Diagnosis and Quantitation of Fibrosis

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Hepatic fibrosis is the final common pathway for many different liver insults. Originally considered to be irreversible, hepatic fibrosis is now known to be a dynamic process with a significant potential for resolution. The diagnosis and quantitation of fibrosis have traditionally relied on liver biopsy. However, there are a number of drawbacks including the invasive nature of the procedure, sampling error, and interobserver variability. This article reviews the current role of liver biopsy in the assessment of hepatic fibrosis and discusses the role of the newer noninvasive methods including serum markers and radiologic tests.

Hepatic fibrosis occurs in response to almost all causes of chronic liver injury. Hepatic fibrosis can occur in response to viral, immune, and toxic-metabolic insults and consists of an accumulation of fibrillar extracellular matrix (ECM) components. This process may ultimately lead to cirrhosis with its consequences of portal hypertension, hepatocellular carcinoma, and liver failure. Although hepatic fibrogenesis was long thought to be an irreversible process, it is now clear that it is a dynamic process with significant potential for reversal. Significant discoveries into the mechanisms of hepatic fibrosis progression and regression have uncovered a number of potential targets for antifibrotic drugs.

Percutaneous liver biopsy has long remained the gold standard for staging of fibrosis. Conventional serologic and biochemical tests have little or no role in assessment of fibrosis. However, with drugs that have the potential to reverse hepatic fibrosis imminent, a simple, noninvasive, reproducible method of assessing fibrosis is essential to monitor disease progression, clinical outcomes, and response to treatment. In addition, the limitations of needle liver biopsy with respect to sampling error and interobserver variation are well described, highlighting the need for further testing strategies.[1,2]

Our deeper understanding of the mechanisms of fibrosis has led to the identification of many potential markers of fibrosis, which appear capable of identifying early and advanced hepatic fibrosis.[3,4] Standard cross-sectional imaging studies will only identify or exclude advanced fibrosis.[5] Novel technologies such as transient hepatic elastography and magnetic resonance imaging (MRI) elastography show promise as noninvasive methods of testing for hepatic fibrosis.[6–8] In this article, we will review our current methods of diagnosing and quantifying hepatic fibrosis and discuss how the newer technologies may be integrated into clinical practice.

Liver Biopsy

Liver biopsy has long remained the gold standard for the assessment of hepatic fibrosis. However, because it is an invasive test with the potential for serious, albeit rare, complications, it is not undertaken lightly. The first percutaneous liver biopsy was performed in 1923, but only in the last 50 years has it become a standard test following Menghini's description in 1958.[9] Significant complications, defined as requiring hospital admission or prolonged hospital stay, occur in 1% to 5% of patients, and mortality has been reported in between 1 in 1000 patients and 1 in 10,000 patients.[10–13] The risk of a complication following liver biopsy has also been reported to be higher with increasing passes and performance of a biopsy in patients with sepsis or the need for correction of coagulopathy.[12,14]

In addition to the potential complications, liver biopsy has 2 well-described limitations: sampling error and in-

Abbreviations used in this paper: APRI, AST to platelet ratio index; ECM, extracellular matrix; HA, hyaluronic acid; MMPs, matrix metalloproteinases; MRE, magnetic resonance elastography; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PIIINP, procollagen type III amino-terminal peptide; ROC, receiver operating curve; TIMPs, tissue inhibitors of metalloproteinases.

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terobserver variability. A needle liver biopsy only removes 1/50,000 of the total organ, and so the potential for sampling error is substantial. Autopsy and laparoscopy studies have demonstrated that cirrhosis is missed on a single blind liver biopsy in between 10% and 30% of cases.[15–17] The recent study by Regev et al concerning laparoscopic liver biopsy of both left and right lobes observed that cirrhosis was noted on one side but not the other in 14.5% of cases, and, in 33.1% of patients, a difference of at least one fibrosis stage between lobes was found.[2] Both the size of the biopsy sample and the number of biopsy samples taken have a major effect on sampling error.[1] Most studies would suggest that an adequate biopsy sample should be at least 15 mm long and contain more than 5 portal tracts.[18,19] A recent study using computer-generated modeling suggested that a 25-mm biopsy sample had a 25% error rate and that a 40-mm biopsy sample was optimal.[20] Even in the best hands, only one sixth of biopsy samples are over 20-mm in length.[21]

The type of needle used to perform the biopsy can also affect the diagnostic accuracy. It appears that cutting needles give a more accurate representation of liver fibrosis, particularly in those with advanced disease, and, in one study, the correct diagnosis of cirrhosis increased from 65% with a Menghini needle to 89% using a Tru-Cut needle.[22,23]

There is a significant degree of subjectivity in the pathologic assessment of liver biopsy samples. A number of staging systems have been developed to reduce both the interobserver and intraobserver variability, including the METAVIR, the Knodell fibrosis score (later modified by Ishak), and the Scheuer score. Most studies have shown excellent inter- and intraobserver reproducibility for the staging of fibrosis. However, the reproducibility of hepatic inflammatory activity is not as consistent.[24–30]

To more accurately quantify fibrosis, a number of studies have used computer-aided morphometric analysis to determine the area of the liver biopsy composed of fibrous tissue. The correlation between fibrosis area and disease stage is quite variable and is most accurate in advanced disease. Fragmented biopsy samples cannot be assessed accurately in this way.[30–32]

Liver biopsy will not be replaced in the foreseeable future and will remain particularly important in the diagnosis of unexplained liver disease. However, because of the potential for complications and the significant sampling error and interobserver variability, its future role in the assessment and quantitation of fibrosis in alcoholic and viral liver diseases is less clear. The newer, noninvasive tests for liver fibrosis are very likely to have a role to play in this situation.

Serum Markers of Fibrosis

A large number of putative serum markers have been evaluated for the assessment of hepatic fibrosis.

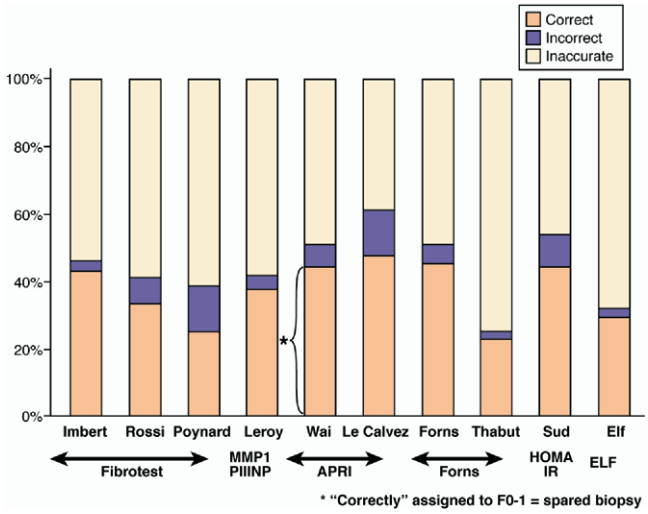

Figure 1. Differentiation of F0–F1 from F2–F4 in multiple biomarker panels. Approximately 30%–35% of patients are correctly classified as mild disease and can be spared liver biopsy. Adapted from Parkes et al.[33]

Despite the dynamic nature of hepatic fibrogenesis, most of the presumed tests are suitable for the cross-sectional diagnosis of fibrosis stage rather than determining the rate of fibrosis progression or regression. No true serum marker that would act as a surrogate marker of hepatic fibrosis has been validated to date. It is almost certain that combinations of biomarkers will probably have to be examined. A systematic review of 14 studies of fibrosis biomarkers in patients with chronic hepatitis C concluded that cut-off levels could rule out or rule in fibrosis in 35% of patients (Figure 1), but the panels of biomarkers could not differentiate stages of fibrosis accurately.[33]

Features that would apply to an ideal biomarker have been described and are shown in Table 1.[34,35] Broadly speaking, serum markers of hepatic fibrosis can be considered in 1 of 2 categories: either indirect or direct. Indirect markers reflect alterations in hepatic function but do not directly reflect hepatic ECM metabolism, for example, platelet count, coagulation studies, and hepatic aminotransferases. Direct serum assays for markers of fibrosis reflect serum ECM turnover. The discovery of many of these direct biomarkers is directly attributable to advances in the understanding of the molecular mechanisms involved in hepatic fibrogenesis. Serum assays for enzymes and products of matrix synthesis or degradation have been evaluated as markers of fibrosis in many studies and show some promise as a simple alternative to liver biopsy.[3,36–46]

Indirect Markers

A number of indirect markers of liver fibrosis have been used in clinical practice over the years, including serum aminotransferase levels, presence of coagulopathy, and platelet counts. A number of indices involving com-