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**Preface: Nonalcoholic Fatty Liver Disease: An Expanding Health Care Epidemic**

David E. Bernstein

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease with an increasing global prevalence associated with tremendous clinical, economic, and health-related quality-of-life burden. Clinically, NAFLD is considered the liver manifestation of metabolic syndrome. However, diagnosing NAFLD presents significant challenges due to the limited noninvasive and accurate diagnostic tools available to not only accurately diagnose nonalcoholic steatohepatitis but also to stage hepatic fibrosis, the major predictor of long-term outcomes, including mortality.

**Clinical and Economic Burden of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis**

Zobair M. Younossi, Linda Henry, Haley Bush, and Alita Mishra

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease with an increasing global prevalence associated with tremendous clinical, economic, and health-related quality-of-life burden. Clinically, NAFLD is considered the liver manifestation of metabolic syndrome. However, diagnosing NAFLD presents significant challenges due to the limited noninvasive and accurate diagnostic tools available to not only accurately diagnose nonalcoholic steatohepatitis but also to stage hepatic fibrosis, the major predictor of long-term outcomes, including mortality.

**The Natural History of Nonalcoholic Fatty Liver Disease—An Evolving View**

Christina C. Lindenmeyer and Arthur J. McCullough

Nonalcoholic fatty liver disease (NAFLD) is a major cause of chronic liver disease worldwide, and its clinical and economic burden will continue to grow with parallel increases in rates of obesity, diabetes, and the metabolic syndrome. Evolving understanding of the natural history of NAFLD suggests that these patients are at risk for disease progression to steatohepatitis, fibrosis, and cirrhosis. Recent studies also suggest that these patients are at elevated risk for cardiovascular-, malignancy-, and liver-related morbidity and mortality, although their risk for progression, decompensation, and hepatocellular carcinoma may be less than that of patients with alternative causes of chronic liver disease.

**Pathophysiology of Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis**

Vignan Manne, Priya Handa, and Kris V. Kowdley

Nonalcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver disorders ranging from hepatic steatosis to nonalcoholic steatohepatitis (NASH) and ultimately may lead to cirrhosis. Hepatic steatosis or fatty liver is defined as increased accumulation of lipids in hepatocytes and results from increased production or reduced clearance of hepatic triglycerides or fatty acids. Fatty liver can progress to NASH in a significant proportion of subjects. NASH is a necroinflammatory liver disease governed by multiple pathways that are not completely elucidated. This article describes the main mechanisms that have been reported to contribute to the pathophysiology of NAFLD and NASH.
Risk Factors for the Development of Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis, Including Genetics

Huei-Wen Lim and David E. Bernstein

Nonalcoholic fatty liver disease is emerging as the most common cause of chronic liver disease worldwide. This trend is, in part, secondary, to the growing incidence of obesity, type 2 diabetes, and metabolic syndrome. Other risk factors include age, gender, race/ethnicity, genetic predisposition, and polycystic ovarian disease. With the introduction of genome-wide association studies, genetic mutations contributing to inherited susceptibility to steatosis have been identified, which hold keys to future improvement in diagnosis and management. This article expands on the aforementioned risk factors and summarizes the current available data on genetic and environmental factors associated with this common entity.

The Genetics of Pediatric Nonalcoholic Fatty Liver Disease

Nidhi P. Goyal and Jeffrey B. Schwimmer

Nonalcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease in children. Severe fibrosis and cirrhosis are potential consequences of pediatric NAFLD and can occur within a few years of diagnosis. Observations suggest that genetics may be a strong modifying factor in the presentation, severity, and natural history of the disease. There is increasing interest in determining at-risk populations based on genetics in the hope of finding genotypes that correlate to NAFLD phenotype. Ultimately, the hope is to be able to tailor therapeutics to genetic predispositions and decrease disease morbidity in children with NAFLD.

Diagnosis and Evaluation of Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis, Including Noninvasive Biomarkers and Transient Elastography

Eugenia Tsai and Tai-Ping Lee

The incidence and prevalence of nonalcoholic fatty liver disease (NAFLD) are increasing and identification of people at risk of disease progression is extremely important. The current gold standard for diagnosing NAFLD/nonalcoholic steatohepatitis (NASH) is by liver biopsy, but it has several limitations. Noninvasive tests via biomarkers and transient elastography to assess NAFLD/NASH are being used in clinical practice. The most validated diagnostic panels include the NAFLD fibrosis score, Fibrosis-4, and FibroMeter. Transient elastography is very useful in evaluating advanced fibrosis and cirrhosis.

Radiologic Imaging in Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

Yonah B. Esterson and Gregory M. Grimaldi

The article reviews the multimodality (ultrasound, computed tomography, and magnetic resonance [MR]) imaging appearance of nonalcoholic fatty liver disease (NAFLD) and discusses the radiologic diagnostic criteria as well as the sensitivity and specificity of these imaging methods. The authors review the role of both ultrasound and MR elastography for the diagnosis of fibrosis and for the longitudinal evaluation of patients following therapeutic intervention. Last, the authors briefly discuss the screening
and diagnosis of hepatocellular carcinoma in patients with NAFLD, as there are special considerations in this population.

The Use of Liver Biopsy in Nonalcoholic Fatty Liver Disease: When to Biopsy and in Whom

Nadege T. Gunn and Mitchell L. Shiffman

Nonalcoholic fatty liver disease (NAFLD) is a common liver disorder that can be divided into benign steatosis or nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). Elastography and scoring systems based on clinical features and routine biochemical testing can be used to assess fibrosis in patients with NAFLD. Patients with fibrosis are thought to have NASH. However, only a liver biopsy can reliably diagnose NAFLD and differentiate NAFL from NASH. Because medical therapy for NASH is not available, it is not necessary to perform a liver biopsy in all patients. Patients suspected of having NASH should undergo liver biopsy.

The Intestinal Microbiome in Nonalcoholic Fatty Liver Disease

Puneet Puri and Arun J. Sanyal

Nonalcoholic fatty liver disease is the most common cause of chronic liver disease in North America and is growing as a cause of chronic liver disease in many other parts of the world as well. It has 2 principal clinical-pathologic phenotypes: (1) nonalcoholic fatty liver and (2) nonalcoholic steatohepatitis. The development of both phenotypes is tightly linked to excess body weight and insulin resistance. This review discusses the emerging tools for the analysis of the microbiome, their limitations, and the existing literature with respect to the intestinal microbiome and their role in nonalcoholic fatty liver.

Nonalcoholic Fatty Liver Disease and Metabolic Syndrome

Donghee Kim, Alexis Touros, and W. Ray Kim

Nonalcoholic fatty liver disease (NAFLD) and metabolic syndrome (MS) are highly prevalent, affecting approximately one-third of the US population. The relationship between NAFLD and MS is complex and may be bidirectionally associated. NAFLD is strongly associated with MS, the components of which include abdominal obesity, hyperglycemia, hypertension, and dyslipidemia. NAFLD associated with certain genetic factors, such as the PNPLA3 G allele variant, is not accompanied by insulin resistance and MS. Lifestyle modification, including diet and physical activity targeting visceral adiposity, remains the standard of care for patients with NAFLD and MS.

The Role of Nonalcoholic Fatty Liver Disease on Cardiovascular Manifestations and Outcomes

Alexander J. Kovalic and Sanjaya K. Satapathy

Cardiovascular disease has been postulated as the leading cause of mortality among patients with nonalcoholic fatty liver disease (NAFLD), rather
than from sequalae of liver disease specifically. Although there is ample evidence validating the association between NAFLD and increased cardiovascular comorbidities, events, and mortality, current data present a challenge in attributing this effect solely due to NAFLD given the rampant presence of insulin resistance and type 2 diabetes mellitus (T2DM). Endpoints of increased cardiovascular risk remain tightly linked to the concomitant presence of insulin resistance and T2DM. Prospective studies accentuating early detection of NAFLD are imperative to institute early intervention and prevent future cardiovascular events.

Current Treatment of Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis

Chun Kit Hung and Henry C. Bodenheimer Jr

Treatment of nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH) is focused on patients with NASH because they are at highest risk for progressive liver disease. Current first-line treatment consists of lifestyle modifications. Patients should lose at least 7% to 10% of body weight via a combination of physical exercise and calorie restriction dieting. Surgical or endoscopic surgery for weight loss can be considered in obese patients, depending on degree of excess body weight and comorbidities. There is no currently approved pharmacotherapy for NASH. Vitamin E and pioglitazone have the most evidence of therapeutic efficacy but have limitations. The treatment modality chosen should be individualized.

Emerging Treatments for Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

Samer Gawrieh and Naga Chalasani

This article discusses completed phase II randomized clinical trials with high-quality published results for compounds that demonstrate effects on nonalcoholic steatohepatitis histology (obeticholic acid, elafibranor, and liraglutide). The authors also review the available preliminary data on cenicriviroc and selonsertib, with or without simtuzumab’s phase II studies. Finally, the authors briefly discuss compounds that have been tested but did not achieve the primary end point of histologic improvement and appeared in high-quality published articles (cysteamine bitartrate and long-chain polyunsaturated fatty acids).

Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis and Hepatocellular Carcinoma

Omar Massoud and Michael Charlton

Although hepatocellular carcinoma (HCC) is more common in the setting of cirrhosis, there is increasing evidence that it can develop in the setting of noncirrhotic nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH) and that steatosis alone can promote carcinogenesis. In addition, obesity, diabetes, and metabolic syndrome are recognized risks for the development of HCC. A better understanding of the mechanisms involved in the development of NAFLD/NASH-related HCC will allow the discovery of new targets for therapeutic and preventive intervention. The surveillance for HCC in the setting of noncirrhotic NAFLD/NASH, obesity, diabetes, and metabolic syndrome remains an area of uncertainty.
The number of transplants caused by nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NASH) has been progressively increasing and this is expected to become the most common indication for liver transplantation in the United States. Patients with NASH show many features of the metabolic syndrome and, as a result, are at higher risk for postoperative cardiovascular morbidity and mortality. Despite this, patients with NASH have long-term graft and patient survival rates comparable with other causes of chronic liver disease. Posttransplant metabolic syndrome is a common occurrence that increases the risk of steatosis in the graft liver.