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EDITORIAL

Editors' Introduction to the NAFLD and NASH Special Issue

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We are pleased to introduce the second annual special supplement to *Digestive Diseases and Sciences* dedicated to Emmet B. Keeffe, which this year focuses on nonalcoholic fatty liver disease (NAFLD) and steatohepatitis (NASH). Coverage of these topics is all the more timely due to the rising prevalence of these liver diseases, with NAFLD now the most common chronic liver disease with its associated substantial disease burden. Not only does NAFLD increase the overall mortality, NASH cirrhosis is predicted to be the number one indication for liver transplantation in the USA within the next 4–5 years. Furthermore, NASH cirrhosis has substantially contributed to the etiology of the rapidly increasing number of liver cancers worldwide. Although the pathogenesis of NASH is becoming better understood with new treatment options on the horizon, many obstacles still remain in regard to its understanding, to making a correct diagnosis, and to providing effective therapy. We would like to briefly summarize and highlight the articles included in this issue in the order in which they appear.

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Epidemiology, Natural History, and Extrahepatic Disease

With an increasing prevalence of NAFLD and NASH accompanying the diabetes and obesity epidemics, NAFLD has a major impact on public health. Dr. Sherif and colleagues revisit the global **epidemiology** of NAFLD with a focus on minority populations within the USA. The authors highlight ethnic differences in NAFLD prevalence, which may reflect differences in the natural history of this common disease. Next, Drs. McCullough and Goh describe the **natural history** of NAFLD with an emphasis on long-term liver-related outcomes. While NAFLD can progress to NASH and then to liver cirrhosis, the presence of liver fibrosis is now considered the single best indicator of liver-related mortality. The incidence of **liver cancer** is rising at an alarming rate, becoming increasingly common in patients with NAFLD. Drs. Reeves, Zaki, and Day describe factors associated with the risk of liver cancer. A better understanding of how these factors contribute to disease pathogenesis will help identify screening and novel therapeutic strategies. Finally, Dr. Mantovani and colleagues summarize current knowledge regarding the association between **NAFLD and coronary artery disease**, as well as with functional and structural cardiac abnormalities and with arrhythmias. The authors suggest that more cardiovascular surveillance combined with early interventions may decrease the risk of these extrahepatic complications, which contribute significantly to the mortality of NAFLD.

Pathogenesis and Animal Models

The first article about disease pathogenesis describes the contribution of the **microbiome** to NAFLD and NASH. Diet is an important determinant for the composition of the intestinal microbiota. Dysbiosis-associated changes act in concert with other factors to affect the development of disease at each stage (obesity, NAFLD, and NASH). Finally, modulating dysbiosis could be a promising intervention strategy for patients with NAFLD and NASH. **Lipid accumulation** in hepatocytes could be derived from dietary intake, esterification of plasma free fatty acids, or *de novo* lipogenesis. Drs. Softic, Cohen, and Kahn illustrate that *de novo* lipogenesis in hepatocytes is a central abnormality in patients with NAFLD. Dietary fructose (more than a high-fat diet) increases the abundance of enzymes involved in *de novo* lipogenesis. Disrupting hepatic fructose metabolism could therefore be an attractive target for therapy of liver disease. Innate immunity is an important contributor to NAFLD and NASH. Dr. Feldstein and colleagues describe the activation of the **innate immune system** as key for liver inflammation and disease pathogenesis. Gut-derived microbial products, damage-associated molecular patterns, and lipids activate the innate immune system. Important immune cell types and their contribution to disease progression are described. Modulation of inflammatory pathways represents a treatment option for patients with NASH. **Autophagy** is a lysosomal degradation pathway that provides energy to the cell in times of starvation or stress. Dr. Czaja comprehensively reviews the contribution of autophagy to NAFLD and NASH pathogenesis. Recent work emphasizes the importance of autophagy not only to the cellular functions of hepatocytes, but also to non-parenchymal liver cells. Autophagy can therefore have differential effects on liver fibrosis and on hepatocellular cancer (HCC). Drs. Szabo and Csak discuss the contribution of **microRNAs** (miRNAs) to NAFLD and NASH, highlighting the potential of miRNAs to serve as diagnostic biomarkers and in particular for the progression of steatohepatitis. Novel miRNA-based therapeutic interventions are in development to treat NASH. Since **animal models** are essential for understanding disease pathogenesis and for testing experimental therapies, models of NAFLD and NASH are described by Dr. Gores and colleagues. The review summarizes key histological features of NAFLD and NASH in experimental models as well as the known diet-induced and genetic models in rodents. The latter includes models that target energy homeostasis as well as inflammatory pathways.

Diagnosis

Despite having made substantial progress in the field of NAFLD, lack of provider and patient awareness negatively impacts diagnosing this disease. Dr. Kinner and colleagues first provide an overview of the utility and limitations of **conventional imaging** techniques for the noninvasive diagnosis of NAFLD. The authors then present advances in imaging biomarkers with an emphasis on multi-parametric quantitative magnetic resonance imaging that could serve as a virtual liver biopsy. Until today, a liver biopsy remains the "gold standard" for diagnosing NASH. The article by Dr. Bedossa reviews the state-of-the-art **histological assessment** of NAFLD and discusses recently developed histological scores that have now been accepted as endpoints of clinical trials that assess the potential benefits of drugs used to treat NASH. **Fibrosis assessment** is important for determination of liver-related mortality. Since sophisticated imaging studies are often not readily available and a liver biopsy for NAFLD fibrosis assessment has limited patient acceptance, other noninvasive biomarkers are being explored. Dr. Kaswala and colleagues provide an overview of such tests currently available, discuss their strengths and weaknesses, and provide guidance regarding when to use the appropriate tests in the evaluation of patients with NAFLD.

Therapy

In the absence of any FDA-approved medication for NAFLD, "lifestyle" interventions, particularly in overweight and obese patients, have been the mainstay of therapy. Although effective, these interventions have proven successful in only a minority of patients. Drs. Hannah and Harrison review our current knowledge of the contribution of **exercise and diet** and other nutrient therapies to the treatment of NAFLD, recommending useful and feasible interventions. As the epidemic of NAFLD also has significant impact on children, Dr. Africa and colleagues review **lifestyle modifications** including exercise, nutrition, and dietary supplements in the pediatric population commonly recommended for the treatment of NAFLD, with a discussion of the numerous challenges inherent in this population. Drs. Corey and Rinella summarize presently available **treatment options** for NASH in the absence of any FDA-approved drugs. Clinicians currently have the option to use compounds developed for non-NASH-related indications including insulin sensitizers and non-specific hepatoprotective agents. The authors also discuss endoscopic or surgical bariatric procedures for the treatment of NASH. There is a growing interest in

developing **novel compounds** that target one or several of the pathways of liver injury in NASH. In his review, Dr. Ratziu highlights some of these compounds with an emphasis on two drugs that target nuclear receptors and that are being currently tested in large international trials. For those patients that have already developed advanced liver cirrhosis or even liver cancer, **liver transplantation** may be the only life-saving therapy available. Dr. Patel and colleagues explore unique aspects of patients with NASH while awaiting liver transplantation as well as their care after surgery. The authors also address the impact of NAFLD in the liver donor population and highlight areas for future research surrounding NAFLD as indication for liver transplantation.