

Noninvasive Markers for the Diagnosis of Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) is an outstanding example of the complex pathophysiology of the metabolic system and represents both a source and consequence of metabolic syndrome. NAFLD can be seen as the hepatic manifestation of metabolic syndrome and is particularly associated with insulin resistance, obesity, and abnormalities of glucose and lipid metabolism [1]. Furthermore, NAFLD is emerging as a risk factor for diabetes and cardiovascular disease, independently of insulin resistance, metabolic syndrome, plasma lipid level, and other traditional risk factors [2].

NAFLD is defined by evidence of hepatic steatosis, either by imaging or by histology, without any causes for secondary hepatic fat accumulation (e.g., significant alcohol consumption, steatogenic medication, hereditary disorders) [3]. NAFLD is further histologically categorized into nonalcoholic fatty liver and nonalcoholic steatohepatitis (NASH), depending on the absence or presence of hepatocellular inflammatory injury with or without fibrosis [3]. The general prevalence of NAFLD in apparently healthy individuals ranges from 3% to 16% in Europe and from 6% to 15% in the United States [4]. Its prevalence is increased in diabetic and obese patients (60% to 80%) and may be as high as 100% in morbidly obese individuals [5]. In a recent cohort study of healthy Korean individuals, NAFLD and its severity were independently and strongly associated with increased incidence of diabetes in men and women, even with euglycemic ranges of glucose and hemoglobin A1c [6].

The gold standard for the diagnosis of NAFLD is liver biopsy, which also differentiates fatty liver from NASH, a critical prognostic determination [7]. However, this procedure is invasive and has a high risk of complication. Therefore, liver biopsy is not adequate as a screening tool for the diagnosis of NAFLD in the general population or in diabetic patients. Some imaging studies such as ultrasonography or computed tomography are an acceptable first-line screening procedure for NAFLD in clinical practice [8]. However, these imaging studies have limitations of relatively low acuity for mild steatosis, low accuracy in morbid obesity, and operator-dependency. For these reasons, numerous noninvasive panels of tests have been developed for the diagnosis of NAFLD consisting of combinations of clinical and routine laboratory parameters, as well as specialized tests [9]. Among them, the fatty liver index (FLI) and the NAFLD fatty liver score were introduced as new noninvasive tools for the diagnosis of NAFLD [10]. Also, adipocyte-specific fatty acid-binding protein (A-FABP), a cytoplasmic protein expressed in macrophages and adipocytes, has been reported as a serum marker involved in metabolic disorders such as metabolic syndrome, type 2 diabetes, and atherosclerosis [11,12]. Although its role and mechanism are not fully elucidated, Milner et al. [13] demonstrated that serum A-FABP levels independently correlate with inflammation and fibrosis of NAFLD in humans.

Jeon et al. [14] investigated the relationship between serum A-

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FABP and FLI as indicators of NAFLD in 238 healthy Korean subjects. They reported that the parameters indicating metabolic syndrome such as blood pressure, fasting blood glucose, and lipid panels were significantly higher in the group with FLI ≥ 30 than in the group with FLI < 30 ($P < 0.001$). The baseline serum A-FABP was significantly associated with FLI after adjusting for age and sex ($P < 0.001$), and aspartate aminotransferase, alanine aminotransferase, fasting insulin, total cholesterol, and high density lipoprotein cholesterol were significantly correlated with FLI. Also, a significant association was demonstrated between FLI and ultrasonographic findings of NAFLD. In addition, when subjects were grouped into A-FABP tertiles, the highest tertile of A-FABP had an increased likelihood of FLI ≥ 30 compared with the lowest tertile (odds ratio, 1.97; $P < 0.05$) [14]. These data were in agreement with other human study which demonstrated that increased serum A-FABP level was a predictive factor for intrahepatic inflammation and fibrosis in patients with histologically confirmed NAFLD with abnormal liver function [13]. Therefore, we can assume that A-FABP with FLI has potential as a predictive marker for the diagnosis of NAFLD. However, to guarantee the role of these noninvasive methods in the diagnosis of NAFLD, several limitations must be overcome. First, a definitive cutoff value of FLI has to be determined for the diagnosis of NAFLD in general populations. Although Bedogni et al. [10] demonstrated that an FLI below 30 rules out fatty liver, while a score greater than 60 indicates fatty liver, these values are suggestive rather than definitive cutoff values. Second, we cannot precisely explain the causal relationship between A-FABP and NAFLD, although several studies have examined the association between A-FABP and fatty liver disease. Although A-FABP plasma level showed a significant progressive increase according to body mass index (BMI) [15], it is not clear whether a high level of A-FABP is a cause of NAFLD or results from a high BMI. Third, subjects in this study were selected from one hospital and are not representative of the general population [14].

Nevertheless, the study is meaningful because it elucidated the relationship between FLI and serum A-FABP as well as other metabolic parameters in healthy Korean subjects. Also, this study suggested these noninvasive markers as potential predictive markers of early diagnosis of NAFLD. Further larger-scale studies are needed to confirm the roles of FLI and A-FABP in NAFLD and obesity. Study for the development of an easy to use method should be ongoing and will be of particular interest.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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