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Nonalcoholic fatty liver disease (NAFLD) is a common cause of chronic liver disease with increasing prevalence, which can progress to cirrhosis and liver failure. Because of the obesity epidemic and increasing prevalence of metabolic syndrome, NAFLD and its progressive form, nonalcoholic steatohepatitis, are seen more commonly in different parts of the world. This article reviews the worldwide epidemiology of NAFLD and nonalcoholic steatohepatitis. The PubMed database was used to identify studies related to epidemiology of NAFLD in the adult population. It is estimated that the epidemic of obesity will continue to fuel the burden of NAFLD and its long-term complications.

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Harmit S. Kalia and Paul J. Gaglio

Nonalcoholic fatty liver disease (NAFLD) is emerging as the most common cause of liver disease in the United States. The prevalence varies dramatically when comparing individuals of different races and ethnicities. Rates are highest in Hispanic patient populations compared with non-Hispanic whites and African Americans, despite similar rates of the metabolic syndrome and risk factors. This observation remains poorly characterized; variations in genes that effect lipid metabolism may play a role. This article describes the prevalence of NAFLD in patients of different races or ethnicities, and discusses pathophysiologic mechanisms that may explain why these differences exist.

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Nonalcoholic steatohepatitis (NASH) and the metabolic syndrome (MetS) are highly prevalent in the Western population. Their pathogenesis is closely linked to insulin resistance, which serves as a therapeutic target for the management of these conditions. This article reviews the research supporting the influence of MetS on NASH and includes studies supporting their similar epidemiology, pathogenesis, and treatment.

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Paul D. Berk and Elizabeth C. Verna

Obesity and its major comorbidities, including type 2 diabetes mellitus, nonalcoholic fatty liver disease (NAFLD), obesity cardiomyopathy, and
certain cancers, have caused life expectancy in the United States to decline in recent years. Obesity is the increased accumulation of triglycerides (TG), which are synthesized from glycerol and long-chain fatty acids (LCFA) throughout the body. LCFA enter adipocytes, hepatocytes, and cardiomyocytes via specific, facilitated transport processes. Metabolism of increased cellular TG content in obesity may lead to comorbidities such as NAFLD and cardiomyopathy. Better understanding of LCFA transport processes may lead to successful treatment of obesity and NAFLD.

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Jerome Boursier and Anna Mae Diehl
Recent progress has allowed a more comprehensive study of the gut microbiota. Gut microbiota helps in health maintenance and gut dysbiosis associates with chronic metabolic diseases. Modulation of short-chain fatty acids and choline bioavailability, lipoprotein lipase induction, alteration of bile acid profile, endogenous alcohol production, or liver inflammation secondary to endotoxemia result from gut dysbiosis. Modulation of the gut microbiota by pre/probiotics gives promising results in animals, but needs to be evaluated in humans before use in clinical practice. Gut microbiota adds complexity to the pathophysiology of nonalcoholic fatty liver disease but represents an opportunity to discover new therapeutic targets.

Clinical Presentation and Patient Evaluation in Nonalcoholic Fatty Liver Disease 277
Vaishali Patel, Arun J. Sanyal, and Richard Sterling
Nonalcoholic fatty liver disease (NAFLD) is a diagnosis of exclusion. Most patients are asymptomatic, and diagnosed incidentally. Most patients remain undiagnosed. A high index of suspicion and serologic work-up to rule out alternative causes of liver disease is required. In NALFD, fibrosis correlates with outcomes, including mortality. To diagnose, assess severity, and monitor fibrosis, two noninvasive methods can be used; however, noninvasive tests are more helpful at extremes of fibrosis: excluding it or diagnosing advanced fibrosis. Liver biopsy is usually reserved for cases whereby noninvasive tests fail to accurately determine the degree of fibrosis or the diagnosis is unclear.

Histology of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis in Adults and Children 293
David E. Kleiner and Hala R. Makhlouf
Nonalcoholic fatty liver disease (NAFLD) is the liver disease associated with obesity, diabetes, and the metabolic syndrome. Although steatosis is a key histologic feature, liver biopsies of patients with NAFLD can show a wide range of findings. Nonalcoholic steatohepatitis (NASH) is a progressive subtype of NAFLD first defined by analogy to alcoholic hepatitis. Young children may have an alternate pattern of progressive NAFLD characterized by a zone 1 distribution of steatosis, inflammation, and fibrosis. Several grading and staging systems exist, but all require adequate biopsies. Although NASH generally shows fibrosis progression over time, some patients show regression of disease.
Liver-related mortality is the third cause of death in patients with nonalcoholic fatty liver disease, but the long-term prognosis basically depends on the presence and severity of liver damage. Thus, life expectancy in patients with simple steatosis is not different from the general population, but liver-related mortality is significantly higher in patients with nonalcoholic steatohepatitis (NASH), particularly in those with advanced fibrosis. Progression of liver disease is observed in up to one-third of patients with NASH. The long-term hepatic prognosis mostly depends on the histologic stage at initial liver biopsy, but multiple risk factors may concur.

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the United States. Childhood NAFLD is associated with hepatic and nonhepatic morbidity and mortality. Nonhepatic associations include cardiovascular, metabolic, pulmonary, and psychological disorders. Cardiovascular conditions observed in childhood include left ventricular dysfunction. Furthermore, childhood obesity is associated with greater odds of having hepatocellular carcinoma as an adult. Evidence suggests that NAFLD may begin in utero in children of diabetic mothers. Thus rigorous efforts for structured diagnosis and follow-up are a priority to better develop the understanding of outcomes in pediatric NAFLD.

Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the metabolic syndrome. NAFLD is the most common liver disease in developed countries. Weight reduction of 3% to 5% is associated with improved steatosis; reductions of 5% to 7% are necessary for decreased inflammation; with 7% to 10%, individuals may experience NAFLD/NASH remission and regression of fibrosis. No specific dietary intervention has proven beneficial beyond calorie restriction. Physical activity without weight loss seems to decrease hepatic steatosis. Bariatric surgery is associated with decreased cardiovascular risk and improved overall mortality in addition to reduction in hepatic steatosis, inflammation, and fibrosis.

Weight loss, regular exercise, and diet composition modification seem to improve biochemical and histologic abnormalities. Other therapies directed at insulin resistance, oxidative stress, cytoprotection, and fibrosis may also offer benefits. Insulin sensitizers and vitamin E seem to be the most promising; however, they cause side effects. A multifaceted approach of lifestyle modifications, weight loss, and pharmacotherapy can be used in combination, but no single treatment approach has proved
universally applicable to the general population with nonalcoholic steato-hepatitis (NASH). Continuous clinical and preclinical studies on existing and potential drugs are needed to improve treatment of nonalcoholic fatty liver disease/NASH.

**Emerging Therapies for Nonalcoholic Fatty Liver Disease**

Bilal Hameed and Norah Terrault

Nonalcoholic fatty liver disease is the most common cause of liver disease in the United States. There are no drug therapies approved for the treatment of nonalcoholic steatohepatitis (NASH). Multiple different pathways are involved in the pathogenesis and each can be the target of the therapy. It is possible that more than 1 target is involved in disease development and progression. Multiple clinical trials with promising agents are underway. Because NASH is a slowly progressive disease and treatment likely to be of prolonged duration, acceptance and approval of any agent will require information on long-term clinical benefits and safety.

**Extrahepatic Complications of Nonalcoholic Fatty Liver Disease**

Kristina R. Chacko and John Reinus

Nonalcoholic fatty liver disease (NAFLD) is an important cause of liver disease that is often associated with the metabolic syndrome. There is a growing awareness that extrahepatic complications occur in individuals with NAFLD, especially an increased risk of cardiovascular disease. Development of diabetes mellitus, chronic kidney disease, colorectal cancer, and endocrinopathies has been linked to NAFLD. This article reviews the extrahepatic complications affecting individuals with NAFLD and the pathogenesis underlying their development.

**Nonalcoholic Fatty Liver Disease and Liver Transplantation**

Tuan Pham, Travis B. Dick, and Michael R. Charlton

Nonalcoholic fatty liver disease (NAFLD) is prevalent in the general population and a growing indication for liver transplant. Longer wait times and challenges with pretransplant survivorship are expected, underscoring the need for improved management of attendant comorbidities. Recognition with potential modification of obesity, sarcopenia, chronic kidney disease, and cardiovascular disease in patients with NAFLD may have important implications in the pretransplant and posttransplant periods. Although patients with NAFLD have generally favorable postoperative outcomes, they are at risk for developing recurrent disease in their allograft, driving the need for pharmacotherapies and dietary innovations appropriate for use in the posttransplant period.