

Non-invasive diagnosis of steatosis and fibrosis

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Abstract

The prognosis and management of liver disease greatly depends on the amount of liver fibrosis. Non-alcoholic fatty liver disease (NAFLD), ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), is emerging as a major cause of liver disease in Western countries because of the increasing prevalence of obesity and type 2 diabetes. A key issue in patients with NAFLD is the differentiation of NASH from simple steatosis. It is particularly important to identify NASH patients as they are at greatest risk of developing complications such as cirrhosis, liver failure and hepatocellular carcinoma. The limitations of liver biopsy (invasive procedure, sampling errors, interobserver variability and non-dynamic fibrosis evaluation) have stimulated the search for non-invasive approaches for the assessment of steatosis and liver fibrosis in patients with NAFLD. A variety of methods, including serum markers, imaging techniques such as ultrasound, CT, MRI and measurement of liver stiffness by transient elastography, have been proposed for the non-invasive assessment of steatosis and hepatic fibrosis. This review discusses the advantages and limitations of these different methods in clinical practice.

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Résumé

Diagnostic non invasif de la stéatose et de la fibrose hépatiques

L'importance et la progression de la fibrose hépatique conditionnent à la fois le pronostic et la prise en charge des maladies chroniques du foie. La stéatose hépatique non alcoolique (NAFLD), qui va de la stéatose simple jusqu'à la stéatohépatite non alcoolique (NASH), est une cause émergente de maladie du foie dans les pays occidentaux, en raison de la prévalence croissante de l'obésité et du diabète de type 2. Différencier la NASH de la stéatose simple est d'une importance fondamentale chez les patients atteints de NAFLD. En effet, les patients atteints de NASH sont les plus à risque de développer d'une part, une fibrose hépatique progressive et, d'autre part, des complications telles qu'une cirrhose, une insuffisance hépatique ou un carcinome hépatocellulaire. Les limites de la biopsie hépatique (examen invasif avec biais d'échantillonnage et variabilité interobservateur qui ne permettent pas une évaluation dynamique de la fibrose) ont stimulé la recherche d'approches non invasives pour évaluer la stéatose et la fibrose hépatiques chez les patients atteints de NAFLD. Plusieurs méthodes comprenant des marqueurs sériques, des techniques d'imagerie comme l'échographie, le scanner ou l'IRM, et plus récemment la mesure de l'élasticité hépatique par élastométrie impulsométrique (FibroScan), ont ainsi été proposées. Cette revue a pour but de discuter les avantages et les limites respectives de ces méthodes en pratique clinique.

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Keywords: Type 2 diabetes; Obesity; Non-alcoholic steatohepatitis; Liver fibrosis; Steatosis; Non-invasive procedure; Transient elastography (FibroScan); Serum markers; Liver biopsy, Review.

Mots clés : Diabète de type 2 ; Obésité ; Stéatohépatite non alcoolique ; Fibrose hépatique ; Stéatose ; Méthode non invasive ; Élastométrie (FibroScan) ; Marqueurs sériques ; Biopsie hépatique ; Revue.

Non-alcoholic fatty liver disease (NAFLD) is emerging as a major cause of liver disease in Western countries because of the increasing prevalence of obesity and type 2 diabetes. NAFLD encompasses a spectrum of diseases, rang-

ing from simple steatosis to non-alcoholic steatohepatitis (NASH), a more severe entity [1]. It is estimated that 30% of the adult population in the US now have NAFLD and that 3-6% have NASH [2]. A key issue in patients with NAFLD is the differentiation of NASH from simple steatosis. It is particularly important to identify NASH patients who are at greatest risk of developing complications of chronic liver

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disease, such as cirrhosis, liver failure and hepatocellular carcinoma [3,4]. The diagnosis of NASH, which includes necroinflammation, ballooning degeneration and fibrosis, is essentially based on histological examination of a liver specimen obtained by liver biopsy. However, liver biopsy is a painful and invasive procedure [5]—with rare, but potentially life-threatening, complications [6,7]—that is prone to sampling error [8,9]. In addition, given the numbers of patients with NAFLD, the use of liver biopsy is clinically and financially impractical.

These limitations have stimulated the search for new non-invasive approaches. Ideally, a non-invasive marker of liver fibrosis should be liver-specific, easy to perform, reliable and inexpensive. It should, in addition, be accurate not only for the staging of fibrosis, but also for monitoring disease progression. A variety of methods, including serum markers, imaging techniques such as ultrasound, CT, MRI and measurement of liver stiffness by transient elastography, have been proposed for the non-invasive assessment of steatosis and hepatic fibrosis. Although most of these methods have been mainly validated in the context of hepatitis C, there has been considerable interest in extending this work into the field of NAFLD because of its increasing prevalence. This review is aimed at discussing the advantages and limitations of these different methods in clinical practice.

1. Non-invasive diagnosis of steatosis

1.1. Imaging techniques

Non-invasive techniques such as ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) and proton magnetic resonance spectroscopy (1H-MRS) can detect hepatic steatosis, but currently cannot distinguish between simple steatosis and NASH.

1.1.1. Ultrasound

Hepatic ultrasound is a simple, non-invasive technique that is widely used in clinical practice to detect fatty infiltration of liver. Hepatic steatosis causes increased echogenicity on ultrasound, making the liver appear brighter than the cortex of the right kidney. Several studies have shown that ultrasound for detecting hepatic steatosis has a sensitivity of 60% to 94%, and a specificity of 84% to 95% [10]. The sensitivity of ultrasound increases with increasing degrees of fatty infiltration. However, ultrasound is unable to provide a precise grading of hepatic fat content. Also, its sensitivity is reduced in the morbidly obese, and its performance is highly operator-dependent.

1.1.2. Computed tomography

Non-contrast-enhanced CT is the most accurate CT technique to detect and characterize hepatic steatosis [11]. The CT diagnosis of hepatic steatosis is made by measuring the difference in liver and spleen attenuation values in Hounsfield units. In subjects with steatosis, as the mean attenuation value of the liver is lower than that of the spleen, the liver appears darker than the spleen. Although non-contrast-enhanced CT is useful for the qualitative diagnosis of macrovesicular steatosis of 30% or greater, there is conflicting evidence as to whether or not it can accurately quantify hepatic fat content. In addition, it exposes subjects to ionizing radiation.

1.1.3. MRI and proton MR spectroscopy

Chemical-shift MRI uses the difference in resonance frequency of water and lipid to differentiate tissue containing only water from those containing water and lipid, known as the Dixon method. Several studies have recently demonstrated a good correlation between the severity of hepatic steatosis on MRI and liver biopsy [12,13]. Multiecho imaging may also be a promising method [14]. Similarly, *in vivo* ¹H-MRS is a fast and safe technique for the quantitative assessment of hepatic steatosis. Several studies have shown a good correlation between quantification of hepatic fat content by H-MRS and liver biopsy [13,15]. Both techniques will be useful tools in the future.

1.2. Serum markers

So far, the only serum test that has been proposed to detect steatosis is the SteatoTest [16]. This test includes the 6 parameters of FibroTest—ActiTest plus BMI, serum cholesterol, triglycerides and glucose adjusted for age and gender. It has been constructed from a training group of 310 patients with various chronic liver diseases, using the presence of steatosis (> 5%) on liver biopsy as the reference, and validated in three different groups of patients with hepatitis C and alcoholic liver disease ($n = 434$). At a cutoff of 0.3, the sensitivity of SteatoTest ranged from 85% to 100% whereas, at a cutoff of 0.7, the specificity ranged from 83% to 100%. Validation of this test in other groups of patients (including NAFLD) by independent studies is awaited.

More interest has been focused on whether or not non-invasive serum tests can differentiate NASH from simple steatosis among patients with NAFLD. Several groups have proposed tests, including the NashTest [17], and scores combining age, gender, AST, BMI, AST/ALT ratio and hyaluronic acid [18] or adiponectin, HOMA-IR, and serum type IV collagen [19] (Table 1).

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