Serum Hyaluronic Acid: A Promising Marker of Hepatic Fibrosis in Chronic Hepatitis B

The chronic hepatitis B (CHB) virus affects 350 million individuals worldwide. The infection that is caused by the virus is accompanied by a progressive deposit of hepatic fibrosis, which in turn may lead to cirrhosis.[1,2] Liver biopsy is the gold standard for the assessment of the fibrosis, but it is hampered by several disadvantages such as poor patient compliance, sampling error, and poor intra- and inter-observation concordance.[3] Noninvasive evaluation of liver fibrosis is thus a subject of great clinical interest.

Many parameters for noninvasive diagnosis of liver fibrosis were studied extensively in the past.[4-8] These parameters include routine laboratory tests, serum markers of fibrosis and inflammation, ultrasonography and radiological imaging studies.[9] However, at present, none of these tests or markers alone is accurate or reliable in predicting hepatic fibrosis, either in CHB or other related diseases like chronic hepatitis C (CHC).

Ideally, a marker of hepatic fibrosis should be liver specific. It should also be able to measure the activity of the matrix deposition, reflect the underlying fibrosis, irrespective of the cause, should be easy to perform and yet sensitive enough to distinguish between the different stages of fibrosis.

In the liver, hyaluronic acid (HA) is mostly synthesized by the hepatic stellate cells and degraded by the sinusoidal endothelial cells.[10] It has been shown that serum HA levels increase in chronic liver diseases and that progressive liver damage can be identified early by serum HA assessment.[11,12] In patients with chronic liver diseases of various etiologies, increases in serum HA levels occur together with the development of liver fibrosis. In alcoholic liver disease, Tran et al., found that HA was the best marker for the prediction of severe fibrosis, where HA had a diagnostic accuracy of 91.1%.[13] Prior to that, Oberti et al., had observed that HA and prothrombin index were the best predictive factors.[14] There are many studies about serum HA as a fibrosis marker in CHC.[9,15-18] One of these studies has suggested cut-off values of HA to discriminate the different stages of liver fibrosis, but it was limited by the number of cirrhotic patients included amounting to only 5% of the study group.[17] In literature, there are few studies about the noninvasive diagnosis of fibrosis in CHB.[3,19-21] The results obtained in patients with CHB appear relevant since HCV infection may differ significantly in terms of fibrosis progression and the presence of related markers.[22,23] This was elegantly demonstrated in a recent study that enrolled both CHB and CHC patients who underwent liver biopsy and had FibroScan performed on the same day. The study concluded that the efficacy of liver stiffness as measured by FibroScan was superior in detecting fibrosis in patients with CHC than in patients with CHB.[24] Therefore, it appears that data pertaining to CHC cannot be routinely applied to CHB.

This adds to the importance of the work done by Geramizadeh et al., in this issue of the Saudi Journal of Gastroenterology, who tried to validate the value of HA as a simple laboratory test to discriminate between patients with and without significant fibrosis in CHB.[25] This study included 93 patients with CHB, who had liver biopsy. Interestingly, any biopsy specimen of less than 2 cm was excluded, which is a very important factor in increasing the accuracy of liver biopsy reports. Also, examining liver pathology specimens by two independent experts, blinded to the clinical and laboratory data, certainly minimized the interobserver differences. This is crucial in studies evaluating noninvasive fibrosis markers, wherein the ‘gold standard’ of liver biopsy should ideally find a replacement in real ‘gold’. This was not the case in similar studies,[19] where the biopsy size was 10 mm only and all biopsies were reviewed by a single pathologist whose experience was not reported.

In the study of Geramizadeh et al., a cut-off value of HA 113 ng/ml was chosen for identifying the absence or presence of mild fibrosis and another value of HA 181.9 ng/ml was chosen for identifying the absence or presence of severe fibrosis and cirrhosis. This is different from the study of Montazeri et al., where a cut-off value of 126.4 ng/ml could discriminate mild fibrosis from extensive fibrosis.[19] It should be noted that in both the studies, the number of patients with severe fibrosis and cirrhosis was small (16 and 17%, respectively) and there was no distinction between incomplete and established cirrhosis, which is potentially important in clinical practice in relation to decision making for treatment and prognosis issues.

Moreover, the present study lacked data about alanine transaminase (ALT) and aspartate transaminase (AST) activities, HBV DNA level and HBeAg status. This is an important limitation, as these biochemical and virological parameters may affect the stage of fibrosis in CHB. This was previously demonstrated in the study by Zeng et al., where their model of noninvasive diagnosis of liver fibrosis in CHB was applied only to patients with HBeAg positive status.
and elevated transaminases activity, and was not applied to patients with negative HBV DNA, normal or minimally elevated ALT activity, or HBeAg negative patients.\[26\] Therefore, future studies concerning the evaluation of HA or other noninvasive markers for the diagnosis of fibrosis of CHB should routinely include these biochemical and virological data. This will not only allow for proper interpretation of fibrosis markers in different phases of CHB, but may also help in comparison of the results of studies including different CHB populations. Besides, a large cohort of cirrhotic patients is needed for the proper evaluation of HA and other noninvasive markers in the diagnosis of cirrhosis. Further large scale studies may allow a more precise cut-off value of HA between each stage of fibrosis, rather than a mere distinction between mild and severe fibrosis. Finally, combining HA level with other serum markers or Fibroscan for assessing hepatic fibrosis should be considered.

In conclusion, this study shows that serum HA is a promising marker of hepatic fibrosis in CHB, but it should be validated in well-designed controlled studies to avoid the limitations of the previous work and consider combination with other simple non-invasive markers of liver fibrosis.

REFERENCES

1. Lee WM. Hepatitis B virus infection. N Engl J Med 1997;337:1733-45.
2. Freidman SL. Liver fibrosis-from bench to bedside. J Hepatol 2003;38:S38-53.
3. Cadranel JF, Rufat P, Degos F. Practices of liver biopsy in France: Results of a prospective nationwide survey. For the Group of Epidemiology of the French Association for the Study of the Liver (AHEF). Hepatology 2000;32:477-81.
4. Hui AY, Chan HL, Wong VW, Liew CT, Chim AM, Chan FK, et al. Identification of chronic hepatitis B patients without significant liver fibrosis by a simple non-invasive predictive model. Am J Gastroenterol 2005;100:616-23.
5. Olga OZ, Nikolay D. Invasive and non-invasive monitoring of hepatitis C virus-induced liver fibrosis: Alternatives or complements? Curr Pharm Biotechnol 2003;4:195-209.
6. Afshar NH. Diagnosing fibrosis in hepatitis C: Is the pendulum swinging from biopsy to blood tests? Hepatology 2003;37:972-4.
7. Myers RP, Tainturier MH, Katziu V, Piton A, Thibault V, Imbert-Bismut F, et al. Prediction of liver histological lesions with biochemical markers in patients with chronic hepatitis B. J Hepatol 2003;39:222-30.
8. Masseroli M, Caballero T, O'Valle F, Del Moral RM, Perez-Milena A, Del Moral RG. Automatic quantification of liver fibrosis: Design and validation of a new image analysis method: Comparison with semi-quantitative indexes of fibrosis. J Hepatol 2000;32:453-64.
9. Fontana RJ, Lok AS. Non-invasive monitoring of patients with chronic hepatitis C. Hepatology 2002;36:537-64.
10. Guechot J, Serfaty L, Bonnard AM, Chazouilleres O, Poupin E, Poupin R. Prognostic value of serum hyaluronan in patients with compensated HCV cirrhosis. J Hepatol 2000;32:447-52.
11. Rosenberg WM, Voelker M, Thiel R, Becka M, Burt A, Schuppan D, et al. Serum markers detect the presence of liver fibrosis: A cohort study. Gastroenterology 2004;127:1704-13.
12. Murawaki Y, Ikuta Y, Okamoto K, Koda M, Kawasaki H. Diagnostic value of serum markers of connective tissue turnover for predicting histological staging and grading in patients with chronic hepatitis C. J Gastroenterol 2001;36:399-406.
13. Tran A, Hastier P, Barjoan EM, Demuth N, Pradier C, Saint-Paul MC, et al. Non-invasive prediction of severe fibrosis in patients with alcoholic liver disease. Gastroenterol Clin Biol 2000;24:626-30.
14. Oberti F, Valsesia E, Pilette C, Rousselet MC, Bedossa P, Aube C, et al. Noninvasive diagnosis of hepatic fibrosis or cirrhosis. Gastroenterology 1997;113:1609-16.
15. Attallah A, Toson E, El-Waseef A, Abo-Seif M, Omran M, Shiha G. Discriminant function based on hyaluronic acid and its degrading enzymes and degradation products for differentiating cirrhotic from non-cirrhotic liver diseased patients in chronic HCV infection. Clin Chim Acta 2006;369:66-72.
16. Esmat G, Metwally M, Zalata K, Gadalla S. Evaluation of serum biomarkers of fibrosis and injury in Egyptian patients with chronic hepatitis C. J Hepatol 2007;46:620-7.
17. Halfon P, Bourliere M, Penaaranda G, Deydier R, Renou C, Botta-Fridlund D, et al. Accuracy of hyaluronic acid level for predicting liver fibrosis stages in patients with hepatitis C virus. Comparative Hepatol 2005;4:6.
18. Mehta P, Ploutz-Snyder R, Nandi J, Rawlins SR, Sanderson SO, Levine RA. Diagnostic accuracy of serum hyaluronic acid, FIB4/Spect II, and YKL-40 for discriminating fibrosis stages in chronic hepatitis C. Am J Gastroenterol 2008;103:928-36.
19. Montazeri G, Estakhri A, Mohamadnejad M, Nouri N, Montazeri F, Mohammadkani A, et al. Prediction of Significant Fibrosis in HBeAg-Positive Patients With Chronic Hepatitis B by a Noninvasive Model. BMC Gastroenterol 2005;12:5:32.
20. Dong Z, Shen H, Zhang FK. Relationship between serum HBV DNA levels and hepatic fibrosis markers in chronic hepatitis B. Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi 2007;21:129-31.
21. Li HY, Dong Z, Ma H. Relationship between serum HBV DNA levels and serum hyaluronic acid levels in hepatitis B cirrhosis patients. Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi 2007;21:256-7.
22. Poynard T, Munteanu M, Imbert-Bismut F, Charlotte F, Thabut D, Le Calvez S, et al. Prospective analysis of discordant results between biochemical markers and biopsy in patients with chronic hepatitis C. Clin Chem 2004;50:1344-55.
23. Imbert-Bismut F, Messous D, Thibault V, Myers RB, Piton A, Thabut D, et al. Intra-laboratory analytical variability of biochemical markers of fibrosis (Fibrotest) and activity (Actitest) and reference ranges in healthy blood donors. Chem Clin Lab Med 2004;42:323-33.
24. Seo Y, Kim E, Kwon Y. Liver stiffness measurement in patients with chronic hepatitis B is not as useful as that in patients with chronic hepatitis C for the assessment of liver fibrosis. 58th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA, November 2-6, 2007. Abstract 1356.
25. Geramizadeh B, Janfeshan K, Saberfiroozi M. Serum hyaluronic acid as a noninvasive marker of hepatic fibrosis in chronic hepatitis B. Saudi J Gastroenterol 2008;14:174-7.
26. Zeng MD, Lu LG, Mao YM, Qui DK, Li JQ, Wan MB, et al. Prediction of significant fibrosis in HBeAg-positive patients with chronic hepatitis B by a noninvasive model. Hepatology 2005;42:1437-45.

Gamal Shiha
Department of Internal Medicine, Gastroenterology and Liver Unit, Almansoura Faculty of Medicine, Almansoura, Egypt.
E-mail: g_shiha@hotmail.com