

Preface



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Guest Editor

Our understanding of nonalcoholic fatty liver disease (NAFLD) has grown exponentially in the past 29 years since Ludwig and colleagues¹ first described the histologic lesions that comprise a subset of NAFLD known as nonalcoholic steatohepatitis (NASH). A recent PubMed search using the term “nonalcoholic fatty liver disease” generated 1475 articles published since 1980, of which 1405 were published since the year 2000. Concern for this liver disease is validated, as NAFLD is becoming, if it has not already become, the number one chronic liver disease in this country and in many others around the world. As the prevalence of obesity and diabetes, both of which are characterized by impairment in insulin signaling, continues to rise, so will the prevalence of NAFLD. We as health care providers are now faced with an epidemic.

How big of a problem is this? Do we just have to worry about liver disease in these patients, or are there extrahepatic problems that deserve attention too? Among patients with NAFLD, are there specific subsets who are likely to progress in their liver disease more quickly? The data in reference to these questions are discussed in the first article of this issue of *Clinics in Liver Disease* by Drs. Argo and Caldwell, who detail the epidemiology and natural history of this disease.

Liver biopsy has long been a mainstay among the hepatologic community in assisting with disease diagnoses. As is pointed out by Dr. Brunt in her article on histopathology of NAFLD, biopsy of hepatic tissue remains the only unequivocal way to make a definitive diagnosis of NASH, identify potential coexisting liver disease such as autoimmune hepatitis, and ensure exclusion of other disease processes. She discusses the salient histopathologic features of both pediatric and adult NASH and the differences that occur among various ethnic groups.

Much has been learned about the pathogenesis of fat accumulation in the liver and its relationship to insulin resistance. Over the past several years, our knowledge of the interaction between insulin resistance and multiorgan lipotoxicity has significantly expanded. For instance, we now know that specific cytokines, induced in part by dysfunctional adipocytes and altered free fatty acid metabolism, trigger the activation and/or alteration of cellular processes that result in the histopathologic lesions seen in patients with NAFLD. Although there is much yet to learn, this edition of *Clinics in Liver*

Disease also focuses on mitochondrial dysfunction, endoplasmic reticulum stress, apoptosis, and their relationship to lipotoxicity, as discussed by Drs. Cusi, Wing-Syn, Choi, Diehl, Kapoor, and Sanyal. This exciting data will inevitably guide future therapeutic development in this field.

It is imperative that novel ways to diagnose and triage patients with NAFLD be developed, given the epidemic that exists in our world today. Most patients with NAFLD do not progress in their liver disease, so although performing a liver biopsy is still considered the gold standard for diagnosing NASH, it does not make sense from a global health perspective, and it is not practical to biopsy all patients. Drs. Pagadala, Zein, McCullough, and Browning discuss newer imaging techniques and other noninvasive strategies, currently under development or under clinical investigation, to triage these patients.

Recent data suggest that obese and diabetic patients are at increased risk for hepatocellular carcinoma (HCC). Given the link between these 2 diseases and NAFLD, one would expect that these patients would be at increased risk for HCC. Although prospective, long-term studies are lacking, evidence suggests that this is indeed the case, and the relationship of NAFLD to HCC is discussed by Drs. Page and Harrison. Furthermore, although hepatitis C has traditionally been the number one reason for liver transplantation in this country, more and more transplant centers are seeing patients with underlying NASH cirrhosis or cryptogenic cirrhosis present for liver transplantation. Drs. Koehler, Watt, and Charlton discuss the increasing demand for liver transplantation in this patient population and the subsequent outcomes after surgery.

Although our knowledge of the pathogenesis is expanding rapidly, therapy to reverse or slow this disease process has been challenging. We know that dietary modification and exercise will improve insulin resistance and subsequent NAFLD/NASH. However, many questions still remain. Specifically, what type of diet is preferred? How much weight loss and/or exercise is necessary to effect both biochemical and histopathologic improvement? If patients are unable or unwilling to lose weight or exercise, what other therapies are available that have been proven effective? These issues are discussed by Drs. Neuschwander-Tetri, Ratzliff, Zelber-Sagi, and Rinella.

In summary, this collection of up-to-date articles on NAFLD/NASH, put together by leading researchers and clinicians in hepatology and endocrinology, is meant to provide the reader with a front row seat to the current understanding, evaluation, and treatment of this most common liver disease. I would like to personally thank the authors and their families for the time and effort put into their contributions. I would also like to thank Kerry Holland for outstanding editorial support and Dr. Norm Gitlin for allowing me to develop this issue of *Clinics in Liver Disease*.

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REFERENCE

1. Ludwig J, Viggiano TR, McGill DB, et al. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. *Mayo Clin Proc* 1980;55:434–8.