Nonalcoholic Fatty Liver Disease

Pathophysiology and Management

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KEYWORDS

• Nonalcoholic fatty liver disease • NASH • Obesity • Hepatic steatosis
• NASH therapeutics • Lipid droplet • Perilipins

KEY POINTS

- Nonalcoholic fatty liver disease (NAFLD) is a systemic disease.
- NAFLD pathogenesis involves hormonal, nutritional, and genetic factors.
- NAFLD mortality is caused by cardiovascular disease, cancer, and hepatic disease.
- Patients with NAFLD should be risk stratified at diagnosis and longitudinally for the presence and degree of fibrosis, and referred if advanced disease is suspected.
- The cornerstone of NAFLD management is 7% to 9% weight loss and management of cardiovascular, oncologic, and hepatic risk factors.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a clinical diagnosis that includes the presence of 5% or more hepatic steatosis as determined by liver imaging or biopsy in the absence of secondary causes of hepatic fat accumulation (**Table 1**). NAFLD spans the spectrum of simple steatosis or nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH), which is defined histologically as hepatic steatosis, hepatic inflammation, and hepatocellular ballooning with or without fibrosis. NASH can progress to cirrhosis and hepatocellular carcinoma (HCC).[1]

Current estimates are that NAFLD affects 30% of the United States population; 32% of the Middle East population; 30% of the South American population; 27% of Asian

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Table 1
Known causes of secondary hepatic steatosis

Macrovesicular Steatosis	Microvesicular Steatosis
Excessive alcohol consumption	Reye syndrome
Viral infection: hepatitis C	Viral infection delta hepatitis
Wilson disease	HELLP syndrome
Autoimmune hepatitis	Acute fatty liver of pregnancy
Parenteral nutrition	Medications (eg, valproate, tetracycline, antiretroviral)
Medications (eg, amiodarone, methotrexate, tamoxifen, corticosteroids, antiretrovirals)	Genetic anomalies and inborn errors of metabolism[a]
Starvation: Kwashiorkor	Jamaican vomiting sickness
Lipodystrophy	
Abetalipoproteinemia	

Abbreviation: HELLP, hemolysis elevated liver enzymes, low platelet count.
[a] Lecithin–cholesterol acyltransferase deficiency, urea cycle defects, cholesterol ester storage diseases, defects of fatty acid beta oxidation, lysosomal acid lipase deficiency, and Alpers syndrome.

populations (highest in east Asians); 24% of the European population; and 13% of the African population.[2–4] In the United States, men are disproportionately affected.[5] Hispanic Americans have a higher prevalence of NAFLD compared with white people; whereas African Americans have the lowest prevalence among all racial and ethnic groups in the United States.[6] Among the Hispanic population, those of Mexican heritage have the highest prevalence, whereas Dominican Republicans have the lowest prevalence.[7,8] The cause of this racial and ethnic disparity is likely multifactorial and includes contributions from genetic, behavioral, and socioeconomic factors.[9]

NAFLD prevalence parallels that of the obesity epidemic and in the United States is expected to become the leading cause of end-stage liver disease by 2020.[10] Like patients with obesity, patients with NAFLD have a higher risk of diabetes, cardiovascular disease, and carcinoma.[11] The metabolic syndrome (defined as the presence of 3 or more of fasting glucose $\geq$100 mg/dL, blood pressure $\geq$130/85 mm Hg, triglyceride level $\geq$150 mg/dL, high-density lipoprotein cholesterol level <40 mg/dL in men or <50 mg/dL in women, waist circumference >100 cm [40 inches] in men or 88 cm [35 inches] in women[12] and if Asian American >88 cm in men or >80 cm [32 inches] in women[13]) is common in patients with NAFLD. Consequently, NAFLD is often considered its hepatic manifestation[14] (although this has recently been challenged).[15]

PATHOGENESIS

NAFLD is a metabolic disorder, and its pathogenesis involves the complex interaction among hormonal, nutritional, and genetic factors (**Fig. 1**).

Role of Hormones

Most patients with NAFLD have obesity resulting from an imbalance between high energy intake (overnutrition) and energy expenditure. Overnutrition of both high-fat foods and sugars has been linked with activating opioid and dopamine receptors in the nucleus accumbens,[16,17] an area of the brain responsible for the development of cravings. In addition, the macronutrient fructose increases cerebral blood flow to areas of the brain responsible for motivation and reward, failing to reduce satiety compared with glucose.[18] Although these pathways have not been examined specifically in NAFLD, it is conceivable that they contribute to obesity in patients with NAFLD as well. Concomitant with the activation of reward centers in response to certain