EDITORIAL

Diagnosis of liver fibrosis in 2008

Diagnostic de la fibrose hépatique en 2008

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It is obvious that liver biopsy has been and remains an essential diagnostic tool in Hepatology. However, its value to assess the degree of liver fibrosis is controversial. Liver fibrosis is the most relevant variable when assessing the degree of liver damage in chronic liver diseases: collagen deposition is the consequence of different inflammatory processes occurring within the liver and its progression will determine the appearance of portal hypertension and clinical decompensation. Thus, assessment of liver fibrosis provides prognostic information and may have therapeutic implications. The main limitations of liver biopsy are the possibility of sampling errors, the intra- and inter-observer variation and the associated morbidity [1,2]. In the last few years, there has been an increasing interest in the development of noninvasive methods to assess liver fibrosis. Patients are currently aware of these methods and are reluctant to undergo an invasive procedure if similar information can be obtained with a blood test or by an imaging technique.

Noninvasive diagnosis of liver fibrosis should rely on markers that are easy to obtain, reproducible, and accurate to predict different fibrosis stages [3]. The most important progress has been made in the field of viral hepatitis, where noninvasive evaluation of liver fibrosis is currently common in clinical practice. In the future, noninvasive assessment of liver fibrosis will be the approach to follow-up the effect of a particular treatment (antiviral, antifibrotic) on liver diseases.

Activation of hepatic stellate cells (HSC) is the dominant event in hepatic fibrogenesis, which is characterized by the transformation of quiescent cells into proliferative, fibrogenic and contractile myofibroblasts. Fibrosis progresses when there is an imbalance between extracellular matrix degradation and production. Although liver fibrosis is a local reaction of the liver to chronic injury, serum levels of fibrogenic cytokines, extracellular matrix proteins, and degradation products are markedly increased in cases of advanced fibrosis (bridging fibrosis or cirrhosis). Thus, there is a growing interest in the identification of patients with advanced fibrosis by serum markers. The most common markers used in current assays are measuring products of extracellular matrix synthesis or degradation and the enzymes that regulate their production or modification, such as hyaluronic acid, serum propetide of collagen type III (PIIINP) and matrix metalloproteinase 1 (MMP-1). Their combination has shown good diagnostic accuracy at identifying individuals with advanced fibrosis [4]. The limitations of these fibrosis biomarkers are their lack of sensitivity at the initial stages of liver fibrosis and their lack of specificity [3]. Although they are not yet available for routine use, we will most likely use them in the near future.

A different approach to identify liver damage by noninvasive methods is to use routine laboratory tests. These tests rely on variables that reflect the consequences of liver damage rather than on its pathophysiology. Most
attempts using this approach have focused on the diagnosis of patients with advanced liver disease (bridging fibrosis or cirrhosis) and combine markers such as age, platelet count, AST/ALT ratio and prothrombin time [5]. The major drawback of these variables is that they are not sensitive enough to identify patients with mild degrees of fibrosis but at risk of progression. In the last years, several studies based on large cohorts of patients including the entire spectrum of the disease (mild and severe fibrosis) have considerably improved the accuracy of routine serological markers to assess liver damage [6-14]. Some of the new scores combine routine laboratory tests with fibrosis biomarkers, which increases the accuracy at identifying significant fibrosis and cirrhosis [12-14] Identification of individual fibrosis stages is still not possible, but some of the published scores allow the classification of 50-70% of individuals with high positive and negative predictive values. More importantly, some of them have been widely validated in different cohorts and its use in clinical practice (particularly in patients with chronic hepatitis) is common to identify good candidates for antiviral therapy (patients with significant fibrosis) [6,7,11].

Another approach to assess the degree of liver fibrosis is by imaging techniques. Classically, ultrasonography, CT scan or magnetic resonance have been used to explore the liver. These methods are able to detect changes in the liver parenchyma when there is significant fibrosis (bridging fibrosis and mainly cirrhosis) and signs of portal hypertension (enlarged spleen, collateral venous circulation, enlarged portal vein). However, they are not useful to identify patients with lower stages of fibrosis. Recently, optical analysis of computed tomography images of the liver (Fibro-CT) has been used to predict fibrosis in patients with chronic hepatitis C [15].

In the last few years a new tool for the noninvasive assessment of liver fibrosis has been widely used: transient elastography (TE). A vibration of mild amplitude and low frequency is transmitted to the liver; the velocity of propagation of the wave is directly related to the tissue stiffness (the harder the tissue the faster the shear propagates), which is measured in kilo Pascals (kPa). The method is rapid, noninvasive and acquires information from a much larger portion of the tissue as compared to liver biopsy. Obviously, increased liver stiffness is not always a surrogate of fibrosis and the presence of necroinflammation may significantly increase liver stiffness values in the absence of fibrosis. Several studies have already evaluated the accuracy of TE to identify patients with significant fibrosis or cirrhosis. Although most studies have been performed in individuals with chronic hepatitis C, the accuracy to identify significant fibrosis and particularly cirrhosis is excellent [16,17]. There are even some data demonstrating a good correlation between liver stiffness and hepatic venous pressure gradient, which is the most important variable regarding clinical outcomes in liver diseases [18,19].

Over the last years, several technological advances have been made in the development of clinical applications of MRI of the liver: contrasted-enhanced MRI, diffusion-weighted MRI and magnetic resonance elastography [20]. It appears that these methods are accurate to identify advanced fibrosis stages, but studies evaluating their accuracy in initial degrees of fibrosis are based in small cohorts and have not been validated so far. Recently, two different studies have evaluated the accuracy of MR elastography to identify significant fibrosis in patients with chronic liver diseases [21,22]. In both studies, MR-elastography showed high sensitivity and specificity for detection of significant fibrosis. The theoretical advantages of this method are the potential assessment of the entire liver parenchyma, the lack of acoustical window requirement and the operator independence. The method, however, is expensive and time-consuming and for this reason, it is soon to predict its future application.

In summary, noninvasive diagnosis of liver fibrosis is a reality. Liver biopsy is necessary to establish a diagnosis, but it is probably not the best method to assess liver fibrosis (particularly in cases where frequent assessment is needed). Although the utility of these methods is clearly demonstrated, particularly in patients with HCV-related liver diseases, their wide application in clinical practice has still several limitations: 1) noninvasive methods do not allow to discriminate among mild to moderate stages of liver fibrosis; 2) there are no large studies assessing the role of these methods to identify “rapid fibrosers” (that is, dynamic follow-ups studies); 3) there are only a few studies analyzing the role of noninvasive methods to evaluate the effect of therapy on liver fibrosis; 4) more studies are necessary to explore the diagnostic accuracy of noninvasive methods in liver diseases not caused by HCV/HBV. Despite these limitations, noninvasive assessment of liver fibrosis has become part of our diagnostic armamentarium.

Conflicts of interest:
Xavier Forns participated at clinical trials on behalf of Schering and Roche. He attended conferences organised by Schering and Roche as contributor and audience member.

References


