1 Non-invasive markers of liver fibrosis: useful or useless?

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LEARNING POINTS

- Liver biopsy enables accurate evaluation of stage of fibrosis using semi-quantitative scoring systems, including both architectural disturbance and evaluation of fibrous deposition.
- Non-invasive markers of fibrosis are useful for screening for cirrhosis but not sufficiently accurate for staging fibrosis.
- Liver fibrosis is only one facet of chronic viral hepatitis, which needs to be interpreted in its full histological context.

Introduction

Liver fibrosis is a non-specific tissue response to chronic inflammation related to an unresolved tissue injury. In the liver, cirrhosis, the end-point of fibrosis, is the major cause of morbidity and mortality in chronic liver diseases [1]. Therefore, assessment of the degree of fibrosis (stage) is often a prerequisite for the management and follow-up of patients with chronic liver disease. Because fibrosis is tissue damage, biopsy is, by definition, the only direct, albeit invasive, tool that assesses fibrosis whereas non-invasive methods (either serum markers or physical and/or imaging techniques) are surrogate indirect approaches. In this chapter, the strengths and weaknesses of non-invasive markers and liver biopsy are reviewed and their respective roles in management of patients with chronic viral hepatitis discussed.

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Non-invasive markers

The main alternative to liver biopsy is based on two very different methods, serum markers and liver stiffness. These have substantially different underlying principles, but both have an obvious advantage: they are non-invasive. Although they generate a significant cost and are not universally available, non-invasive markers are easy to use and well adapted to mass screening and, with some adequate precautions, can be considered highly reproducible procedures.

Stiffness, as assessed by ultrasound (Fibroscan) and more recently by magnetic resonance imaging (MRI), evaluates the velocity of propagation of a shock wave within the liver tissue. This method measures a physical parameter of liver tissue that is related to its elasticity. The rationale is that normal liver is viscous and not favourable to wave propagation, whereas fibrosis increases the hardness of the tissue and favours more rapid wave propagation. The main drawback is that additional space-occupying lesions within the liver, such as steatosis, oedema and inflammation, develop within an organ wrapped in a distensible but non-elastic envelope (Glisson's capsule). This contributes to modification of liver texture and acts as a confounding factor where stiffness is concerned (see ref. 2 for review). Nevertheless, the results of large studies evaluating several thousands of patients confirm that elasticity parallels the state of fibrosis at pre-cirrhotic or cirrhotic stages. A recent meta-analysis of Fibroscan has shown that the area under the receiver operating curve (AUROC) is very highly correlated with the presence of cirrhosis [3]. However, it is noteworthy that this approach is essentially valid for the diagnosis of cirrhosis but is not adequate for assessing milder fibrosis or transition from one stage to a higher one. Finally, a potential additional advantage of Fibroscan is that it provides a wide range of stiffness values within the broad group of cirrhotic livers,

which would overcome one of the major limitations of biopsy (i.e. one histological stage for all types of cirrhosis) and thus could provide additional prognostic value within this group.

Serum markers represent combinations of blood constituents that are optimized to mirror the histological stage of liver fibrosis. Several markers are available, with some only obtainable commercially (for review see ref. 4). Despite the wide number of proposed combinations, they are all designed in the same way: a predefined choice of blood parameters is combined and optimized in order to match as closely as possible the histological stages of fibrosis in a group of patients undergoing both liver biopsy and serum marker measurement. This is fundamentally different from Fibroscan. While Fibroscan assesses a genuine characteristic of liver tissue (i.e. stiffness), the serum marker algorithm is designed to mimic biopsy results irrespective of biopsy accuracy. Therefore, any limitation of the biopsy procedure (e.g. sampling variation) will decrease the functionality of serum marker measurement. Nevertheless, the most widely tested serum marker has demonstrated acceptable accuracy in the differential diagnosis of significant and non-significant fibrosis [5].

Surrogate markers have been set up and tested to dicholomize between significant vs. non-significant fibrosis. This is imposed by the use of AUROC, which tests a binary hypothesis. Using this approach there is significant loss of information. In most studies these limitations have been artificially bypassed by considering the different histological stages as linear variables and extrapolating intermediate values for each of the stages. However, this is an erroneous supposition since scores are categories not continuous variables. Such an approximation explains why, when considering only adjacent stages (F1 vs. F2, or F2 vs. F3), AUROC values are unacceptably low, leading to the supposition that these surrogates are inadequate tools for individual staging [6].

Liver biopsy

Liver biopsy has been considered the gold standard for the evaluation of tissue damage including fibrosis. However, the well-recognized limitations involved in this procedure have fuelled discussion on the position of liver biopsy in the management of patients with chronic viral hepatitis.

The main drawbacks of liver biopsy are sampling and observation errors. These errors are specific to biopsy and theoretically should be eliminated when using serum marker measurements. Because liver biopsy involves only a very tiny part of the whole organ, there is a risk that the area biopsied might be irrelevant for evaluation of any lesion in the whole liver due to heterogeneity in its distribution. Extensive literature has shown that increasing the length of liver biopsy decreases the risk of sampling error [7,8]. Except for cirrhosis, for which microfragments may be sufficient, a 25-mm biopsy is considered an optimal specimen for accurate evaluation, although 15 mm is considered sufficient in most studies.

Observer variation is another potential limitation of biopsy, related to the discordance between pathologists in biopsy interpretation. The use of histopathological scoring systems for evaluation of fibrosis and necroinflammation has limited this drawback and several studies have shown that concordance between pathologists is considered satisfactory, especially when staging of fibrosis is performed by specialized liver pathologists [9]. Thus, although liver biopsy has its limitations, appropriate precautions may reduce the flaws inherent to this method.

Because liver biopsy is invasive, the only serious limitations to its use are potential adverse effects and complications, which have been comprehensively reviewed in several studies [10]. Transient and moderate pain, along with anxiety and discomfort, are common. Severe complications such as haemoperitoneum, biliary peritonitis and pneumothorax are rare (0.3–0.5%). Death is exceedingly rare, but has been occasionally reported for biopsies in advanced liver disease and haemorrhagic tumours and in patients with major comorbidities. A biopsy via the transjugular route greatly reduces the risk of bleeding in patients with advanced liver disease and coagulation disorders. Performance of biopsy by a trained physician, use of only a limited number of passes and ultrasound guidance can significantly decrease the risk of complications, thereby enhancing the safety of biopsy. Nevertheless, liver biopsy should be performed only after carefully balancing the risks of the procedure with the potential benefits in terms of patient management. Overlooking these limitations, liver biopsy provides invaluable information that none of the non-invasive markers provide. Because of their accuracy, standardized scoring systems for evaluation of fibrosis (staging) have proven to be relevant for describing the natural history of chronic liver diseases by assessing the rate of progression of disease.

Although strongly favoured as a major decision criterion for hepatologists, fibrosis is only one of many elementary histopathological features present simultaneously on liver biopsy. Indeed, fibrosis is not an autonomous feature but rather scar tissue resulting from other pathobiological

mechanisms such as inflammatory, degenerative or dystrophic processes. Simultaneous evaluation of necroinflammation (portal tract inflammation, interface hepatitis, lobular inflammation) enables an assessment about whether fibrosis is the result of a past event that has stabilized or even regressed, or is an ongoing process that may continue to worsen. Biopsy also frequently detects associated lesions such as steatosis, steatohepatitis and iron overload, providing useful information for patient management and prognosis.

Finally, it is noteworthy that in diseases with a high burden like hepatitis C, liver biopsy may also reveal that abnormal liver function tests are related to another unexpected and additional liver disease. Clearly, all this information may influence patient management. Therefore, equating chronic liver disease only with the extent of fibrosis is an oversimplification that may be misleading.

Markers of non-invasive fibrosis: useful or useless?

Based on the evaluation of non-invasive markers in several thousands of patients, it appears that surrogate markers are useful methods for assessing significant fibrosis or cirrhosis but are useless for individual follow-up or in the case of associated comorbidities (often discovered when reading the biopsy). This suggests that surrogate markers alone should be used when there is no disagreement about the indications for treatment, for example patients with relatively recent onset hepatitis C virus (genotype 2 or 3) who will always be treated or patients where treatment is mandatory for other reasons such as severe extrahepatic manifestations. In addition, patients with contraindications to antiviral drugs should not undergo liver biopsy on first evaluation. In these situations, a simple evaluation of significant versus non-significant fibrosis with one or several non-invasive markers seems sufficient, although biopsy should be performed if any abnormal symptom or atypical evolution occurs. Similarly, biopsy is not mandatory in patients with obvious cirrhosis, where the excellent performance of non-invasive markers allows confirmation of the diagnosis.

When there is disagreement about whether or not to treat a patient, then biopsy comes first. This encompasses all patients with hepatitis B virus and hepatitis C virus (genotype 1). Because antiviral drugs are far from completely efficacious and have significant adverse effects, an accurate evaluation of liver lesions with biopsy is needed. The level of accuracy provided by liver biopsy is particularly important in this context, where staging is often used to endorse the decision to treat a patient with antiviral therapy or to screen and prevent complications such as portal hypertension and hepatocellular carcinoma. Such evaluation will rely on biopsy since non-invasive markers can confidently diagnose only cirrhosis, a stage where antiviral treatments are less effective and the chances of cure are lower.

There is an urgent need to pursue the development of surrogate markers for staging fibrosis. Because of the conditional relationship with biopsy, the development of serum markers will always have limitations. Hopefully, physical imaging will eventually be refined to an acceptable level of accuracy, especially for evaluation of early stages of fibrosis. In the future these considerations might become invalid as antiviral treatment evolves towards much efficient drugs with fewer side effects.

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