ORIGINAL ARTICLES

Soluble urokinase plasminogen activator receptor levels are associated with severity of fibrosis in nonalcoholic fatty liver disease

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The identification of individuals with severe liver fibrosis among patients with chronic liver disease is of major importance when evaluating prognosis, potential risk for complications, and when deciding treatment strategies. Although percutaneous liver biopsy is still considered a "gold standard" for staging of liver fibrosis, attempts to find reliable noninvasive markers of liver fibrosis are frequent. Inflammation is essential for the progression of fibrosis. The urokinase plasminogen activator and its receptor have been associated with hepatic inflammation and fibrosis in mice. High serum concentrations of soluble urokinase plasminogen activator receptor (suPAR) are suggested to be involved in inflammation, tissue remodeling, and cancer metastasis. Here, we evaluated serum suPAR as a noninvasive test to detect liver fibrosis in 82 well-characterized patients with nonalcoholic fatty liver disease (NAFLD), and in 38 untreated patients with chronic hepatitis C virus (HCV) infection at the time of their first liver biopsy. suPAR levels were increased in chronic liver disease compared with blood donors ($P < 0.001$). Patients with HCV had higher suPAR concentrations than patients with NAFLD ($P < 0.002$). suPAR levels were associated with the severity of fibrosis, particularly in NAFLD, but did not correlate with inflammation. Regarding the performance in predicting severity of fibrosis, suPAR was essentially as good as other commonly used noninvasive fibrosis scoring systems. The results in HCV confirm previous observations. However, this is the first study to investigate suPAR as a biomarker in NAFLD, and the results indicate that suPAR may constitute a severity marker related to fibrosis and prognosis rather than reflecting inflammation. (Translational Research 2015;165:658–666)

Abbreviations: ALT = alanine aminotransferase; APRI = AST-to-platelet ratio index; AST = aspartate aminotransferase; AUC = area under the curve; CRP = C-reactive protein; D_I = domain I; D_{II} = domain II; D_{III} = domain III; GUCI = Göteborg University Cirrhosis Index; HC = healthy controls; HCV = hepatitis C virus; HSC = hepatic stellate cells; NAFLD = nonalcoholic fatty liver disease; NAS = NAFLD activity score; suPAR = soluble urokinase plasminogen activator receptor; uPAR = urokinase plasminogen activator receptor

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AT A GLANCE COMMENTARY

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Background

There is a need for new reliable biomarkers in chronic liver disease. The soluble urokinase plasminogen activator receptor (suPAR) has emerged as a potential marker of inflammation and disease severity, and an outcome predictor in several disparate conditions. We evaluated suPAR as a noninvasive test to detect liver fibrosis in patients with nonalcoholic fatty liver disease and chronic hepatitis C virus infection, respectively.

Translational Significance

Finding individuals with severe liver fibrosis among patients with chronic liver disease is essential when evaluating prognosis, potential risk for complications, and when deciding treatment strategies. Herein, we demonstrate a significant association between serum suPAR levels and severity of fibrosis, but not with systemic or histopathologic inflammation. Further translational studies are warranted to scrutinize the biological relevance of suPAR in chronic liver disease and address the question if suPAR provides additional information compared with the present noninvasive scoring systems for liver fibrosis.

INTRODUCTION

Hepatic fibrogenesis is a maladaptive wound-healing process that occurs in response to persistent, injurious stimuli affecting the hepatocytes. This results in a stereotypical chronic inflammatory response leading to hepatic stellate cell (HSC) activation that produces an accumulation of extracellular matrix complexes.[1] The crosslinking of collagen fibrils within the extracellular matrix leads to fibrous scar formation and eventual distortion of the hepatic architecture.[1] The presence and stage of liver fibrosis is of paramount importance in patients with chronic liver disease when deciding treatment strategies, response to therapy, prognosis, and the potential risk for complications.

The "gold standard" for staging liver fibrosis is still percutaneous liver biopsy.[2] However, important limitations to biopsy exist. Significant complications, requiring hospital admission or prolonged hospital stay, occur in 1%–5% of patients, and mortality has been reported to range between 0.1 and 1 in 1000 patients.[3] In addition, liver biopsy has 2 major limitations: sampling error and interobserver variability. A needle liver biopsy only represents 1/50,000 of the total organ, that is, the potential for sampling error remains substantial. Autopsy and laparoscopy studies have demonstrated that cirrhosis is missed on a single blind liver biopsy in between 10% and 30% of cases.[4,5] The intra- and interobserver variability may range from 15% to as high as 33% for determining fibrosis stage.[5]

The attempts to find reliable noninvasive markers of liver fibrosis have recently increased dramatically as a result of the evolving novel therapies for hepatitis C and B.[6,7] By analogy, a considerable interest has arisen in extending this work into the field of nonalcoholic fatty liver disease (NAFLD) because of its increased prevalence.[8,9] Moreover, recent long-term studies suggest that the development of fibrosis in NAFLD has an important prognostic significance.[10]

The soluble urokinase plasminogen activator receptor (suPAR) constitutes the circulating form of the glycosylphosphatidylinositol-linked membrane protein urokinase-type plasminogen activator receptor (uPAR; CD87), and is involved in inflammation, tissue remodeling, and cancer metastasis.[11,12] uPAR is expressed by a wide range of immune cells, whereas suPAR can be detected in different body fluids, including serum and plasma.[11-17] Cell-surface uPAR expression is upregulated on stimulation with growth factors and cytokines such as interleukin 1β and tumor necrosis factor.[18,19] The full-length suPAR shed from the cell surface contains 3 domains ($D_{I\text{-}III}$), and suPAR can occur in different cleaved forms consisting of only D_I or $D_{II\text{-}III}$, with partly divergent biological functions.[12,20] Increased levels of suPAR have been found to predict disease outcome in various forms of cancer and infectious diseases.[21,22] Furthermore, suPAR blood levels correlate with markers of organ dysfunction such as creatinine, urea, cystatin C, bilirubin, and albumin in the severely ill.[21] In chronic liver disease with progressive liver fibrosis, suPAR has also been shown to be increased and correlates with poor prognosis.[23-25] In patients with systemic lupus erythematosus, suPAR seems to reflect organ damage and disease severity rather than ongoing inflammation.[26]

The main aim of the present study was to evaluate serum suPAR as a noninvasive test to detect liver fibrosis in patients with NAFLD and chronic hepatitis C virus (HCV) infection, respectively. The secondary aim was to compare the diagnostic performance of suPAR with a number of simple noninvasive tests previously reported to be of clinical value in identifying advanced liver fibrosis.

METHODS

Patients and controls. The basis for this investigation is formed by patients referred for evaluation to the