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RESEARCH ARTICLE

Enhanced Liver Fibrosis test can replace liver biopsy in detection of liver fibrosis in chronic hepatitis C patients

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Abstract

Background: Due to hazards of liver biopsy, serum fibrosis markers have been utilized as surrogates for a liver biopsy as the Enhanced liver fibrosis (ELF) test. **Objective:** The aim of this study is to investigate the diagnostic value of ELF test in assessment of liver fibrosis in chronic hepatitis C patients and compared it to liver biopsy and the transient elastography Fibroscan(TE). **Subjects and methods :** This study was conducted on 78 subjects divided to patients and control groups . The fibrosis was diagnosed by biopsy and fibroscan(TE) . ELF test was done using specifically ADVIA Centaur XP Immunoassay Systems. **Results**: ELF test values were significantly higher in patients group than control group .ELF test values were higher in significant fibrosis than mild fibrosis . Sensitivity and specificity of ELF were 86 % and 92.9 % respectively. **Conclusion:** ELF test has a good role in diagnosis of liver fibrosis in chronic hepatitis C patients. Implementation of ELF test can replace liver biopsy and it can use to monitor the efficacy of treatment .The combination of TE and ELF test together give accurately assessment of liver fibrosis.

INTRODUCTION

Chronic liver injury and extracellular matrix proteins deposition of liver parenchyma change the hepatic architecture with subsequent development of liver fibrosis which progresses rapidly to cirrhosis in most types of chronic liver diseases (Bataller and Brenner,2005). The liver biopsy which used to identify the grading and staging of the liver fibrosis. It is considered a gold standard test to diagnosis of liver fibrosis. There are some restrictions of liver biopsy as it is invasive technique resulting in patient hazards as pain, bleeding and billiary system injury in addition to variable accessibility, high cost, sampling mistakes and inaccuracy due to variability of pathologic interpretations(Zhang etal.,2005; Regev, 2002). Non-invasive diagnostic techniques as Transient Elastography and laboratory investigations as the Enhanced liver fibrosis (ELF) test are effective alternatives to liver biopsy, they have been sought to provide information about liver fibrosis to restriction of liver biopsy (Sebastiani G,2006).The Enhanced liver fibrosis test (ELF) is a non- invasive diagnostic test has been wanted to identify the stage of liver fibrosis even in patients without symptoms or signs. It depends on combinations of some proteins produced as a result of the fibrogenic process. These proteins are fragments of the liver matrix components produced by hepatic stellate cells (Parkes J ,2011). Enhanced liver fibrosis score derived from the combination of three direct markers of fibrosis, which are hyaluronic acid (HA), procollagen III amino terminal peptide (PIIINP), and tissue inhibitor of metalloproteinase (TIMP-1), this an algorithm developed by the European Liver Fibrosis Group, which could be used to determine the severity of liver fibrosis with good accuracy(Valva P et al.,2011; Martinez SM et al.,2011).

SUBJECTS AND METHODS

This study was conducted in Zagazig University Hospitals during the period between September 2013 to April 2014. It was approved by the local research ethics committee where all subjects gave their informed consent prior to their inclusion in the study. This research were included 78 subjects, 28 matched healthy adults as control group 20 male and 8 female with age ranging from 21 to 45 years with mean ±SD 33±12 years, and 50 chronic hepatitis C patients as patient group they were prepared for interferon therapy, they were 40 males and 10 females with age ranging from 26 to 48 years with mean ±SD 37±11years. Inclusion criteria of patients were chronic liver disease due to hepatitis C virus infection ,the hepatic fibrosis was diagnosed by liver biopsy and Vibrating controlled Transient Elastography Fibroscan (TE) for assessment of the severity of liver fibrosis and inflammation prior to treatment. Exclusion criteria included decompensated liver cirrhosis and hepatitis B infection. Chronic hepatitis C infection was diagnosed by serologic detection of hepatitis C antibody which was performed on cobas e 411 and serum hepatitis C virus RNA by Real Time PCR which was performed on COBAS® ampliPrep/COBAS®TaqMan. Both analyzers were provided by (Roche diagnostics). Each subject included in this study was subjected to clinical assessment, ultrasonography and laboratory investigations, which included complete blood picture, prothrombin time and concentration, liver and kidney functions tests, viral markers, PCR for HCV and Enhanced liver fibrosis markers together with calculated ELF score. ELF algorithm comprises hyaluronic acid (HA) (10-100ng/ml) procollagen III amino terminal peptide(PIIINP) (2-4ng/ml), and Tissue inhibitor of metalloproteinase(TIMP-1) (80-500ng/ml) using specifically ADVIA Centaur XP Immunoassay Systems by direct chemiluminescence method (Siemens. ADVIA Centaur enhanced liver fibrosis (ELF) test specifications2011 27 August 2013).

Calculation of ELF test =2.278+0.851(HA ng/ml)+0.751(P3NPng/ml)+0.394(TIMP1ng/ml).

ELF score in diagnosis of fibrosis was as follows: < 7.7 means None to mild fibrosis,

≥ 7.7 to < 9.8 means moderate fibrosis and ≥ 9.8 indicates severe fibrosis. The patients group was subdivided according to fibrosis grade into no or mild fibrosis (F0 to F2 fibrosis grade) and significant fibrosis (F3 to F6 fibrosis grade) .Fibrosis was graded on a 0-6 score as follows: F0, no fibrosis; F1, fibrous expansion of some portal area ± fibrous septa ; F2, fibrous expansion of most periportal area ± fibrous septa ; F3, fibrous expansion of most portal area ± occasion portal to periportal bridging ; F4, fibrous expansion of most portal area with marked bridging portal to portal as well as portal to central ; F5, marked bridging portal to portal or portal to central with occasional nodule ;F6, cirrhosis. Fibrosis was considered significant when the fibrosis grade was F2 or more (Ishak K, et al.,1995; Montazeri G, et al.,2005).

Statistical analysis: The results are expressed as mean ± standard deviation . Comparisons between groups were achieved by the Paired t-test. Receiver operating characteristics (ROC) analysis was used to evaluate the diagnostic value of ELF score to identify sensitivity and specificity, positive and negative predictive value. Calculations were done with the Statistical Package for the Social Sciences version 19 (SPSS,Inc.,Chicago, IL,USA). A value of $P<0.05$ was considered significant.

RESULTS

Table 1: There were non-significant difference among the studied groups as regard the mean values of hyaluronic acid (ng/ml) and TIMP (ng/ml), while there was highly significant difference in patient group compared to control group as regard the mean values of PIIINP. On the other hand, there were statistically significant difference among the different groups of this study as regard mean values of ELF score .

Table 2: Showed ELF parameters and score among fibrosis grades in patients group .There was non-significant difference in the mean values of H.A(ng/ml) between mild and significant fibrosis groups while there was highly significant decreased in patients with mild fibrosis compared to patients with significant fibrosis as regard the mean values of PIIINP, TIMP and ELF score. TE classified 32 (64%) patients with no or mild fibrosis (F0-F1) while ELF test considered this group have moderate fibrosis (score ≥ 7.7 - < 9.8). There were 18 (36%) patients with significant fibrosis diagnosed by TE and ELF test (F3 to F6 , ELF score ≥ 9.8) .

Table 3: At a cutoff value 7.7 of ELF score can detect the significant fibrosis with sensitivity 86 % specificity 92.9 % , the positive predictive value, negative predictive value and diagnostic accuracy were 95.5%, 78.8%, 88.5% respectively ,TE had 84% sensitivity. The combination between ELF score and TE gave sensitivity 93.5% . There were discrepancy in detection of fibrosis by biopsy, TE and ELF score as TE classified 8 patients with no fibrosis while ELF score detected 7 patients without fibrosis, although all of them had fibrosis as diagnosed by biopsy. In combination between ELF score and TE there were only three patients without fibrosis .

Table 1
ELF test (parameters and score) in both patients and control groups

Parameters	Patients N=50	Control N=28	t	P
H.A (ng/ml) X±SD	41.6± 3.76	43.5± 1.83	0.76	>0.05
PIIINP:(ng/ml) X±SD	10±0.57	2.7±0.46	7	< 0.001
TIMP (ng/ml) X±SD	221±76	176±73	2.8	<0.05
ELF score X±SD	8.9±0.9	6.6±0.84	8.4	<0.001

TIMP: tissue inhibitor of metalloproteinase, ELF:enhanced liver fibrosis **,** HA:hyaluronic acid , PIIINP: ProcollagenIII terminal peptide

Table 2
Relation between ELF test (parameters and score) with fibrosis grades**.**

parameters	No or Mild Fibrosis (N=35)) (70%	Significant fibrosis (N=15) (30%)	t	P
H.A(ng/ml) X±SD	45.75±3.36	48.6±0.1	1.8	> 0.05
PIIINP (ng/ml) X±SD	9.45±3.4	23.7±1.6	5.15	< 0.001
TIMP (ng/ml) X±SD	214±59	525±0.1	7.2	< 0.001
ELF score X±SD	8.8±1	10±0.07	2.64	<0.05

Mild fibrosis (F0 to F2)**,** Significant fibrosis (F3 to F6)

Table 3
Diagnostic performance of ELF score in diagnosis of liver fibrosis

ELF Score	Sensitivity	Spesificity	PPV	NPV	Accuracy
	86 %	92.9 %	95.5%	78.8%	88.5%
TE sensitivty	84%				
Sensitivty of TE&ELF score combination	93.5%				

PPV: Positive predictive value ,NPV: Negative predictive value

DISCUSSION

Liver biopsy is often mandatory in the management of patients with liver disease, physicians and patients might be reluctant to do this due to its concomitant risks (Rockey et al.,2009; European Association for the Study of the Liver,2009).The development of noninvasive methods to identify fibrosis grade throughout the entire liver would characterize a major advance in the management of liver disease. These capabilities would enable serial follow-up of patients, records of temporal changes, and assessment of therapy effect , provide direct benefits to patients and serve as a powerful research implement for therapy development (Rockey et al.,2009; Anna, et al.,2009) . In the present study, two ELF markers (HA&TIMP) showed no significant difference between patient and control groups ,whil PIIINP showed high significant increased in patient group,in addation the ELF score mean value in patient group was significantly higher than control group ,these result were not in accordance with Martinez et al.,(2011) and Yasser et al., (2013) they reported that all the ELF parameters were significantly elevated in hepatitis C virus patients. In our study, mean value of ELF score in patient group was significantly higher than control group this result supported by Rosenberg et al. (2004) they described that assessment of liver fibrosis with many serum markers used in combination is sensitive, specific, and precise. In our study the mean value of ELF score was higher in severe fibrosis than in mild fibrosis, this result was in agreement with Petersen et al.,(2014) they reported that ELF test was accurate in differentiating mild from significant liver fibrosis. In our study, ELF score diagnosed 36% of patients having ELF score ≥ 9.8 , so they were classified as having severe fibrosis and will progress to cirrhosis. Dolman et al., (2014) suggested that ELF test could be used to stratify hazard of subsequent progression to clinical outcomes in advanced fibrosis secondary to hepatitis C infection. In present study, ELF score at cutoff value >7.7 presented sensitivity and specificity of 86% and 92.9 % respectively. Catanzaro et al., (2013) determined that at cutoff value >7.72 provided a sensitivity of 93.0% and a specificity of 83.0% which were used for diagnosis of significant fibrosis. In our study ELF test had sensitivity higher than TE sensitivity, this result was supported by Kristin et al., (2012) they revealed that sensitivity of ELF was higher than that of fibroscan in detection of advanced fibrosis (100% vs 91%). Fernandes et al., (2014) reported that no statistically significant difference between ELF and TE for diagnosing fibrosis or cirrhosis and they determined that ELF test is a good noninvasive fibrosis marker and showed a parallel result to TE in chronic hepatitis C patients. Kim et.al (2012) demonstrated that , TE was significantly better than ELF for predicting $F \geq 3$ and F4, the difference between our results and others depend on the difference in cases number and the choice of patients. The results of the present study showed that, the combination between ELF score and TE increased the sensitivity to 93.5% to estimate liver fibrosis grade, this result supported by Trembling et al.,(2014) where they demonstrated that the performance of ELF is enhanced with the addition of TE ,both ELF and TE represented different and potentially complementary approaches to assess liver fibrosis and were concomitanted with minimal distress and risk to the patient when compared with biopsy.

Kristin et al., (2012) showed that the ELF test revealed good diagnostic accuracy to expect significant (≥F2) or advanced stages of fibrosis and looked to be less discriminative in lower degree of fibrosis(F1) . Parkes et al., (2011) reports the simplification of using the ELF test and its capability to identify severity of liver fibrosis in chronic hepatitis C patients . ELF test can be used as a good tool for the staging of cirrhosis in HCV patients, the ELF test evaluates the effect of liver fibrosis on liver function as well as the architectural destruction associated with histological fibrosis and cirrhosis (Martinez et al.,2011, Castera,2012,Xie ,2014). ELF test had prognostic value, it can reveal pathophysiological processes and functions that a biopsy cannot detect (Parkes et al.,2010).

The simplified ELF test was able to expect severety of fibrosis grade, it is an objective not subjective test, so there is no individual error or variation in interpretation. Determination of ELF test through a blood sample makes it easy to assess patient either at the bedside or in the outpatient clinic. ELF is an easy non invasive technique when compared to liver biopsy, it is easy to perform in obese patients . However there are some drawbacks of ELF teset as , may be present sampling errors as cross matching,although marker levels are highly reproducible, they are not specific for liver disease and do not allow easy discrimination of intermediate stages of fibrosis (Kim et al.,2010). TE is suitable when employed to follow-up disease progression and to expect hepatic events preceding cirrhosis (Fraquelli and Branchi,2011). However, it is difficult to detect liver fibrosisin obese patients and patients with narrow intercostal spaces, ascites, space-occupying tissue abnormalities, extrahepatic cholestasis, or congestion (Kim etal.,2010;Fraquelli and Branchi,2011). There are some restrictions to this study. Firstly, and the most important limitation is the high investigation cost which leads to take small number of cases and we do not do the fibroscan (TE) to control group. Secondly, the number of our patients with extensive fibrosis was relatively small and none of them having cirrhosis.

CONCLUSION

ELF test has a good role in diagnosis of liver fibrosis in chronic hepatitis C patients. Implementation of ELF test can replace liver biopsy and it can use to monitor the efficacy of treatment .The combination of TE and ELF test together give accurately assessment of liver fibrosis..

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References

1. Anna S, and Brian J, Chronic hepatitis B: update 2009. Hepatology, 2009; 50: 661- 62.
2. Bataller R and Brenner DA. Liver fibrosis.Clin Invest. 2005; 115(2):209-18
3. Castera L**.** Noninvasive methods to assess liver disease in patients with hepatitis B or C. Gastroenterology.2012;142:1293-302.e4**.**
4. Catanzaro R, Milazzo M, Arona S, Sapienza C, Vasta D, Arcoria D, et al. Diagnostic accuracy of enhanced liver fibrosis test to assess liver fibrosis in patients with chronic hepatitisC. HepatobiliaryPancreat Dis Int. 2013 ; 12(5):500-7.
5. Dolman GE, ZaitounA, IrvingWL and Guha NI.PTH-081 enhanced liver fibrosis (ELF) test performs better than histological parameters in predicting clinical outcomes in patients with advanced fibrosis due to chronic hepatitis C infection**.** Gut 2014; 63: A245, Issue Suppl 1 .
6. European Association for the Study of the Liver. EASL clinical practice guidelines management of chronic hepatitis B. J Hepatol 2009; 50:227- 42.
7. Fernandes FF,Ferraz ML, Andrade LE, Dellavance A,Terra C,Pereira G, et al **.**Enhanced Liver Fibrosis Panel as a Predictor of Liver Fibrosis in Chronic Hepatitis C Patients. [abstract] Clinical Gastroenterology ,2014; April 5.
8. Fraquelli M, and Branchi F, The role of transient elastography in patients with hepatitis B viral disease. Digestive and Liver Disease , 2011;43 :25-31
9. Ishak K, Baptista A, Bianchi L, Callea F, Groote JD, Guadat F, et al. Histological grading and staging of chronic hepatitis. J Hepatol 1995; 22:696-99
10. Kim BK, Kim HS, Park JY, Kim do Y, Ahn SH, Chon CY, Park YN, et al**.** Prospective validation of ELF test in comparison with Fibroscan and Fibro test to predict liver fibrosis in Asian subjects with chronic hepatitis B. [abstract].PLoSONE . 2012;7(7):e41964.
11. Kim SU, Han KH, and Ahn SH**.** Non-invasive assessment of liver fibrosis: time to move from cross-sectional studies to longitudinal ones. GastroenterolHepatol. 2010 ;25:1472-73.

12. Kristin Wahl, William Rosenberg, Bernhard Vaske, Michael P., Klaus Schulze-Osthoff,and Matthias J . Biopsy-controlled liver fibrosis staging using the Enhanced Liver Fibrosis (ELF) score compared to Transient Elastography . [abstract].PLOS ONE,2012**;** 7,Issue12 ,e51906.

13. Martinez SM, Fernandez-Varo G,Gonzalez P, Sampson M, Bruguera, M. Navasa, M. et al.Assessment of liver fibrosis before and after antiviral therapy by different serum marker panels in patients with chronic hepatitis C. Alimentary Pharmacology and Therapeutics; 2011;33: 138-48.

14. Montazeri G, Estakhri A, Mohamadnejad M, Nouri N, Montazeri F, Mohammadkani A, et al. Serum hyaluronate as a non-invasive marker of hepatic fibrosis and inflammation in HBeAg-negative chronic hepatitis B. BMC Gastroenterology, 2005; 5-32 .

15. Parkes J , Guha IN, Roderick P and Harris S, Cross R, Manos MM, et al**.** Enhanced Liver Fibrosis (ELF) test accurately identifies liver fibrosis in patients with chronic, hepatitis C.Viral Hepatitis**,** 2011;8(1):23-31.

16. Parkes J, Roderick P, Harris S, Day C, Mutimer D, et al. (2010) Enhanced liver fibrosis test can predict clinical outcomes in patients with chronic liver disease. Gut 59: 1245–1251.

17. PetersenJR, StevensonHL, KasturiKS, Naniwadekar A, Parkes J, Cross R, el al**.** Evaluationof the Aspartate Aminotransferase/Platelet Ratio Index and Enhanced Liver Fibrosis tests to detect significant fibrosis due to chronic hepatitis C**.**Clinical Gastroenterology, 2014; 48 :370-76.

18. Regev A, Berho M, Jeffers LJ, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol. 2002; 97: 2614-18.

19. Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD **..** American Association for the Study of Liver Diseases. Liver biopsy. Hepatol. 2009 ; 49(3):1017- 44.

20. RosenbergWM ,Voelker M, Thiel R, Becka M, Burt A, Schuppan D,et.al. Serum markers detect the presence of liver fibrosis: a cohort study, Gastroenterology. 2004 127(6):1704-13.

21. Sebastiani G, and Alberti A**.** Noninvasivefibrosis biomarkers reduce but not substitute the need for liver biopsy. World J Gastroenterol, 2006;21;12(23):3682-94.

22. Siemens. ADVIA Centaur enhanced liver fibrosis (ELF) test specifications2011 27 August 2013]: Available from: http://www.healthcare.siemens.com

23. TremblingP, Lampertico P,Parkes J, Tanwar S ,Viganò M ,Facchetti F, et al**.** Performance of Enhanced Liver Fibrosis test and comparison with transient elastography in the identification of liver fibrosis in patients with chronic hepatitis B infection,Viral Hepatitis, 2014; 21,430- 38.

24. Valva P , Casciato P, Diaz Carrasco JM, Gadano A, Galdame O, Galoppo MC etal. The role of serum biomarkers in predicting fibrosis progression in pediatric and adult hepatitis C virus chronic infection. PLoS One. 2011; 6(8):e23218.

25. Xie Q, Zhou X, Huang P, Wei J, Wang W, Zheng S, et al. The Performance of Enhanced Liver Fibrosis (ELF) Test for the Staging of Liver Fibrosis: A Meta-Analysis. PLoS ONE , 2014; 9(4): e92772.

26. Yasser E, Mones M, Essam M, and Manal A **.** Performance of diagnostic biomarkers in predicting liver fibrosis among hepatitis C virus-infected Egyptian children.Rio de Janeiro,**2013;**108(7): 887- 93.

27. ZhangM, SunXD and Mark SD**.** Hepatitis C virus infection, Linxian, China. Emerg Infect Dis, 2005; 11: 17-21.