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<p>Current imaging methodologies can detect steatosis with increasing accuracy but cannot detect inflammation or pre-cirrhotic fibrosis or remodeling of the liver parenchyma. Imaging also cannot assess types or localization of hepatic steatosis. With the increased use of rodents to study NAFLD/NASH, careful analysis or reading highlights the fact that liver tissue evaluations reported in many of the popular animal models of NAFLD/NASH often do not imitate many of the significant aspects of the human disease, despite similar terminology applied by investigators. This review will focus on the findings in human disease.</p>	
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<p>It is well established that the development of NAFLD and NASH are closely linked to an excess flow of free fatty acids (FFA) arising from dysfunctional/insulin resistant adipose tissue causing ectopic fat deposition in many organs. In the liver, when chronic lipid supply surpasses the metabolic ability to adapt it will induce hepatocellular damage as FFA are redirected into harmful pathways of non-oxidative metabolism with intracellular accumulation of toxic lipid-derived metabolites. Multiple mechanisms have been implicated including mitochondrial dysfunction, endoplasmic reticulum stress, and activation of multiple inflammatory pathways. Understanding the role of insulin resistance and lipotoxicity in NASH as part of a broader metabolic disorder is likely to assist practitioners in the successful management of these challenging patients.</p>	
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clinicopathological states, ranging from simple steatosis to non-alcoholic steatohepatitis (NASH). Although dysregulated lipid accumulation occurs across the spectrum of NAFLD, features of liver cell injury, such as hepatocyte ballooning, cytoskeletal changes (Mallory-Denk bodies), and hepatocyte apoptosis, occur predominantly in NASH and distinguish NASH from simple steatosis. Indeed, NASH is a more serious form of liver damage because cirrhosis and hepatocellular carcinoma are potential outcomes of NASH. Meanwhile, cirrhosis and hepatocellular carcinoma rarely occur in individuals with simple steatosis. Hepatic injury and apoptosis that occur in adults are often dysregulated and accompanied by the accumulation of immune cells, which produce cytokines and growth factors that drive chronic inflammation and may result in fibrosis. This article summarizes the process of apoptosis and roles of putative cytokines in progressive NAFLD.

### **Endoplasmic Reticulum Stress and the Unfolded Protein Response**

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Ashwani Kapoor and Arun J. Sanyal

The endoplasmic reticulum (ER) is the key cellular organelle involved in protein homeostasis. The unfolded protein response (UPR) is a fundamental cellular process triggered by ER stress because of lack of ATP or primary ER dysfunction. The UPR is activated and dysregulated in non-alcoholic fatty liver disease (NAFLD). The UPR has been shown to be involved in both normal physiologic functions and the cellular response to a host of pathologic states. This article reviews the pathways by which the UPR unfolds and its potential role in the development and progression of NAFLD.

### **Predictors of Steatohepatitis and Advanced Fibrosis in Non-Alcoholic Fatty Liver Disease**

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Mangesh Pagadala, Claudia O. Zein, and Arthur J. McCullough

Non-alcoholic fatty liver disease is the most common cause of chronic liver disease in the United States. The development of non-alcoholic steatohepatitis increases the risk for cirrhosis and its complications. The gold standard for diagnosis is liver biopsy, the costs and risks of which make it impractical. Some demographic factors, blood tests, and imaging studies can be used to predict a higher risk of steatohepatitis or advanced fibrosis, but are of limited sensitivity and specificity. More accurate predictors and scoring systems would allow identifying who would benefit most from liver biopsy and monitor disease progression and response to therapy.

### **New Imaging Techniques for Non-Alcoholic Steatohepatitis**

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Jeffrey D. Browning

No imaging modality has yet been proven to reliably differentiate simple hepatic steatosis from steatohepatitis. This review focuses on the predominant non-nuclear imaging modalities available to clinicians at the present time. The key feature of the techniques outlined in this review that demonstrate the most interesting results have one thing in common: imaging is

not performed in a passive manner but is undertaken as a method to investigate functional differences between simple hepatic steatosis and steatohepatitis based upon the current working model for pathogenesis and progression. The purpose of this article is to review the strengths and weakness of current clinical and experimental imaging modalities for non-invasive detection of NAFLD, with an emphasis on NASH.

### **Fatty Liver and Liver Transplantation**

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Edith Koehler, Kymberly Watt, and Michael Charlton

Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis are common complications of overnutrition and obesity. In the setting of worsening epidemics of obesity in developed and developing countries, the global prevalence and impact of NAFLD seems likely to increase. The large number of patients at risk will translate into major challenges for the liver transplant community, affecting donors and recipients. The comorbidities and hepatic effects of obesity and NAFLD present important new challenges in the management of donors and recipients. This article addresses some of these challenges.

### **NASH and HCC**

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John M. Page and Stephen A. Harrison

Primary liver cancer is the fifth most common malignancy worldwide and the third leading cause of cancer mortality. Non-alcoholic fatty liver disease is the most common cause of chronic liver disease in the United States encompassing a spectrum of entities marked by hepatic steatosis in the absence of significant alcohol consumption. Although simple steatosis follows a generally benign course, the more aggressive form, non-alcoholic steatohepatitis, can progress to cirrhosis and result in complications including hepatocellular carcinoma. A significant number of cases of hepatocellular carcinoma remain cryptogenic without known underlying chronic liver disease. It is increasingly recognized that non-alcoholic steatohepatitis likely accounts for a substantial portion of cryptogenic hepatocellular carcinoma.

### **Lifestyle Modification as the Primary Treatment of NASH**

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Brent A. Neuschwander-Tetri

This article reviews the rationale and data behind recommending lifestyle changes to prevent and reverse NASH, focusing specifically on changes that lead to increased physical activity in sedentary patients, changes in dietary habits, and decreased calorie consumption to achieve gradual and sustained weight loss in those who are overweight or obese. In a culture that values avoiding even minimal exertion these are not easy changes to make. Ultimately, the success of care providers in helping patients to recognize and overcome these barriers depends on a patient's motivation, but clinicians can be more persuasive and able to bolster this motivation

when armed with a conviction based on data that establish this to be the best course of action for patients with NASH.

### **Pharmacologic Therapy of Non-Alcoholic Steatohepatitis**

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Vlad Ratziu and Shira Zelber-Sagi

Specific therapy for non-alcoholic steatohepatitis (NASH) is needed because of the potential severity of this liver disease. NASH is a recognized cause of cryptogenic cirrhosis and, increasingly, of hepatocellular carcinoma. Therefore, there is an unmet medical need for the therapy of NASH. This article discusses this therapy, with particular emphasis on pharmacologic therapy.

### **Non-Alcoholic Fatty Liver Disease: Is Bariatric Surgery the Answer?**

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Anjana A. Pillai and Mary E. Rinella

As the worldwide obesity epidemic continues to increase, the prevalence of non-alcoholic fatty liver disease (NAFLD) and specifically non-alcoholic steatohepatitis (NASH) will become increasingly prominent. NASH will surpass chronic hepatitis C infection as the primary indication for orthotopic liver transplantation in the near future. With the evolution of surgical techniques, bariatric surgery is currently recognized as the most effective method for achieving sustained weight loss and reversing numerous comorbidities in severely obese individuals. This review focuses on the potential risks and benefits of bariatric surgery in subjects with NAFLD and explores its role in the management of NASH in the obese patient.

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