Serum levels of angiotensin converting enzyme as a biomarker of liver fibrosis

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Abstract

The renin angiotensin system (RAS) is classically conceived as a circulating hormonal system involved in blood pressure control and hydroelectrolyte balance. The discovery that RAS components are locally expressed in a wide range of organs and tissues, including the liver, pointed to a role for this system in the pathogenesis of several conditions including hepatic fibrosis and cirrhosis. It has been widely reported that the classical RAS axis composed by the angiotensin converting enzyme (ACE)-angiotensin (Ang) Ⅱ-Ang type 1 (AT1) receptor mediates pro-inflammatory, pro-thrombotic, and pro-fibrotic processes. On the other hand, the alternative axis comprising ACE2-Ang-(1-7)-Mas receptor seems to play a protective role by frequently opposing Ang Ⅱ action. Chronic hepatitis B (CHB) is one of the leading causes of liver fibrosis, accounting for the death of nearly one million people worldwide. Liver fibrosis is a key factor to determine therapeutic interventions for patients with CHB. However, the establishment of non-invasive and accurate methods to detect reversible stages of liver fibrosis is still a challenge. In an elegant study published in the 36th issue of the *World Journal of Gastroenterology*, Noguchi *et al* showed the predictive value of serum ACE levels in detecting not only advanced stages of liver fibrosis but also initial and

intermediate fibrotic stages. The serum levels of ACE might represent an accurate, non-invasive, widely available, and easy method to evaluate fibrosis related to CHB. Moreover, therapies involving the inhibition of the classical RAS axis components might be promising in the control of CHB-related liver fibrosis.

Key words: Renin angiotensin system; Angiotensin converting enzyme; Angiotensin Ⅱ; Angiotensin-(1-7); Chronic hepatitis B; Hepatic cirrhosis; Liver fibrosis

Core tip: The therapeutic intervention for patients with chronic hepatitis B frequently relies on the pathological classification of liver fibrosis severity in biopsy. The establishment of non-invasive and accurate methods to detect reversible stages of liver fibrosis is still a challenge. High serum levels of angiotensin converting enzyme seem to better predict intermediate liver fibrosis than other classical fibrotic markers. Non-invasive methods to detect intermediate stages of liver fibrosis with very good accuracy may permit the introduction and/or evaluation of treatments during reversible stages of the disease. Further studies are urgently necessary to fully clarify the role of RAS components in liver disease.

INTRODUCTION

The discovery of renin-angiotensin system (RAS) components locally expressed in several organs and tissues, including the kidney, brain, and liver, challenged the classical view of the RAS as a solely circulating hormonal system involved in blood pressure control and hydroelectrolyte balance[1]. Currently, the RAS is considered a system formed by two opposing axes: the classical axis, which includes the angiotensin-converting enzyme (ACE)-angiotensin (Ang) II-Ang type 1 (AT1) receptor, and the alternative axis, which comprises the ACE2-Ang-(1-7)-Mas receptor. In general, the classical arm seems to mediate pro-inflammatory, pro-thrombotic, and pro-fibrotic processes, mainly through the activation of AT1 receptors[2]. On the other hand, the heptapeptide Ang-(1-7) seems to play a protective role as a biologically active RAS mediator by frequently opposing the action of Ang II *via* stimulation of Mas receptors[3,4]. In this scenario, over the past decades, an imbalance in the components of the RAS classical and alternative

axes has been implicated in the pathogenesis of a wide range of conditions such as atherosclerosis, obesity, insulin resistance, asthma, renal and liver diseases[3-5]. Accordingly, many therapeutic strategies have been designed to inhibit ACE-Ang II-AT1 receptor activity and to stimulate ACE2-Ang-(1-7)-Mas receptor activity[4,5].

Chronic hepatitis B (CHB) is one of the major causes of liver fibrosis, which, along with hepatitis C, alcohol use, and obesity-related steatohepatitis, has resulted in a significant elevation in the occurrence of cirrhosis and in the mortality of at least 800000 individuals worldwide per year[6]. Purnak *et al*[7] detected high serum concentrations of ACE in patients with CHB and they considered this RAS enzyme as a marker of fibrosis. This finding is in line with a more recent study that supported the role of serum ACE level as a noninvasive marker for the prediction of necroinflammatory activity in CHB patients[8]. Taken together, these studies point to a role of the RAS in liver injury in response to CHB, and pave the way for measuring components of this system as potential predictors of disease evolution.

It is worth mentioning that although the pathophysiology of hepatic fibrosis is still not totally clarified, current opinions have proposed that cirrhosis might be in theory reversible, above all in the compensated stage. Therefore, the evaluation of predictive biomarkers and of novel therapeutic targets is of utmost importance[9].

STUDY ANALYSIS

In the 36th issue of the *World Journal of Gastroenterology*, Noguchi *et al*[10] conducted an observational study to investigate the predictive value of serum ACE levels in CHB-associated fibrosis. A total of 100 patients diagnosed with CHB were enrolled in the study and underwent routine liver biopsy. Thirty patients with a history of hypertension, fatty liver, and alcohol abuse were excluded. The degree of hepatic fibrosis in the liver biopsy specimen was evaluated and classified based on the METAVIR score for chronic hepatitis, ranging from F0, no fibrosis, to F4, cirrhosis. The F2 degree (portal fibrosis with few septa) was considered significant liver fibrosis. Additionally, serum levels of ACE and well-known fibrotic markers including the number of platelets (PLT), the aspartate aminotransferase (AST)-to-platelet ratio index (APRI), the Mac-2 binding protein glycosylation isomer (M2BPGi) concentration, and the fibrosis index according to four factors (FIB-4) were also evaluated. For differentiating mild fibrosis (F0-F1) from substantial fibrosis ($\geqslant$ F2), the 12.8 U/L cut-off value of ACE had a high sensitivity (91.7%) with a good specificity (75%). The receiver-operating characteristic (ROC) curve analysis showed that the area under the curve (AUC) value of ACE serum level measurements was 0.871. The AUC of serum ACE

was bigger than that of other tests for liver fibrosis, including APRI, FIB-4, M2BPGi, and PLT. Importantly, CHB patients in early stages of fibrosis (F0-1) had significantly lower serum levels of ACE than those with significant, advanced fibrosis and cirrhosis (F2-4). The authors concluded that serum levels of ACE might represent an accurate, non-invasive, widely available, and easy method to evaluate fibrosis related to CHB. This conclusion is particularly true for CHB patients without other associated conditions such as fatty liver and/or habitual alcoholic consumption.

The general severity of liver fibrosis influences therapeutic clinical decisions in CHB patients. Serum levels of ACE have been previously evaluated in CHB patients as a potential marker of hepatic fibrosis[7,8]. For instance, Purnak *et al*[7] reported higher serum levels of ACE in 22 patients with advanced liver fibrosis compared with 28 patients with mild fibrosis, indicating that the utilization of measurements of serum ACE levels for CHB patients may provide further prognostic data. A more recent study in 54 patients with severe fibrosis showed that serum ACE levels, together with hepatitis B virus deoxyribonucleic acid and serum transaminase levels, might be used as noninvasive markers for predicting necroinflammation in CHB patients[8]. Even though these previous studies pave the way for the hypothesis that increased serum levels of ACE might be a marker of CHB-associated fibrosis, both included only patients at advanced stages of liver fibrosis for which treatment may not be as efficient as for earlier stages. The study of Noguchi *et al*[10] was thus designed to overcome this limitation. The authors provide a more accurate classification of the degree of hepatic fibrosis, allowing the predictive value of serum ACE levels to be investigated not only for severe fibrosis but also for initial (F1) and intermediate (F2-F3) stages. Furthermore, Noguchi *et al*[10] showed that measurement of ACE serum levels was better than other tests for detecting liver fibrosis. It should also be mentioned that the possibility of adopting a non-invasive yet accurate method to detect intermediate stages of liver fibrosis might allow the introduction and/or evaluation of treatments during reversible stages of the disease. Moreover, these findings also suggest that the therapeutic role of inhibitors of the classical RAS axis, such as ACE inhibitors and AT$_1$ receptor antagonists, should be more deeply investigated for controlling liver fibrosis in CHB patients.

PERSPECTIVES

The establishment of non-invasive and accurate methods to detect reversible stages of liver fibrosis remains a challenge. Many biomarkers have been investigated in this context. However, most of these biomarkers are accurate only for advanced stages of liver disease, when therapies are no longer efficient. Components of the RAS have a clear role in the pathophysiology of liver disease. Therefore, the measurement of these molecules seems to be very reasonable not only for predicting the progression of liver disease but also for establishing its prognosis, and for being tested as therapeutic targets. In this regard, Noguchi *et al*[10] clearly showed the ability of serum ACE levels to differentiate initial (F0 and F1) from intermediate (F2-F3) stages of liver fibrosis in CHB patients without other associated conditions. These findings open many different clinical and research approaches. First, measurement of serum ACE levels should be tested in larger samples of patients with CHB and other liver diseases. Second, serum levels of other RAS components, including serum levels of ACE2, Ang Ⅱ, and Ang-(1-7), should be measured in patients with liver diseases to evaluate these molecules as biomarkers of liver fibrosis and/or disease prognosis. Third, randomized clinical trials with ACE inhibitors or AT$_1$ receptor antagonists should be conducted in patients in reversible stages of liver diseases. Fourth, the role of components that stimulate the alternative RAS axis (ACE2 activators, Ang-(1-7) analogs, and Mas receptor agonists) should be tested in phase Ⅰ /phase Ⅱ studies of liver diseases. In conclusion, the role of RAS components in liver diseases deserves further investigation.

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