Natural History of Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) and its progressive form, nonalcoholic steatohepatitis (NASH), are common causes of chronic liver disease worldwide. NAFLD is closely associated with the epidemic of obesity, and it ranges from simple steatosis or nonalcoholic fatty liver (NAFL) to NASH. Although NAFL may be proportionally more common, only patients with NASH have the potential to progress to cirrhosis.[1]

Guideline Definitions for NAFL and NASH From the American Association for the Study of Liver Diseases

NAFL is defined as an accumulation of fat (≥5%) in the hepatic parenchyma and the absence of inflammation and other cellular damage. On the other hand, NASH is characterized by the presence of fat as well as inflammation and/or ballooning degeneration of hepatocytes with or without Mallory bodies. In the context of this definition, excessive alcohol consumption must be excluded (>21 drinks per week in men and >14 drinks per week in women over a 2-year period before the baseline liver biopsy).[2] Although, various other conditions such as hepatitis C infection and drug toxicity may cause fatty infiltration of the liver, the term NAFLD is reserved for the liver disease that is predominantly associated with obesity and metabolic syndrome. Therefore, a diagnosis of NAFLD requires the exclusion of other causes of chronic liver disease.[3]

Natural History of NAFLD

The natural history of NAFLD is complicated by the absence of large-scale population-based studies and the lack of noninvasive tests for monitoring its progression. Additionally, large proportions of patients with NAFLD have normal liver enzymes and are completely asymptomatic (45%-100%).[3] However, a few community-based[4,5] and population-based[6] studies have contributed to our understanding of the progressive nature of NAFLD. Although these studies are variable in the number of patients involved (103-817 patients), the years of follow-up (average follow up 7.6-13.7 years), and the methods employed for the diagnosis of NAFLD, they have reported similar patterns of NAFLD progression.

There is a general consensus that patients with NAFL have a very slow progression (if any). On the other hand, patients with NASH can exhibit histological progression and can develop fibrosis (37%-41%) and cirrhosis (Approximately 5%).[4,5] The presence of NASH can be associated with higher liver-specific mortality in comparison with the general population.[4-11] Additionally, cardiovascular disease and cardiovascular mortality also seem to be important causes of morbidity and mortality (13% of deaths).[1,11] The increased mortality is also associated with impaired fasting glucose, insulin resistance, and risk factors associated with metabolic syndrome.[10]

The progressive nature of NASH is further supported by the presence of cryptogenic cirrhosis. Patients with cryptogenic cirrhosis (mortality rate = 9%-26%)[7] are heavily burdened with metabolic risk factors (type 2 diabetes, obesity, and metabolic syndrome) that are typical of patients with NAFLD.[10] Patients with NAFLD are also at increased risk for hepatocellular carcinoma, but this risk is likely limited to those with advanced fibrosis and cirrhosis (1%-42%).[5-9] Furthermore, a comparison of the natural history of NASH cirrhosis with hepatitis C cirrhosis reveals that patients with NASH cirrhosis have a significantly lower risk of hepatocellular carcinoma.[8]

In summary, NAFLD is the hepatic manifestation of metabolic syndrome, and its prevalence is rising. Only patients with NASH have been shown to progress. This progression predisposes some of these patients to adverse liver- and cardiovascular-related outcomes. ■

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Abbreviations: NAFL, nonalcoholic fatty liver; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

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