Noninvasive evaluation of NAFLD

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Abstract | A common clinical concern in patients with NAFLD is whether they have NASH or simple steatosis and, more importantly, what the stage of fibrosis is and whether the level of fibrosis has increased over time. Such concern is based on the fact that patients with NAFLD with advanced fibrosis are at greatest risk of developing complications of end-stage liver disease. Although it lacks sensitivity, ultrasonography is an accepted tool for steatosis screening. The controlled attenuation parameter or CAP seems a promising screening technique, but requires further validation. Cytokeratin-18 has been extensively validated, but it is an imperfect serum marker of NASH. Ultrasonography-based transient elastography can exclude advanced fibrosis and cirrhosis, but its main limitation is its reduced applicability in patients with NAFLD, which is not completely solved by use of the XL probe. Of the noninvasive serum markers, the NAFLD fibrosis score is the most validated and has appropriate accuracy in distinguishing patients with and without advanced fibrosis. Although noninvasive methods require further validation, they could be useful for selecting those patients with NAFLD who require a liver biopsy. This Review discusses the advantages and limitations of noninvasive methods for the management of adults with NAFLD, including diagnosis and quantification of steatosis, diagnosis of NASH and staging of hepatic fibrosis.

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Introduction

Key issues in the diagnosis of patients with NAFLD are the differentiation of NASH from simple steatosis and staging of fibrosis, as those patients with advanced fibrosis are at greatest risk of developing complications of chronic liver disease, such as cirrhosis, liver failure and hepatocellular carcinoma (HCC).[1] The diagnosis of NASH and staging of fibrosis are essentially based on histological examination of a tissue specimen obtained by liver biopsy. However, liver biopsy has well-known limitations (invasiveness and sampling variability) and cannot be proposed for all patients, especially given the high prevalence of NAFLD worldwide.

Over the past decade, there has been a growing interest in alternative novel noninvasive strategies for the evaluation of NAFLD.[2] These techniques rely on two different, but complementary, approaches: either measuring the levels of serum biomarkers or the use of imaging techniques including conventional ultrasonography, CT, MRI and ultrasonography-based elastography for measuring liver stiffness. This Review discusses the advantages and limitations of noninvasive methods for the management of adults with NAFLD, including diagnosis and quantification of steatosis, diagnosis of NASH and staging of hepatic fibrosis.

Diagnosis and quantification of steatosis

Imaging techniques

Ultrasonography

Hepatic steatosis causes increased echogenicity on ultrasonography owing to increased acoustic interfaces because of intracellular accumulation of lipid vesicles. Liver appears brighter than renal cortex and spleen; other features include attenuation of the ultrasound wave, loss of definition of the diaphragm and blurring of vascular margins.[3] Several studies have shown that ultrasonography has 60–94% sensitivity and 84–95% specificity for detecting hepatic steatosis;[4] the sensitivity of ultrasonography increases with the severity of fatty liver. A computerized hepatorenal sonographic index enables quantification of steatosis and can aid diagnosis of small amounts of liver fat, but is not currently used in clinical practice.[5] Sensitivity of ultrasonography is reduced when <30% of the liver parenchyma is infiltrated by fat, and in the morbidly obese.[4] Finally, how ultrasonography performs is operator dependent. Nevertheless, ultrasonography is a simple, widely available and acceptable tool for first-line screening for steatosis in clinical practice.[6]

Controlled attenuation parameter

A novel parameter, the controlled attenuation parameter (CAP), has been proposed for noninvasive grading of hepatic steatosis. CAP measures the degree of ultrasound attenuation by hepatic fat using a process based on vibration control transient elastography (VCTE™; FibroScan®, Echosens, Paris, France). Results are expressed as dB/m for a given ultrasound frequency, ranging between 100–400 dB/m. In a preliminary study of 115 patients with various chronic liver diseases, using liver biopsy as reference, CAP was able to accurately detect >10%, >33% and >67% steatosis with AUROCs (area under receiver operating characteristics curve) of 0.91, 0.95 and 0.89, respectively.[7] Several studies have confirmed these results (Supplementary Table 1 online).[7–12] However,

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Key points

- Liver biopsy remains the reference standard for diagnosing NASH and staging fibrosis in patients with NAFLD
- Identifying advanced fibrosis and cirrhosis is paramount as it dictates the need to screen for gastro-oesophageal varices and hepatocellular carcinoma
- Noninvasive methods for fibrosis assessment rely on two different, but complementary, approaches: the biological approach based on serum biomarker levels and the physical approach based on liver stiffness (measured mainly using transient elastography)
- The main limitation of ultrasonography-based transient elastography in clinical practice is its failure to obtain reliable liver stiffness measurements (~20% of cases, mainly obese patients), which diminishes its application in NAFLD
- The XL probe could be used as second line in the subset of patients in whom the regular (M) probe fails, but appropriate cut-off levels remain to be defined
- Several biomarkers have been proposed to reliably identify advanced fibrosis and cirrhosis and could be useful to select patients with NAFLD who might benefit most from a liver biopsy

although CAP correlated well with pathological grades of steatosis in these studies, the results overlapped between grades and CAP showed poor accuracy for the differentiation of adjacent grades of steatosis. Also, the number of patients with NAFLD included in these studies is too small (<150) to draw any firm conclusions. When CAP performances were compared with serum indices of steatosis (SteatoTest™ [BioPredictive, Paris, France], Fatty Liver Index and Hepatic Steatosis Index), conflicting results were observed; one study suggested that CAP might perform better,[8] whereas another did not.[9] Further studies with larger cohorts are now required for validation; studies comparing CAP with ultrasonography are also awaited.

Computed tomography

Fatty liver can be diagnosed by CT if the attenuation of the liver is at least 10 HU less than that of the spleen, or if the attenuation of the liver is <40 HU.[4] In severe cases of fatty liver, intrahepatic vessels might appear hyperattenuated relative to the fat-containing liver tissue.[4] In contrast-material-enhanced CT scans, the comparison of liver and spleen attenuation values is not as reliable for the diagnosis of fatty liver.[4] Although noncontrast-enhanced CT is accurate for the diagnosis of steatosis, CT is not sensitive for detecting mild or moderate elevations of hepatic lipid content (5–30%).[13] Moreover, CT is associated with radiation exposure, which limits its use in longitudinal studies and in children.

MRI and proton magnetic resonance spectroscopy

The principle of magnetic resonance spectroscopy (MRS) is to directly measure the chemical composition of tissue on the basis of the frequency composition of the signal arising from the voxel (volumetric pixel) of interest. Thus, fat detection with MRS is performed by identifying spectral peaks at resonance frequencies specific to the protons in triglycerides. MRS can detect a very low fat quantity, which is not possible with other MRI techniques, and is considered to be the most sensitive method. MRS has often been used as the reference standard in a number of clinical studies and has determined the prevalence NAFLD in the general adult population.[14,15] Using MRS, the prevalence of NAFLD in a Chinese and US adult general population with no identifiable risk factors has been estimated at 27.3% and 33.6%, respectively.[14,15] However, MRI is not in routine use and is time consuming.

Among the basic MRI techniques for fat detection, chemical shift MRI is the most common. Chemical shift MRI utilizes the difference in resonance frequency of water and lipid to differentiate tissues containing only water from those containing water and lipid, known as the Dixon method.[16] This acquisition is a dual-echo, gradient-echo T1-weighted sequence made of in-phase and opposed-phase imaging, such that the signal from fat protons is added (in-phase) or subtracted (opposed-phase), from the signal from protons in water. Detection of fat can be assessed qualitatively with reduction of signal on opposed-phase imaging or quantitatively. Precise fat quantification requires correction for T2* decay, which can be obtained by using triple-echo, gradient-echo sequence.[17] Several studies have demonstrated a good correlation between the severity of hepatic steatosis on MRI and liver biopsy results.[4] Multi-echo, gradient-echo MRI has been developed and has the advantage of depicting fat and iron overload simultaneously.[18] A study has compared the diagnostic performance of ultrasonography, CT, dual-echo MRI and proton MRS for the assessment of hepatic steatosis in patients undergoing liver resection. In contrast with ultrasonography and CT, dual-echo MRI and proton MRS strongly correlated with steatosis detected by liver biopsy and were able to demonstrate differences across steatosis grades.[19]

Serum biomarkers

Five biomarker-based indices have been developed to diagnose steatosis. One index is the SteatoTest™, a proprietary formula based on the six variables of FibroTest™–ActiTest (BioPredictive, Paris, France) plus BMI, cholesterol, triglycerides and glucose adjusted by age and gender.[20] The fatty liver index includes four variables: BMI, waist circumference, triglycerides and γ-glutamyltranspeptidase.[21] The lipid accumulation product includes three variables: waist circumference, triglycerides and gender.[22] The NAFLD liver fat score is based on five variables: metabolic syndrome, type 2 diabetes, fasting insulin level, fasting aspartate aminotransferase (AST) level, and the AST:ALT (alanine aminotranferase) ratio.[23] Using the same variables as the NAFLD liver fat score, a liver fat equation was created for prediction of the percentage of liver fat. Another score is the hepatic steatosis index, which includes three variables: AST:ALT ratio, BMI and diabetes.[24]

All these indices, however, have not gained much popularity and they might not add much to the information provided by clinical, laboratory and imaging studies done routinely in patients with suspected NAFLD. In summary, imaging techniques are optimal for the diagnosis of steatosis in clinical practice, among which ultrasonography, despite its low sensitivity, is the most widely used.

Diagnosis of NASH

Differentiating NASH from simple steatosis is important because simple steatosis follows a fairly benign clinical