Nonalcoholic Fatty Liver Disease and Metabolic Syndrome

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KEYWORDS

• Nonalcoholic fatty liver disease • Low-density lipoprotein • Metabolic syndrome
• Hyperglycemia • Abdominal obesity • Hypertension • Nonalcoholic steatohepatitis

KEY POINTS

- Nonalcoholic fatty liver disease (NAFLD) and metabolic syndrome (MS) are highly prevalent, affecting approximately a third of the US population.
- Common pathogenetic mechanisms for NAFLD and the MS are associated with the development of cardiovascular disease, type 2 diabetes, and severe forms of liver disease.
- NAFLD is associated with MS and the abdominal obesity, hyperglycemia, hypertension, and dyslipidemia as each component of MS.
- NAFLD associated with the *PNPLA3* G allele variant is not associated by MS and insulin resistance.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is known as the most common chronic liver disease in the United States.[1] With the advent of effective antiviral therapy for hepatitis C and the ongoing epidemic of obesity, the significance of NAFLD as the dominant cause of chronic liver disease is expected to increase over the next 20 years.[2] The increasing prevalence of NAFLD, specifically nonalcoholic steatohepatitis (NASH) with fibrosis, is concerning, because patients appear to experience higher mortality from liver-related and non-liver-related causes compared with the general population.[3] This has occurred within the greater context of prevalent metabolic syndrome (MS), both in the United States and worldwide.

MS is a cluster of metabolic derangements that predicts risk of type 2 diabetes and cardiovascular disease. There is robust evidence in support of common pathogenetic

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mechanisms for NAFLD and the MS, which are associated with the development of type 2 diabetes, cardiovascular disease, and severe forms of liver disease including cirrhosis and hepatocellular carcinoma (HCC). However, not all patients with NAFLD exhibit the typical features of MS; approximately 30% of NAFLD patients are estimated to lack metabolic abnormalities. For example, NAFLD patients who carry at least 1 palatin-like phospholipase domain-containing 3 (PNPLA3) gene variant allele display a favorable metabolic profile, characterized by normal triglycerides and insulin sensitivity.

PREVALENCE AND DIAGNOSIS OF NONALCOHOLIC FATTY LIVER DISEASE

NAFLD is estimated to affect as many as a third of the general population and up to 70% of diabetic and obese subjects in the United States.[1] As a result of the obesity epidemic in many parts of the world and lack of effective therapy, the global burden of NAFLD is projected to increase over the next decade, raising concerns that an increasing proportion of the population will develop cirrhosis and end-stage liver disease with age.

NAFLD is defined as the presence of fatty infiltration in the liver, determined either by imaging or by histology after the exclusion of other causes of hepatic fat accumulation (eg, significant alcohol consumption, medications known to cause fatty liver, and other causes of liver disease). Hepatic ultrasonography, computed tomography, and MRI are accepted modalities for detecting hepatic fatty infiltration. For the evaluation of advanced fibrosis, 2 modalities, namely transient elastography[4,5] and magnetic resonance elastography,[6,7] are often useful in differentiating NAFLD with or without advanced fibrosis.

PREVALENCE AND DIAGNOSIS OF METABOLIC SYNDROME

MS is highly prevalent in the United States and becoming increasingly common worldwide. In the National Health and Nutrition Examination Survey (NHANES), the overall prevalence of the MS increased from 32.9% in 2003 to 2004 to 34.7% in 2011 to 2012, with significantly higher prevalence in women compared with men, and in Hispanics compared with non-Hispanic whites and blacks.[8]

MS consists of a cluster of inter-related factors, including central obesity, dysglycemia, dyslipidemia, and raised blood pressure. It increases the risk for type 2 diabetes and cardiovascular disease. Over the past few decades, various societies have proposed diagnostic criteria, albeit with considerable heterogeneity. In 2009, representatives from the International Diabetes Federation; American Heart Association; National Heart, Lung, and Blood Institute; World Heart Federation; International Atherosclerosis Society; and the International Association for the Study of Obesity developed consensus criteria (**Table 1**).[9] Salient differences compared with prior definitions include: 3 abnormalities out of 5 diagnostic criteria would qualify a person for the MS; sex and ethnicity-specific thresholds for waist circumference were recommended for defining abdominal obesity; and abdominal obesity would not be a prerequisite for diagnosis, but it is 1 of 5 criteria.[9]

METABOLIC SYNDROME AND NONALCOHOLIC FATTY LIVER DISEASE

It is well known that NAFLD often occurs in the context of MS. The prevalence of MS in patients with NAFLD increases with higher body mass index (BMI), from 18% in nonobese NAFLD to 67% in obese NAFLD in a series of 304 patients.[10] In the same series, the presence of MS was associated with a higher risk of NASH and severe fibrosis; 88% of patients with NASH met the criteria for MS, compared with 53% of patients