Serum Biochemical Markers of Liver Fibrosis

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ABSTRACT

Progressive liver fibrosis with development of cirrhosis is a feature of almost all chronic liver diseases. Carriers of hepatitis B and C virus are at increased risk of developing cirrhosis, hepatic decompensation/ insufficiency, hemorrhage, and hepatocellular carcinoma (HCC). Therefore, periodic evaluations of these patients are necessary. Fibrosis is deleterious but variable consequence of chronic inflammation. It is characterized by deposition of extra cellular matrix component leading to distortion of hepatic architecture with impairment of liver microcirculation and liver cell function. Although liver biopsy is the gold standard for assessment of liver fibrosis, it has several disadvantages. Considering these limitations and patient redundancy to undergo liver biopsy, it is vital that non-invasive predictors/ methods for assessment of liver fibrosis be developed and validated. Application of this method could be used to evaluate the efficacy of treatment, which is a simple and meaningful way.

Recently, clinical investigators have been searching for noninvasive serum markers of fibrosis, which have the following characteristics: they must be reliable, accurate, reproducible and easy to perform. Several markers or combination of several markers have shown promise for the detection of advanced fibrosis, although their sensitivities for detecting milder fibrosis are poor. Non-invasive laboratory bio-markers of liver fibrosis might be applied to patients who either have contra-indication or refuse liver biopsy for management of their chronic liver diseases.

***Keywords**: hepatitis B virus, liver fibrosis, liver biopsy*

INTRODUCTION

An estimated 350 million persons worldwide are chronically infected with hepatitis B virus (HVB), and 170 millions are chronically infected by hepatitis C virus (HCV).[1] Carriers of hepatitis virus are at increased risk of developing cirrhosis, hepatic decompensation/insufficiency hemorrhage, and hepatocellular carcinoma/HCC.[2] Although most carriers will not develop hepatic complications, some will develop serious sequels during their life time. Staging hepatic fibrosis by liver biopsy is necessary to guide prognosis and treatment in chronic hepatitis, and recommendation in the guideline pertain to evaluation of patients with chronic infection periodically.[3] Although liver biopsy is the gold standard for assessment of hepatic fibrosis.[4,5,6] It has several disadvantages, such as invasive, poor patient compliance, the risk of poorly standardized collection of liver tissues, sampling error, limited usefulness for dynamic surveillance and follow up, and poor intra and inter-observation concordance.[5,6,7] Considering these limitations and patient redundancy to undergo liver biopsy, noninvasive predictors of liver histology are urgently needed. Recently, clinical investigators have been searching for noninvasive serum markers of fibrosis which have the following characteristics, i.e. they must be reliable, accurate, reproducible, and easy to perform.[8] Routinely measured serum markers, have been examined as alternative for staging fibrosis among chronic hepatitis. So far, no single serum marker has been able to correctly diagnose and assess the degree and progression of hepatic fibrosis. A combination of reliable, noninvasive serum markers were developed to predict fibrosis and assess prognosis and treatment of liver fibrosis.[7]

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PATHOGENESIS OF LIVER FIBROSIS

Activity and fibrosis are two major histological features of chronic hepatitis. Fibrosis is deleterious but variable consequence of chronic inflammation. It is characterized by deposition of extra cellular matrix component leading to distortion of hepatic architecture with impairment of liver microcirculation and liver cell function.[2]

Extra cellular matrix deposition is consecutive to the activity of fibrogenic cells known as liver myofibroblasts. Myofibroblasts are almost absent from the normal liver, they derive from activation of precursor cells, the best studied being hepatic stellate cells.[5] Hepatic stellate cells are probably "resting pericyte" and do not proliferate, which can be rapidly activated, acquiring contractile properties which in turn can regulate local blood pressure. It is increasingly recognized that HCV can directly exert profibrogenic effect on the liver.

Hypothesis on the occurrence of liver fibrosis are as follows: (1) Recurrent necrosis and regeneration will stimulate the activation of hepatic stellate cells. (2) Activation of hepatitis stellate cells (HSCs) resulting in increased proliferation, and release of profibrogenic cytokines (e.g. TGF-beta, PDGF, etc) by sensitized T lymphocyte and monocytes (by virus). (3) Hepatic stellate cells then will differentiate to cells resemble to myofibroblast, so that it will increase synthesis of contractile matrix protein, enhancement of type I collagen secretion and development of liver fibrosis.[2]

Several factors have been shown to be associated with fibrosis progression rate, e.g. duration of infection, age, male, gender, heavy consumption of alcohol, human immunodeficiency virus (HIV), co-infection, low CD4 count, and necrosis grade.[2] The progression from infection to cirrhosis depends strongly on age as expressed by duration of infection, age of infection, or age at last biopsy. Metabolic condition such as overweight, steatosis, and diabetes are emerging as independent co-factors of fibrogenesis.[2]

There is a strong correlation for fibrosis stages, that almost linear with age at biopsy and duration of infection. Distribution of fibrosis progression rate suggests the presence of at least three populations: a population of rapid fibrosers, a population of intermediate fibrosers and a population of slow fibrosers.

Using median fibrosis progression rate, in untreated patients, the median expected time to cirrhosis is 30 years.[2] Infection by HCV is usually lethal when it lead to cirrhosis, the last stage of liver fibrosis, therefore an estimate of fibrosis progression represent an important surrogate end-point for evaluation of vulnerability of an individual, and for assessment of treatment impact on natural history.

SERUM MARKERS TO CHARACTERIZE LIVER FIBROSIS

Liver fibrosis is the main complication of all chronic liver diseases with progression to cirrhosis as its end-stage clinical expression. Information and knowledge about the stage of liver fibrosis is essential for prognostication and decisions on antiviral treatment in chronic hepatitis B and C.[9] Several predictive indices using more commonly performed laboratory tests have been proposed. Model for predicting both significant fibrosis and cirrhosis included platelets count, aspartate aminotransferase (AST), and alkaline phosphatase with an area under ROC curve (AUC) of 0.82 and 0.92 respectively.[9] A novel index consisting two readily available laboratory results: AST to platelet ratio index (APRI) was developed to amplify the opposing effects of liver fibrosis on AST and platelet count. The area under ROC of APRI for predicting significant fibrosis and cirrhosis were 0.80 and 0.89 respectively in the training set, and in the validation set were 0.88 and 0.94 respectively.[9] Informative serum markers (fibrosis index) were developed lately to assess significant fibrosis of the liver and cirrhosis. The most informative markers were Alpha 2 macroglobulin, alpha 2 globulin (or haptoglobin) gamma globulin, apolipoprotein A1, gamma glutamyltranspeptidase and total bilirubin.[10]

FIBROTEST is the most frequently described test proposed by Poynard's team, provide a liver fibrosis index which results from combination of 5 (five) biological markers synthesized by the liver: alpha 2 macroglobulin, haptoglobin, apolipoprotein A1, total bilirubin and gamma glutamyl-transpeptidase.

The ACTITEST, L-alanine aminotransferase (ALT) is added, allowing the assessment of necro-inflammatory histological activity.[12] The fibrotest score ranging from 0 to 1, is correlated with the Metavir stage of fibrosis, with a positive predictive value > 90% for score between 0.60 to 1 (definite presence of F2, F3 or F4 fibrosis stages), and a negative predictive value = 100% for score ranging from 0 to 0.10 (definite absence of F2, F3 or F4 stages of fibrosis). So, fibrotest is an important tool for non-invasive evaluation of liver fibrosis.[11]

HEPASCORE: Another accurate validated predictor of liver fibrosis in chronic hepatitis C infection. It is as model of 4 (four) serum markers (bilirubin, gamma glutamyltransferase, hyaluronic acid, alpha 2 macroglobulin) plus age and sex, which produced areas under the ROI curve (AUC) of 0.85, 0.96 and 0.94 for significant fibrosis, advanced fibrosis and cirrhosis respectively.[6]

To conclude, application of these parameters: Fibrotest, as well Hepascore as a real alternative to liver biopsy still requires standardization of measurement methods and validation in a larger number of chronic hepatitis C. A number of other markers associated with matrix deposition could also be used, such as hyalunionic acid (HA), type III pro-collagen, (PC III), Laminin (LN) and type IV collagen (C IV), but they can be influenced by the grade of inflammation, some liver function indexes, and clinical manifestations. A comprehensive analysis is necessary for this purpose and requires further validation.[14]

CONCLUSION

Non-invasive laboratory bio-markers of liver fibrosis alternative to liver biopsy have been developed and validated. Combination of several laboratory markers of liver fibrosis may be promising to improved diagnostic accuracy.

Non-invasive markers of liver fibrosis will likely reduce but not substitute the need for liver biopsy. They should be considered as supportive toward the common goal of correct classifying the stage of liver fibrosis.

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