of mean value of LSM to 6.21±1.14 kPa was observed in 10 patients after 1 year of ALT normalization (TE 3). In acute hepatitis phase, Patients with F1 represented 10% (3 patients), patients with F2 represented 23.4% (7 patients), patients with F3 represented 33.3% (10 patients) and patients with F4 represented 33.3% (10 patients). LSM of 20/30 of patients showed significant fibrosis while 10/30 of patients reached cirrhotic level. After resolution of hepatitis, liver stiffness measurements decreased to values below the cutoff for cirrhosis (Table 2). A progressive significant reduction in liver stiffness values was observed (P<0.01) in the follow-up period in parallel with the reduction of ALT levels (P < 0.01) (Table 3). There was significant correlation between ALT 1, AST 1, ALT 2 and AST 2 as regards TE before and after resolution of hepatitis (P< 0.01). There was significant correlation between age, ALT 2, AST 2, albumin and INR as regards TE 2 (P< 0.01) (Table 4) and (Figures 1&2). As regards total bilirubin, there was no statistically significant difference between different fibrosis stages measured by fibroscan before and after resolution of hepatitis (P > 0.05) (Table 5).

Table 1 Descriptive data and patient's characteristics in all studied patients

Studied variables	Mean±SD (n=30)	Range
Age (in years)	32.87±10.2	18 - 49
Body mass index kg/m^2	24.82±2.15	21.53 - 29.81
TE 1 (In acute hepatitis phase) kPa	13.91±6.7	5.6 - 27.7
IQR 1 (Inter Quartile Range)	1.4±0.72	0.4 - 3.4
SR 1 (Success Rate)	98.23±4.23	83 - 100
TE 2 (after resolution of hepatitis) kPa	7.7±3.08	3.4 - 14.3
IQR 2(In acute hepatitis phase)	1.12±0.57	0.3 - 3.3
SR 2(Success Rate)	99.1±2.75	91 - 100

Table continued...

Studied variables	Mean±SD (n=30)	Range
ALT1 (In acute hepatitis phase) U/L	1369.7±761.1	540 - 3800
AST 1 (In acute hepatitis phase) U/L	1151.3±759.4	312 - 3910
ALT 2 (after resolution of hepatitis) U/L	65.5±16.5	27 - 87
AST 2 (after resolution of hepatitis) U/L	59.6±16.45	23 - 91
Albumin gm/dl	4.38±0.43	3.65 - 5.3
Total bilirubin1(In acute hepatitis phase) mg/dl	4.28±3.78	0.44 - 11
Total bilirubin2 (after resolution of hepatitis) mg/dl	0.99±0.27	0.38 - 1.4
PC (Prothrombin Concentration)	87.6±6.4	72.1 - 96
INR (International Normalized Ratio)	1.13±0.065	1.04 - 1.28

Kg, kilogram; m, meter; SD, standard deviation; AST, aspartate aminotransferase; ALT, alanine aminotransferase

Table 2 Classification of all studied patients according to LSM by TE before and after resolution of hepatitis

Stage of Fibrosis by TE	TE 1(number) (%)	TE 2(number) (%)
F1	3 (10%)	12 (40%)
F2	7 (23.4%)	10 (33.3%)
F3	10 (33.3%)	8 (26.7%)
F4	10 (33.3%)	0 (0%)

Table 3 Follow up of ALT, AST and TE after resolution of hepatitis

	Mean	SD	Wilcoxon test	P- value
TE 1 (In acute hepatitis phase) kPa	13.91	6.7	4.78	< 0.01*
TE 2 (after resolution of hepatitis) kPa	7.7	3.08		
ALT1 (In acute hepatitis phase) U/L	1370	761	4.78	< 0.01*
ALT 2 (after resolution of hepatitis) U/L	65.5	16.5		
AST1(In acute hepatitis phase)U/L	1151	759.4	4.78	< 0.01*
AST 2 (after resolution of hepatitis) U/L	59.6	16.45		

SD, standard deviation; kPa, kilopascal; ALT, alanine aminotransferase; AST, aspartate aminotransferase

Table 4 Spearman correlation between TE and laboratory variables in studied patients

		TE 1	TE 2
Age (in years)	R	0.04	0.42
	p- value	>0.05	<0.05*
BMI (Body Mass Index) kg/m^2 (kilogram/meter^2)	R	0.20	0.29
	p- value	>0.05	>0.05
ALT 1 (In acute hepatitis phase) U/L	R	0.38	
	p- value	<0.05*	
AST1(In acute hepatitis phase) U/L	R	0.41	
	p- value	<0.05*	
ALT 2 (after resolution of hepatitis) U/L	R		0.45
	p- value		<0.05*
AST 2 (after resolution of hepatitis)U/L	R		0.44
	p- value		<0.05*0
Albumin gm/dl	R	-0.26	-0.51
	p- value	>0.05	<0.01*
Total Bilirubin mg/dl	R	0.3	-0.13
	p- value	>0.05	>0.05
PC (Prothrombin concentration) %	R	-0.25	-0.34
	p- value	> 0.05	> .05
INR (International Normalized Ratio)	R	0.27	0.37
	p- value	>0.05	<0.05*

Table 5 Association between total bilirubin level and TE

		Mean	SD	Mann Whitney test	p-Value
TE1 (kPa)	Bilirubin ≤1.2 (mg/dl)	12.74	8.89	1.05	> 0.05
	Bilirubin >1.2(mg/dl)	14.27	6.09		
TE2 (kPa)	Bilirubin ≤1.2(mg/dl)	7.41	3.24	0.49	> 0.05
	Bilirubin >1.2(mg/dl)	7.79	3.098		

Discussion

Assessment of the stage of liver fibrosis is very important not only for estimation of prognosis, but also for indication of antiviral therapy .[12]. Acute viral hepatitis was estimated by elevation of serum ALT to more than ten times the upper limit of normal in a previously healthy person.[13] The wide utilization of serum aminotransferases due to the fact that the aminotransferases were considered to be indicators of hepatocellular damage that reflecting active disease.[14] TE using TE which is a noninvasive and reproducible technique that evaluates tissue stiffness. LSM has been demonstrated to be a reliable tool for assessing hepatic fibrosis and cirrhosis, mainly in patients with chronic hepatitis. Because TE can be performed rapidly, painlessly, and has high patient acceptance, it might become a common way of assessing fibrosis in routine practice.[15] It has been accepted as a highly reproducible and noninvasive technique to assess liver fibrosis with low inter- or intraobserver variability.[16] The extent of histological necroinflammatory activity has been shown to influence TE results in patients with viral hepatitis, resulting in an overestimation of TE values that increases in parallel with the degree of necroinflammatory score.[17] A risk of overestimation of TE values has been reported in cases of ALT flares in patients with acute viral hepatitis.[18] In acute hepatitis, the positive correlation of LS with ALT levels and bilirubin levels has been reported. These positive correlations in acute hepatitis may be attributed to the dominance of inflammatory liver injury instead of increased hepatic hydrostatic pressure.[19] The decrease in LS correlated best with the decrease in AST. No significant changes in LS were observed below AST levels of 100 U/L. In a cohort study of 101 patients with histologically confirmed Alcoholic steatohepatitis, LS was measured only in patients with AST<100 U/L at the time of LS assessment. The AUROC for cirrhosis detection by TE improved from 0.921 to 0.945 while specificity increased from 80% to 90%, at a sensitivity of 96%. A similar AUROC was obtained for F3 fibrosis stage, if LS measurements were restricted to patients with AST <50 U/L.[20] Severe hepatic necroinflammation is the most important factor leading to falsely-high liver stiffness measurements. Case series have shown that patients with acute viral hepatitis, drug-induced liver injury and severe acute exacerbation of chronic hepatitis B could have LS values well within the cirrhotic range, despite no evidence of fibrosis on histology.[21] Arena et al.[4] had similar results in 18 patients with acute viral hepatitis without history of liver disease, progressive normalization of LS values was observed in parallel with the decrease of aminotransferase levels.[4] Also, Coco et al.[3] reported that 1.3 to 3-folds increase in LS values at the time of ALT flares with progressive return to baseline values afterwards in 10 patients with chronic viral hepatitis associated with acute exacerbations.[3] As further confirmation, LS tends to decrease dramatically after the resolution of acute hepatitis. Using TE in these patients would therefore be misleading. The risk of a false diagnosis of cirrhosis is increased significantly when the serum ALT level is above five times the upper limit of normal.[22] It is advisable to critically consider LSM values obtained in the concomitance of aminotransferase flares, especially in patients with viral hepatitis. The association between LS and disease activity or necroinflammatory score has been observed by Fraquelli et al.[23] who showed a step-wise increase of LSM with necroinflammatory activity in a cohort of patients with disease of varied etiology.[23] In agreement with our findings, Sagir et al. .[24] in reported high liver-stiffness values suggestive of cirrhosis in 15 out of 20 patients with acute liver damage, but no signs of liver cirrhosis on physical examination, ultrasound examination or liver histology (performed in 11 patients). In six patients in whom a follow-up was available, liver stiffness values decreased to values below the cut off for cirrhosis on normalization of aminotransferase levels.[24] Finally, it appears clear that LSM does not represent a reliable instrument to detect the presence of advanced fibrosis and cirrhosis in patients presenting with a clinical picture of acute hepatitis.[25]

Conclusion

Acute hepatitis can be diagnosed easily both clinically and with simple laboratory tests. Clear correlation between aminotransferases and LSM has been described, with LSM values falling to normal range after resolution of the acute liver injury. TE has not demonstrated reliable diagnostic accuracy in patients with acute viral hepatitis.

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Conflicts of interest

The authors declare no conflicts of interest.

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