Non-invasive tests for fibrosis detection: still in search for the best way

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Eilenberg and colleagues' paper highlights the importance of non-invasive detection by using vibration controlled transient elastography (VCTE) and controlled attenuation parameter (CAPTM) for the assessment of fibrosis, steatosis, and non-alcoholic steatohepatitis (NASH). In a real-world cohort of patients with severe obesity (1). The authors enrolled 170 patients who were scheduled for bariatric-metabolic surgery and closely examined them for metabolic liver disease. The majority of patients (89.4%) and patients with NASH (60.6%), respectively, displayed symptoms of non-alcoholic fatty liver disease (NAFLD). Severe steatosis was found in 22.9% of patients, whereas fibrosis (F2) was present in 21.8% of cases and advanced fibrosis (F3) was present in 14 patients (8.2%). Particularly in patients with body mass indices (BMIs) below the median of 44.4 kg/m^2, liver stiffness measurement (LSM) by VCTE, CAPTM, and FibroScan-aspartate aminotransferase (FAST) achieved an acceptable accuracy for the various degrees of fibrosis.

It is well recognized that NAFLD and NASH have a natural history that is marked by the progression of liver cirrhosis and its adverse aftereffects, such as the emergence of hepatocellular cancer or the complication of portal hypertension. NAFLD fibrosis typically advances one stage every 14 years (2), and NASH fibrosis advances one stage every 7 years. According to the stage, the evolution can vary in terms of time and/or severity and is frequently not linear (3). NAFLD is thought to affect up to 46% of European adults (on average, 25%), including children. Chronically consuming too many calories, not exercising, and being overweight or obese are all strongly related to this illness. Therefore, those who have type 2 diabetes (T2D) and obesity are at risk for developing NAFLD.

In a previously published paper on 90 morbidly obese NAFLD patients undergoing bariatric surgery, where histology was obtained, we hypothesized that a decreased glucose clearance during the oral glucose tolerance test (OGTT) measured by the "oral glucose insulin sensitivity" (OGIS) index might be a possible mechanism of NAFLD onset and progression. In other words, indicators of the histological severity of liver disease are found in OGTT-indices of IR rather than insulin response (4).

The clinical assessment of a patient with obesity includes obesity staging, patient's lifestyle, comorbidities, and drugs evaluation. A comprehensive history, physical examination and laboratory assessment should be obtained. The progression to cirrhosis should be promptly identified

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and avoided with dietary, pharmacological, and behavioral interventions. Non-invasive testing are new technologies that can aid in and streamline the diagnosis of NAFLD and NASH, which are normally asymptomatic and need a liver biopsy. The development and validation of non-invasive methods that allow both to identify the presence of steatosis and an effective staging of liver disease is now widely under deep investigation, even more so in patients at high prognostic risk such as obese and comorbid. It therefore appears appropriate to focus both on non-invasive methods aimed at identifying and quantifying hepatic steatosis, and on those that study the presence and degree of fibrosis in all degrees of obesity. "Steatosis scores" could be used to diagnose steatosis in at-risk patients, but sadly, they don't contribute much to the knowledge offered by standard clinical laboratory and imaging exams of patients with suspected NAFLD (5-8).

The need for noninvasive, efficient, and economical methods to grade NAFLD and to detect severe NAFLD, advanced fibrosis, and possibly NASH in individuals with morbid obesity is significant. Furthermore, the validity of these results in the context of severe obesity was not established. In a group of 90 morbidly obese adults who had liver biopsy in order to detect fatty liver and determine the presence of fibrosis, our prior article assessed the diagnostic effectiveness of noninvasive scores of NAFLD/NASH and of acoustic radiation force impulse (ARFI).

We discovered that OGIS and the visceral adiposity index (VAI) work effectively together to separate NASH from NAFLD. In addition, we suggested revised thresholds for the most used noninvasive indexes [hepatic steatosis index (HSI), fatty liver index (FLI), NAFLD-liver fat score (NAFLD-LFS), lipid accumulation product (LAP), and triglyceride-glucose (TyG)] to identify steatosis in morbidly obese individuals. Finally, we had demonstrated that conventional fibrosis scores are frequently incorrect since fibrosis grade is typically less severe in morbidly obese people, with the exception of APRI, which increases with fibrosis grade even in the absence of advanced fibrosis (9).

The most popular approach for diagnosing steatosis is ultrasound. It is readily available, safe, well-established, and performs well when compared to liver biopsy, although it has certain drawbacks, such as lower accuracy in obese patients.

Magnetic resonance is a precise, repeatable, imaging-based method that can quantify liver fat with a high degree of accuracy for detecting and grading steatosis, but it is only suitable for obese patients and is expensive. Controlled attenuation parameter (CAP), as described in the current publication, is a promising point-of-care method for quickly and consistently detecting steatosis. The number of liver cells with fat droplets (steatosis), the degree of liver cell damage and inflammation (the "activity" of the disease), and the degree of liver fibrosis (the "stage" of the disease), can all be determined by liver biopsy; however, there are certain drawbacks: requires an accurate liver sample, a qualified pathologist, is subject to inter-observer variability, involves invasive surgery that may cause serious complications, and is quite expensive. Of note, sampling errors can underestimate or overestimate the histological stigmata highlighted. To avoid or limit this problem, numerous non-invasive tools and scoring systems have been proposed over the years, having progressively modified and reduced the need for biopsy. Non-invasive tests (NITs) are non-invasive, repeatable, prognostic, and easy to interpret. Moreover, allow for the long-term monitoring of liver fibrosis and associated effects without undergoing a risky or intrusive treatment. The characteristics, benefits, and drawbacks of the primary NITs in use are listed in *Tables 1,2*. Recent guidelines from the European Association for the Study of Liver Diseases state that "in patients with NAFLD, liver biopsy remains the reference standard for the diagnosis of NASH because none of the available NITs has acceptable accuracy (level of evidence: 2)" despite retrospective studies suggesting that non-invasive serum markers and elastography can help predict the long-term prognosis of patients with NAFLD (10). Therefore, further research is required to establish the real effectiveness of NITs, even in a particular setting such as obesity, both for identifying steatosis and the disease severity and to evaluate over the time the response to any given treatment. NAFLD and NASH, including associated comorbidities such as obesity and/or T2D, require a close management that combines dietary, educational, behavioral, pharmacological and in some cases even surgical interventions. Therefore, the need for an instrument that, like a thermometer for a fever, can allow the clinician to follow the patient and monitor the effects of a proposed

Table 1 Advantages of main NITs used to diagnose and stage liver fibrosis

Serum markers	Transient elastography	pSWE	2D-SWE	MRE
Good reproducibility	Most widely used and validated technique	Can be performed in combination with regular ultrasound if the device is provided with adequate software	Can be performed in combination with regular ultrasound if the device is provided with adequate software	Can be implemented on a regular MRI machine
High applicability (95%)	Point-of-care	ROI smaller than TE and location chosen by the operator	Large ROI that can be adjusted in size and location chosen by the operator	Examination of the whole liver
No cost and wide availability	Bedside; rapid, easy to learn	Higher applicability than TE	Measures liver stiffness in real time	Higher applicability than TE
Well validated	Quality criteria well defined	Ascites and obesity	Good applicability	Ascites and obesity
Can be performed in the outpatient clinic	Good reproducibility	Performance equivalent to that of TE for advanced fibrosis and cirrhosis	High performance for the diagnosis of significant fibrosis and cirrhosis	High performance for the earlier fibrosis stages and for diagnosis of cirrhosis
Prognostic value of some has been validated for some aetiologies of chronic liver disease at population level	High performance for cirrhosis	Prognostic value in cirrhosis	Prognostic value in compensated cirrhosis	
	AUROC >0.9	High applicability for spleen stiffness measurement		
	Prognostic value in compensated cirrhosis well validated			

Adapted from: reference (10). NITs, non-invasive tests; pSWE, point-shear wave elastography; 2D-SWE, bidimensional shear wave elastography; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; ROI, region of interest; TE, transient elastography; AUROC, area under the receiver operator characteristic curve.

Table 2 Disadvantages of main NITs used to diagnose and stage liver fibrosis

Serum markers	Transient elastography	pSWE	2D-SWE	MRE
Non-liver-specific	Requires a dedicated device	False positive in case of acute hepatitis, extrahepatic cholestasis, liver congestion, food intake, and excessive alcohol intake	False positive in case of acute hepatitis, extrahepatic cholestasis, liver congestion, food intake, and excessive alcohol intake	Not applicable in case of iron overload
Performance not as good as TE and patented serum markers	ROI cannot be chosen			Requires an MRI facility
False-positive results with FIB-4 and NFS in case of age >65 years	Applicability lower than for serum biomarkers (obesity, ascites, operator experience)			Time consuming
False-positive results in case of extrahepatic inflammatory conditions, profibrotic, extrahepatic disease, and other	False positive in case of acute hepatitis, extrahepatic cholestasis, liver congestion, food intake, and excessive alcohol intake			Costly
Cost of patented tests				No clear data on prognostic value

Adapted from: reference (10). NITs, non-invasive tests; pSWE, point-shear wave elastography; 2D-SWE, bidimensional shear wave elastography; MRE, magnetic resonance elastography; TE, transient elastography; ROI, region of interest; MRI, magnetic resonance imaging; FIB-4, fibrosis-4; NFS, NAFLD fibrosis score; NAFLD, non-alcoholic fatty liver disease.

intervention(s), appears to be extremely significant. Such a tool must be inexpensive, reproducible in results, easily accessible, non-invasive, and safe.

Footnote

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