Predictors of Steatohepatitis and Advanced Fibrosis in Non-Alcoholic Fatty Liver Disease

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KEYWORDS

- Fatty liver • Liver fibrosis • Serum markers
- Biomarkers • Non-invasive assessment
- Diabetes • Predictors

The prevalence of non-alcoholic fatty liver disease (NAFLD) in the American population is approximately 30% in adults and 10% in children, making it the most common cause of chronic liver disease in the United States.[1,2] Although the majority of patients with NAFLD have a benign clinical course, the development of non-alcoholic steatohepatitis (NASH), with necroinflammation and progressive fibrosis, increases the risk for development of cirrhosis and its complications.[3,4] Among patients with NASH, approximately 28% develop cirrhosis over an 8-year follow-up period.[4,5]

The gold standard for diagnosing and staging NAFLD is liver biopsy. Liver biopsy is associated with costs and risks that make it impractical for generalized use in a condition that affects such a high portion of the population. Furthermore, liver biopsy is also limited by significant sampling error in NAFLD.[6,7] Thus, there is a pressing need for accurate non-invasive predictors of NAFLD that would also allow differentiation of those subjects at higher risk of disease progression. At present, in the clinical setting, some demographic factors, blood tests, and imaging studies can be used to predict a higher risk of disease in patients being evaluated for NAFLD. These predictors, however, are of limited sensitivity and specificity compared with liver biopsy. The development and validation of accurate predictors and scoring systems to identify patients at higher risk for NASH and fibrosis would allow identification of subjects who would benefit the most from liver biopsy and potentially help monitor disease

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progression and response to therapeutic modalities in the future.[8] Nevertheless, it is important to emphasize the importance of establishing the diagnosis of NASH and advanced fibrosis in NAFLD[9,10] (discussed later).

PREDICTORS OF NON-ALCOHOLIC STEATOHEPATITIS

Several demographic, anthropomorphic, clinical, and laboratory factors are associated with NAFLD and with histologic severity of disease. Among these, the factors most reliably associated with the presence of NASH and of advanced fibrosis include older age, insulin resistance (IR)/diabetes mellitus (DM), obesity, and hypertension. However, the potential applicability of these variables in predicting severity of disease in the clinical setting is limited.

Demographic Factors

Race

Ethnic differences in the prevalence of NAFLD are reported, with lower prevalence in African Americans compared with non–African Americans and highest prevalence in Hispanic patients followed by white patients.[1,11] Some studies have reported similar findings regarding steatohepatitis.[12,13] Campos and colleagues[13] observed a higher prevalence of NASH in obese white and Hispanic patients compared with African Americans (35% versus 11%) and higher risk of NASH independent of presence of the metabolic syndrome (odds ratio [OR] 8.4, P = .005). Kallwitz and colleagues[14] also noted lower prevalence of liver steatosis, NASH, and advanced fibrosis in obese patients who were African Americans compared with non-Hispanic white and Hispanic patients. These and other studies suggest that African Americans might be protected from development of NAFLD and disease severity.[15] Variations in visceral adipose tissue distribution and on IR influenced by genetic and physiologic factors may explain these differences.[16–18]

Gender and age

Reports regarding the association between risk for NASH and gender are variable. Some studies report a higher risk for NASH in women,[19,20] others a higher risk in men,[21] and others are unable to demonstrate a definitive association.[13,22,23] Older age also is associated with a higher risk of NASH.[20]

Elements of the Metabolic Syndrome

Insulin resistance and diabetes mellitus

IR is known to play a key role in the pathophysiology of NAFLD.[24–26] In addition, the results of several studies suggest that a higher degree of IR is associated with a higher likelihood of development of steatohepatitis in patients with steatosis.[20,27–29] Patients with NASH have higher homeostasis model assessment (HOMA) score, serum insulin level, and C-peptide level compared with controls.[24] Furthermore, various studies have demonstrated the value of measures of IR as predictors of NASH. In one study, a HOMA index greater than 5.8 was a significant predictor of NASH in obese subjects.[28] Similarly, another series reported the Quantitative Insulin Sensitivity Check Index (QUICKI) model as useful in predicting NASH compared with simple steatosis with an accuracy (area under the curve [AUC]) of 0.70.[20]

It is well established that patients with type 2 DM are at higher risk of NAFLD and of developing NASH and advanced fibrosis compared with non–DM subjects.[21,22,30]