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Chapter

Elastography in Chronic Liver Diseases

Samuel N. Gitau and Issa K. Menge

Abstract

Elastography is useful for diagnosing and grading hepatic fibrosis in patients with chronic liver diseases (CLD). In addition, it may be used as a noninvasive tool for surveillance and prognostication of patients with complications related to CLD. Elastography uses real-time ultrasound to assess for tissue elasticity and is a fast, simple, reproducible, and reliable method for noninvasive liver fibrosis evaluation. Management of chronic liver disease is dependent on the grade of liver fibrosis to ascertain the urgency and choice of treatment and advice on further screening for cirrhosis and hepatocellular carcinoma. This chapter will highlight the role of elastography in the evaluation of chronic liver disease including hepatitis B and C and HIV-related liver disease and nonalcoholic fatty liver disease (NAFLD).

Keywords: diffuse liver disease, hepatitis B, hepatitis C, nonalcoholic fatty liver disease

1. Introduction

Chronic liver diseases are a major cause of morbidity and mortality worldwide with around 800,000 deaths per year attributable to liver cirrhosis [1]. There are a myriad of causes of chronic liver disease including viral infections, alcohol abuse, nonalcoholic fatty liver disease, biliary disease, autoimmune disease, genetic causes, and metabolic disorders [2]. Liver fibrosis results from chronic injury induced by a variety of causes with infection being the leading one. Most patients with chronic liver disease are often asymptomatic with symptoms only setting in when complications of the disease such as portal hypertension, cirrhosis, and hepatocellular carcinoma develop.

Management of chronic liver disease is dependent on the grade of liver fibrosis to ascertain the urgency and choice of treatment and advice on further screening for cirrhosis and hepatocellular carcinoma. Though liver biopsy has traditionally been the gold standard for diagnosis and staging of liver fibrosis, the procedure has paramount shortfalls as a medical screening test. It lacks the safety profile, accuracy, and accessibility of a standard medical screening test. It is an invasive technique with rates of morbidity of 3 in 100 and mortality of 3 in 10,000 reported [3]. In addition, sampling errors may arise because only 1/50,000 of the liver is sampled during the procedure. Inter- and intra-observer variability of between 10 and 20% in interpretation and staging of hepatic fibrosis have been reported which may lead to under-staging or over-staging of fibrosis [4]. A study by Maharaj et al. [5], where three percutaneous liver biopsies were performed in the same patients using the same entry points, found a concordance rate for cirrhosis in all three

biopsy specimens of only 50%. Taking into consideration all these shortfalls, the "gold standard" for the true liver disease status would be the histological analysis of nearly the entire liver which is not feasible. Effectively, liver biopsy is an "imperfect gold standard," and the definitive diagnosis of liver fibrosis in routine clinical practice is practically impossible [6].

Elastography uses real-time ultrasound to assess for tissue elasticity and is a fast, simple, reproducible, and reliable method for noninvasive liver fibrosis evaluation.

Elastography as a tool for evaluation of disease relates to one of the first physical exam skills every physician learns, i.e., palpation. This is based on the premise that diseased organs feel harder than the normal surrounding tissue. Using elastography, tissue stiffness (or hardness) can be measured and converted into an image. Young's modulus is used to quantify the elasticity or stiffness of a tissue and is calculated from the ratio between a uniform compression (stress, s) applied to the tissue and the resulting induced tissue deformation (strain, e) as shown in the equation below [7].

$$\text{Young"s modulus (elasticity)} = \text{Stress/Strain or } E = s/e \quad (1)$$

Using a reference amount of force applied to the tissue, its elasticity can be determined. Elasticity is measured in pressure units, pascal, or kilopascals (kPa).

The stiffness (elasticity) of normal, healthy liver is very low (of the order of 2 kPa, comparable to a soft gelatin gel) [8]. In response to inflammation, liver cells die and are replaced by scar tissue. As fibrosis progresses, the scar tissue becomes progressively rigid, and as a result the stiffness of the tissue increases. The stiffness of fibrotic liver is a reflection of the severity of the disease. Using elastography, an image of the shear stiffness of a tissue can be created [9]. It can therefore be used to monitor the extent of liver damage. Elastography is a painless and rapid procedure and does not require any preparation.

There are two main ways of performing elastography. The maiden method which has been widely used is transient elastography (TE) popularly known as FibroScan. The other relatively new methods are real-time elastography (RTE) using shear waves and acoustic radiation force impulse imaging (ARFI) [10–12].

Transient elastography uses both ultrasound (around 5 MHz) and low-frequency (50 Hz) mechanically generated shear waves to determine tissue elasticity. The propagation velocity of the shear waves is directly related to elasticity with the speed greater in stiff (fibrosed) tissue than in a softer tissue. The shear wave is generated by an external low-frequency vibrator which strikes the patient's skin and produces the shear wave whose propagation in the tissue of interest is measured and provided as an average elasticity [10]. In evaluation of liver elasticity, the measurements are acquired from the right lobe of the liver through the intercostal space. Ten liver stiffness measurements are obtained and the median considered as the representative value.

The limitations of this technique include the low volume of parenchyma explored, absence of real-time ultrasound guidance, measurement difficulties in cases of obesity and presence of ascites, and lack of specificity for the distinction of significant fibrosis level. The learning curve in correctly performing the examination without imaging guidance also serves to limit its reproducibility [10]. These drawbacks have led to the quest for a better elastographic method the birth of which is real-time elastography (RTE).

RTE does not require an external vibrator to generate the shear wave as is the case with transient elastography. The probe of the ultrasound machine produces a localized radiation force deep in the tissue of interest. This radiation force induces a shear wave, which then propagates through the tissue from a focal point. Several

focal points are then generated in a line perpendicular to the surface of the patient's skin (**Figure 1**).

The transmission of the shear wave is then detected by the rapid acquisition of ultrasound which takes only a few milliseconds, thus the patient or operator movement does not impact the result. The speed at which the shear wave propagates is then estimated from the measurement of the displacement induced by the shear wave and a real-time two-dimensional color map displayed. This color map is color-coded for the different shear wave speeds representing the degrees of stiffness from soft to hard. This color map is accompanied by an anatomic reference gray-scale (or B-mode) image; hence the area of sampling can be identified on the image (**Figure 2**).

Elastographic reference ranges have been developed for distinguishing mild fibrosis from significant fibrosis and cirrhosis following using histology (METAVIR score) as the reference standard [13–15] (see details in **Table 1**).

2. Elastography in hepatitis B and C

An estimated 240 and 160 million people in the world have chronic hepatitis B and C virus infections, respectively, according to the Centers for Disease Control and Prevention [16].

Elastography has been validated as a surrogate marker of liver fibrosis in a great number of studies, mainly in patients with chronic hepatitis B and C infections, and has enabled decision on when to start antiviral treatment without the need of performing liver biopsy [17].

The recommended velocity cutoffs for degree of liver fibrosis in patients with hepatitis C using the different elastography techniques are summarized in **Table 1** [18]. These cutoffs have been adapted for all cases of chronic liver disease.

In chronic hepatitis C, elastography has been shown to perform better for diagnosis of significant fibrosis (METAVIR score F ≥ 2) and cirrhosis (METAVIR score F4). The area under the ROC curve (AUROC) for the assessment of significant fibrosis ranged from 0.77 to 0.90 (F ≥ 2) and 0.90 to 0.97 for assessment of cirrhosis [17, 19–21]. Similar findings have been observed in patients with chronic viral

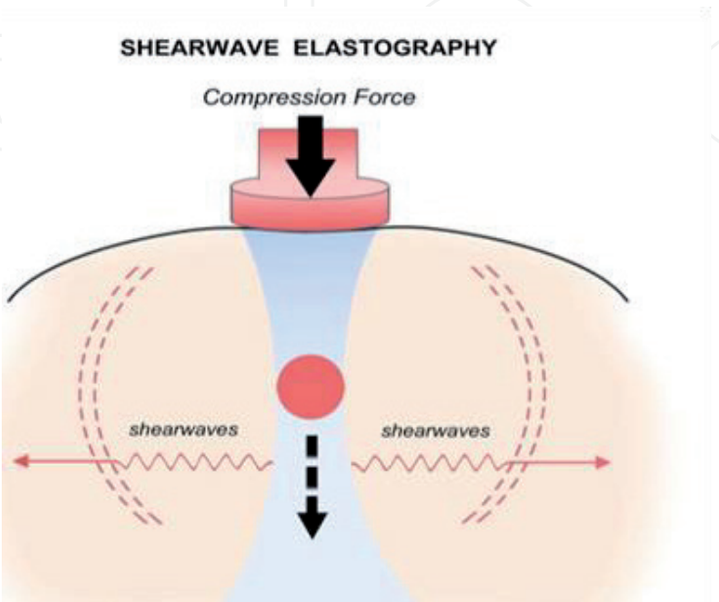

Figure 1.
Image illustrating propagation of shear waves from a focal point.

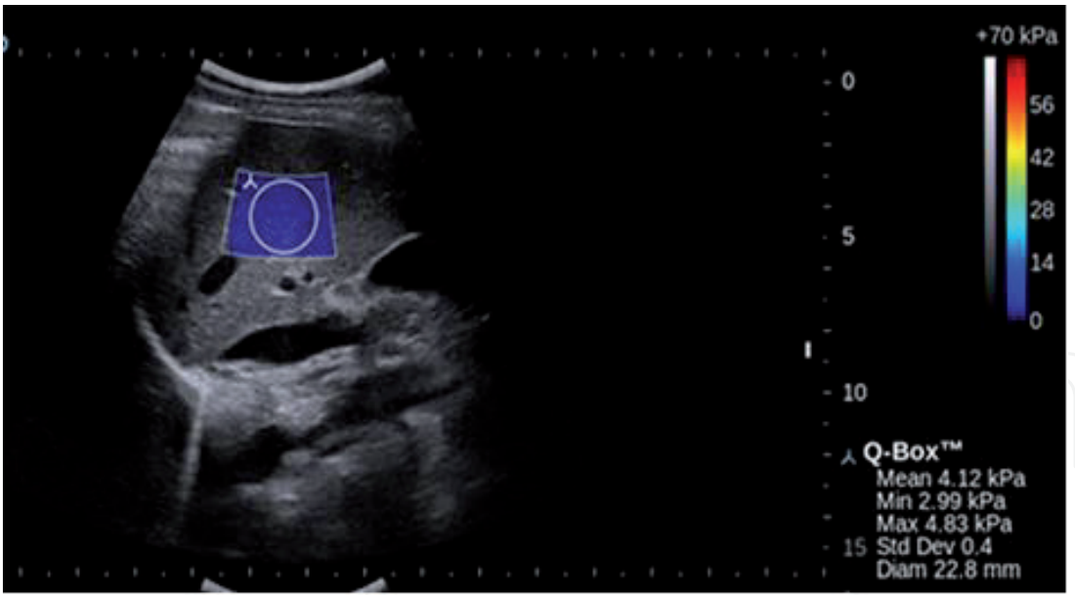

Figure 2.
Gray-scale image showing acquisition of an elastography reading using RTE.

			Velocity Cutoff				
Pathologic Findings	METAVIR Score	Proposed Risk-based Group	Transient Elastography (FibroScan)	Point SWE (Siemens)	Point SWE (Philips)	2D SWE (Aixplorer)	Point SWE (GE)*
No fibrosis Fibrous portal expansion Few bridges or septa	F0 F1 F2	Low risk (≤F2): unlikely to need follow-up	<7 kPa (<1.5 m/sec)	<5.6 kPa (<1.2 m/sec)	<5.7 kPa (<1.37 m/sec)	<7 kPa (<1.5 m/sec)	<8.29 kPa (<1.66 m/sec)
Numerous bridges or septa Cirrhosis	F3 F4	High risk (F3 or F4): clinically significant fibrosis	>15 kPa (>2.2 m/sec)	>15 kPa (>2.2 m/sec)	>15 kPa (>2.2 m/sec)	>15 kPa (>2.2 m/sec)	>9.40 kPa (>1.77 m/sec)

Table 1.
Recommended velocity cutoffs for degree of liver fibrosis in patients with hepatitis C using the different elastography techniques. Source: [18].

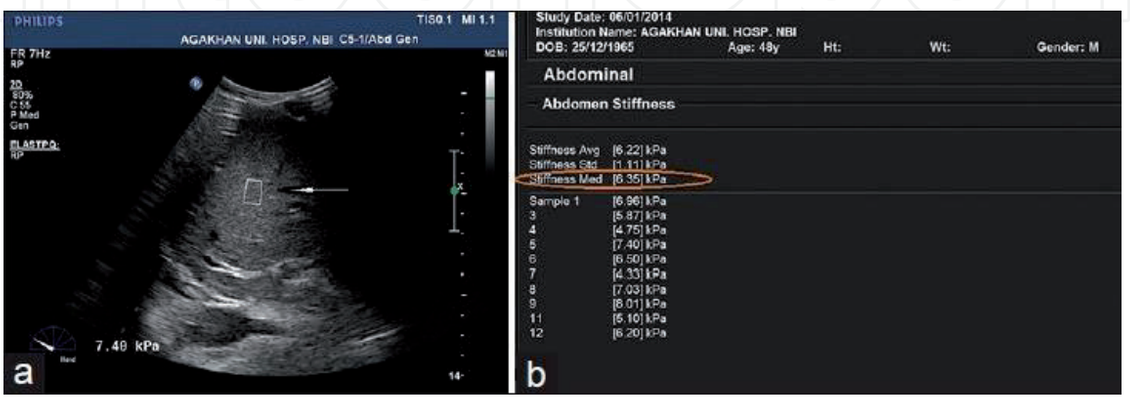

Figure 3.
A 39-year-old male with the human immunodeficiency virus and hepatitis B virus coinfection. (a) Grayscale ultrasound image of the liver shows a shear wave elastography acquisition box (arrow) with a high elastography score of 7.4 kPa. (b) a table showing 10 liver stiffness measurements readings for the same patient with a high median elastography score of 6.35 kPa (encircled). Source: [25].

hepatitis B where AUROC values ranged from 0.81 to 0.95 for significant fibrosis and from 0.80 to 0.98 for patients with cirrhosis [22, 23]. This shows that elastography forms an important screening tool for identifying patients with significant fibrosis that would warrant treatment.

There has been an increase in the proportion of liver-related deaths due to HCC in patients with HIV (from 15% in 2000 to 25% in 2005) with underlying HIV-HCV coinfection in the majority of the deaths [24]. In a study on liver fibrosis in patients with HIV-HBV coinfection using shear wave elastography, HBV coinfection was associated with 4.5 times increase in the prevalence of significant fibrosis which impacts progress of liver disease with its potential associated morbidity and mortality in patients with HIV [25]. Monitoring of degree of fibrosis in these patients is therefore very important, and elastography provides a noninvasive means of doing this (**Figure 3**).

The World Health Organization recommends the use of elastography (where available) for screening for liver fibrosis in patients with chronic hepatitis B infection [26].

3. Nonalcoholic fatty liver disease

Due to the increasing rates of sedentary lifestyle and obesity, nonalcoholic fatty liver disease (NAFLD) is now the most common cause of abnormal liver function tests (LFTs) in the Western world [27]. NAFLD is defined as the presence of more than 5% of steatotic hepatocytes in patients who do not consume excessive alcohol (less than 30 g/day for men and less than 20 g/day for women) [28, 29]. It is a spectrum of disease starting from simple steatosis progressing to nonalcoholic steatohepatitis (NASH), through advanced fibrosis and cirrhosis. Up to 80% of patients with central obesity and type 2 diabetes have evidence of NAFLD on imaging [28].

In most patients, NAFLD coexists with other liver pathologies including hepatitis C, hemochromatosis, and alcoholic liver disease. The presence of NAFLD on a background of these diseases causes more rapid disease progression. Treatment with steatogenic drugs including steroids, tamoxifen, and amiodarone can also cause fatty liver infiltration [30].

Most patients with NAFLD have simple steatosis, which has good clinical outcome and no overall increase in mortality. However, up to a third of these patients have NASH which is the progressive form of NAFLD. Up to 40% of patients with NASH develop progressive liver fibrosis with 20–30% culminating in cirrhosis. Patients with cirrhosis secondary to NASH are at an increased risk of developing hepatocellular carcinoma (2.6% per year) [31–36].

NAFLD can be diagnosed by the demonstration of hepatic steatosis on imaging or histology where other etiologies of liver disease or steatosis have been excluded. Although most clinicians rely on deranged liver function tests to identify patients with NAFLD, this can be inaccurate as majority of the patients will remain within normal-range ALT levels. Furthermore, even for those patients identified to have elevated ALT, the ALT typically falls (and AST may rise) as fibrosis progresses to cirrhosis. Importantly ALT values do not demonstrate positive correlation with histological findings. Therefore, isolated measurement of ALT is of little value in both the diagnosis of NAFLD and determination of its severity [37–39].

When fatty liver disease is suspected clinically, this should be confirmed with imaging. Ultrasound is usually the first-line investigation for patients suspected to have hepatic steatosis. It provides a qualitative assessment of fatty infiltration of the liver where gray-scale findings are used. The echogenicity of the liver parenchyma is compared to that of the kidney and other internal liver structures such the vascular

walls to diagnose and grade hepatosteatosis. Normal liver is hypoechoic relative to the renal cortex and becomes relatively hyperechoic with the presence of fatty infiltration. Ultrasound is effective in diagnosing steatosis if the percentage of involved hepatocytes is >33%; its diagnostic performance is however low with lesser degrees of fatty liver infiltration. Consequently, a normal liver ultrasound finding does not invariably rule out the presence of mild liver steatosis. Additionally, conventional ultrasound cannot assess the degree of fibrosis [40].

Liver elastography technique can measure steatosis simultaneously with the assessment of liver stiffness. It is paramount to stage the degree of fibrosis in patients with NAFLD as this will help identify patients with advanced fibrosis and resultant increased risk of liver-related complications such as liver failure and hepatocellular carcinoma [41].

It has been shown that there is a positive correlation between shear wave velocity and increasing hepatic fibrosis. In a study of 246 subjects with NAFLD, the AUROCs for the detection of $F \geq 2$ and $F \geq 3$ were 0.84 and 0.93, respectively. The sensitivity and specificity for advanced fibrosis ($F \geq 3$) were 91% and 75% with an elastography score cutoff of 7.9 kPa [42].

Inflammation is also known to increase shear wave velocity since the presence of edema results in reduced elasticity. It is therefore important to exclude active inflammation as this can confound the staging of liver fibrosis in the setting of NASH [43].

In summary, elastography plays a critical role in the evaluation of patients with NAFLD since early diagnosis of severe liver fibrosis allows for the institution of appropriate therapy as well as prognostication.

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