Value Of Noninvasive Transient Elastography For Assessment Of Liver Fibrosis Stages In Chronic Hepatitis C

Thesis

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List of Abbreviations

AUC	:	Area under curve
B.M.I	:	Body mass index.
C.B.C	:	Complete blood Cytology
C.T	:	Computerized tomography
ECM	:	Extra cellular matrix
H.C.V	:	Hepatitis C. Virus
H.C.V ab	:	Hepatitis C virus antibodies
HBV	:	Hepatitis B. virus.
HIV	:	Human Immunodeficiency Virus
HSCs	:	Hepatic stellate cells
KPa	:	Kilo Pascals
MHz	:	Mega Hertiz
N.A.S.H	:	None alcoholic steatohepatitis.
P.C.R	:	Polymerase chain reaction
PBC	:	Primary biliary cirrhosis
PSC	:	Primary sclerosing cholingitis
ROC	:	Receiver operating characteristics
U.S	:	Ultra sound.

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Abstract

Background: The accurate diagnosis of hepatitis C virus (HCV)-related fibrosis is crucial for prognosis and treatment decisions. Due to the limitations of biopsy, noninvasive alternatives including FibroScan have been developed. Our objective was to systematically study the accuracy of Fibroscan for predicting HCV-related fibrosis.

Methods: We prospectively enrolled *30* consecutive adult patients who have undergone a liver biopsy at Hepato-Gastroenterology department at Ahmed Maher teaching Hospital,Cairo,Egypt .

All patients were studied using the non-invasive method of transient elastography (Fibroscan, Echosens, Paris, France).

Measurements are totally non-invasive and performed on the right lobe of the liver through intercostal spaces , the results are expressed in kilopascals (kPa). Transient elastography measures the liver stiffness in a volume that approximates a cylinder 1-cm wide and 6-cm long.

The technique was performed by the same gastroenterologist and at least 10 validated measurements were carried out in each patient.

All biopsy specimens were analysed independently by the same pathologist according to the METAVIR scoring system. Fibrosis was staged on a 0-4 scale: F0, no fibrosis; FI, portal fibrosis without septa; FII, portal fibrosis and few septa extending into lobules; FIII, numerous septa extending to adjacent portal tracts or terminal hepatic venules; and FIV, cirrhosis.

The statistical analyses was done to compare the efficacy of fibroscan in relation to liver biopsy.

Results:In our study we evaluated the effectiveness of fibroscan in comparison to liver biopsy ,and we found that fibroscan can diagnose no or mild fibrosis stages F0 & F1 with sensitivity, Specificity, PPV, NPV, equal 96.3%, 66.7%, 96.3, 66.7%, and 93.3% diagnostic accuracy respectively.

For diagnosis of cirrhosis, sensitivity, Specificity,PPV ,NPV equal 83.3%,91.7%,71,4%,95,7% and 90% diagnostic accuracy respectively.

For identification of the target group of patients who will be included in programs of interferon therapy ; (stages F2 & F3) sensitivity, Specificity,PPV ,NPV,equal 85.7%,77.8%,. 90%,70%,and 83.3% diagnostic accuracy respectively.

For differentiation between mild and moderate fibrosis (F0, F1, F2) from severe fibrosis and cirrhosis (F3 & F4). We found that fibroscan differentiate mild, moderate fibrosis from severe fibrosis and cirrhosis perfectly with sensitivity, Specificity,PPV ,NPV and diagnostic accuracy equal 100%.

In conclusion, transient elastography is an easy and quick clinical non-invasive method to perform. Results are available immediately, and this technique is accurate in predicting significant fibrosis. Hence, transient elastography could be useful not only to evaluate liver fibrosis as to monitor liver disease progression, but also to monitor anti-viral or antifibrotic therapy effects and to help taking decisions in daily clinical practice.

INTRODUCTION

The prognosis of chronic liver disease patients is related to the development of fibrosis and the risk of cirrhosis with complications such as portal hypertension, liver failure or hepatocellular carcinoma. This evidence has led to the compelling need of acquiring the most adequate clinical approaches for the evaluation of fibrogenic progression of chronic liver disease **(*Blanc et al., 2005 and Iacobellis et al., 2005*).**

Liver biopsy is considered as a 'gold standard' technique because it confirms clinical diagnosis; assesses the severity of necroinflammatory activity and fibrosis; evaluates possible concomitant disease process and guides therapeutic interventions **(*Bravo et al., 2001 and Grant & Neuberger, 1999*).** Histological staging is recommended by the American and European Associations for the Study of Liver Diseases to identify patients at risk of progressive liver disease and eligible to antiviral therapy **(*Blanc et al., 2005*).** However, liver biopsy is an invasive and expensive method, and can have the remote risk of life-threatening complications **(*Reiss, 2005*).** Moreover, the accuracy of liver biopsy for assessing fibrosis has also been questioned because of sampling errors and intra- and interobserver variability **(*Regev et al., 2002*).**

At present, there is an increasing need for alternative non-invasive methods to estimate the stage of liver fibrosis **(*Blanc et al., 2005 and Iacobellis et al., 2005*).** Among these methods, transient elastography seems to be one of the most promising **(*Sandrin et al., 2003*).** Transient elastography (FibroScan system) is a novel, non-invasive and safe technique for the evaluation of fibrosis in chronic liver disease. The FibroScan system applies low amplitude, low frequency vibration to the tissue, which propagates an elastic shear wave through the liver. The speed of the propagation, which increases with increasing tissue hardness, is measured with pulsed ultrasound. Transient elastography was proposed as surrogate marker of fibrosis with high accuracy to identify cirrhosis **(*Mendoza et al., 2006 and Castera et al., 2005*).**

Currently, few studies that exist value the efficacy of transient elastography in chronic liver diseases, mainly in hepatitis C virus (HCV)-infected patients **(*Sandrin et al., 2003 and Mendoza et al., 2006*).**

The liver stiffness found by transient elastography was compared with the liver fibrosis found by liver biopsy in patients with HCV infection achieving a positive correlation between liver stiffness and hepatic fibrosis **(*Blanc et al., 2005 and Iacobellis et al., 2005*).**

AIM OF THE STUDY

The aim of our study is to evaluate the effectiveness, objectivity, reproducibility and safety of transient elastography, a new non-invasive technique, in the evaluation of fibrosis in patients with chronic viral hepatitis C. Comparing it with the gold standard tool i.e liver biopsy.

LIVER FIBROSIS

Liver fibrosis is the excessive accumulation of extracellular matrix (ECM) proteins including collagen that occurs in most types of chronic liver diseases ***(Friedman, 2003)***. It is considered a model of wound healing response to chronic liver injury ***(Albanis et al., 2001).***

The accumulation of ECM proteins distort the hepatic architecture by forming a fibrous scar, with subsequent development of nodules of regenerating hepatocytes that defines cirrhosis. Cirrhosis produces hepatocellular dysfunction and increases intrahepatic resistance to blood flow, which results in hepatic insufficiency and portal hypertension, respectively ***(Gines et al., 2004).*** In contrast with the traditional view that cirrhosis is an irreversible disease, recent evidence indicates that even advanced fibrosis is reversible ***(Arthur, 2002).***

Progression of Liver Fibrosis:

The development of fibrosis usually requires several months to years of ongoing injury, however liver fibrosis progresses rapidly in several clinical settings including repeated episodes of severe acute alcoholic hepatitis, subfulminant hepatitis, and HCV reinfection after liver transplantation ***(Berenguer et al., 2003).***

The natural history of liver fibrosis is influenced by both genetic and environmental factors. Epidemiological studies have identified polymorphisms in a number of candidate genes that may influence the progression of liver fibrosis in humans. These genetic factors may explain the broad spectrum of responses to the same etiological agent found in patients with chronic liver diseases ***(Bataller et al., 2003).***

Hepatic fibrosis can be viewed as a disease in which multiple genes interact with environmental factors. Although many causal agents of liver fibrosis have been identified, not all patients exposed to a similar agent develop the same degree of liver fibrosis. For example, host factors such as age or gender seem to play an important role. Large-scale studies have allowed the identification of patients with rapid fibrosis progression per unit time ('rapid fibrosers') and those with slow fibrosis progression ('slow fibrosers'). The genetic determinants involved in this different individual behaviour remain largely unknown, but candidate genes are currently under evaluation.

The most commonly studied genes are the ones encoding alcohol-metabolizing enzymes and haemochromatosis gene HFE $C_{282}Y$ heterozygosity. Mutations of the latter gene have been reported to play an important role in fibrosis progression in patients with HCV.

Histology of The Liver:

The normal liver parenchyma is composed of an epithelial component (Hepatocytes), an endothelial lining distinguished by fenestrations or pores (Sinusoids), tissue macrophages (Kupffer cells), and liver specific pericytes known as hepatic stellate cells (HSCs). The sinusoid is the liver microvascular unit, with the subendothelial space of Disse separating the hepatocytes from the sinusoidal endothelium. This space contains a basal membrane-like matrix essential for maintaining the function of all resident liver cells and for ensuring optimal metabolic exchange between the blood stream and hepatocytes. Portal tracts are key structures in the architecture of liver tissue and include branches of the portal vein, the hepatic artery, bile ducts, lymphatic ducts and stromal cells (Portal myofibroblasts and fibroblasts) ***(Schuppan et al., 2001).***

Responce to Injury:

Hepatic fibrosis or scarring is considered a wound healing response to limit tissue damage after chronic liver injury, regardless of aetiology. However, progressive scarring in response to a persisting liver insult eventually leads to cirrhosis with disorganization of the normal liver architecture, characterized by fibrotic bands, parenchymal nodules and vascular distortion. The composition of the hepatic scar is similar regardless of the cause of injury including hepatitis B