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Commonalities and Distinctions Between Alcoholic and Nonalcoholic Fatty Liver Disease

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The special supplement issues of *Gastroenterology*, published each year since 2000, are dedicated to a topic of great public health relevance in which there have been substantial advances made in recent years. The overall goal is to frame what is not known and provide direction to health care and research in the area in the context of what is known and to also identify areas of uncertainty, where more information is needed. This year, the special issue takes on the common and overlapping conditions of alcoholic and nonalcoholic fatty liver disease.

The relevance of the topic is underscored by recent data indicating that the life expectancy of Americans, in contrast to other Western nations, is decreasing and one of the principal contributors to this decline is an increase in chronic liver disease-related mortality.[1] This has been linked to the growing contribution of alcohol-related liver disease in North America. The impact of sustained periods of risky alcohol drinking behavior in the context of the current epidemic of obesity takes on great relevance given epidemiological data linking a higher risk of liver disease when heavy drinking is associated with obesity.[2] Importantly, to date, no drugs have been approved for the treatment of alcoholic hepatitis, a principal cause of liver disease-related hospitalization and mortality.[3]

Obesity and insulin resistance are well-recognized risk factors for nonalcoholic fatty liver disease (NAFLD), arguably the most common form for chronic liver disease in many Western countries. Recent years have seen major advances in the understanding of the basic pathobiology of NAFLD and its more aggressive form nonalcoholic steatohepatitis (NASH). This has led to identification of novel targets for therapy, several of which are now in advanced phase clinical trials. There has also been an explosion of interest in clarification of the regulatory pathways for drug approval for NASH[4] which has brought the topic of regulatory science to focus both for NASH as well as hepatology in general.

Alcoholic and nonalcoholic fatty liver disease share many aspects in common including several histological features, and activation of pathways linked to disease development. They are also quite distinct in many ways including their histological phenotypes, behavioral and social underpinnings, and factors linked to mortality. The goal of this special issue is to review the state of knowledge of fatty liver disease and to identify where common pathways and mechanisms are shared and where the conditions are clearly distinct. It is hoped that our

featured commentaries and reviews will catalyze acceleration of research related to these conditions, particularly in those who have risk factors for NAFLD and who consume pathological quantities of alcohol. Finally, it is anticipated that this special issue will allow the lessons learned in the context of NASH to promote therapeutics for alcoholic hepatitis and introduce regulatory science as an important research area in alcoholic liver disease.

The special issue is divided in to four sections. The first section includes a series of commentaries by experts in the field providing a broad overview of emerging concepts related to several clinical and scientific questions where the fields of alcoholic and nonalcoholic fatty liver disease intersect. Following the broad theme of translation, the subsequent sections focus on basic, clinical and therapeutic aspects, respectively, with in depth reviews of the literature framing the state of the field.

A common clinical quandary is the issue of alcohol consumption and its health impact in those who are overweight or obese. Drs Silvia Sookoian and Carlos J. Pirola (pages 1698–1703) provide an objective analysis of the clinical literature relating the largely retrospective data on the impact of moderate and large amounts of alcohol consumption on allcause and liver-related outcomes focusing on the need for better quality, prospectively collected and adjudicated data on the topic.[5] A key area of interest related to the impact of alcohol consumption in those who have risk factors for NAFLD and NASH is the identification of common biological mechanisms that are activated in both conditions and which could be amplified by the co-existence for these two forms of liver disease. Emerging data point to an important role for inflammation in driving this process. Drs Bin Gao and Hidekazu Tsukamoto (pages 1704–1709) provide a critical review of the pathways that have been implicated and how they could relate to disease progression.[6]

The commentary by Drs Nicolas Goossens and Yujin Hoshida (pages 1710–1717) focuses on the development of hepatocellular cancer in alcoholic and nonalcoholic fatty liver disease.[7] This is an area of great scientific and public health relevance. Both forms of liver disease are important risk factors for hepatocellular cancer which is increasing rapidly as a cause of liver-related mortality in those with cirrhosis.[8] Specifically, a substantial proportion of cases of hepatocellular cancer occur in those with NAFLD even prior to the development of cirrhosis. Recent data from Dr Hoshida’s group has provided novel information on the activation of specific pathways related to oncogenesis in hepatocellular cancer and led to a molecular reclassification of this condition. The insights from these data, with regard to oncogenic drivers and potential therapeutic targets for hepatocellular cancer, are hoped to drive additional research questions to better understand these interactions. Dr Lawrence Serfaty (pages 1718–1722) tackles the important clinical question of the interactions between obesity and alcohol consumption in the context of viral hepatitis.[9] These are all commonly present in the general population, and the scientific and clinical implication of such interactions are of obvious public health significance.

The rapid expansion of the knowledge base in fatty liver disease has not been accompanied by translation to preventive and therapeutic strategies that are implemented in our communities. The lack of clarity on the regulatory path to approval has been a major barrier to engagement by all potential stakeholders in the field. Drs Arun J. Sanyal and Veronica

Miller (pages 1723–1727) review the progress in regulatory science and paths to approval for NASH therapeutics and begin to frame potential endpoints and paths related to alcoholic hepatitis and liver disease in the context of regulatory science.[10] Indeed, endorsement by health agencies of plans of development with different end-points adapted from phase I to phase III studies is a prerequisite to allow pharmaceutical companies and scientific societies to plan the development of future molecules in the setting of alcoholic hepatitis.

The Basic Science second section starts with the important topic of genetics for alcoholic and nonalcoholic fatty liver disease. While the PNPLA3 gene mutation has been strongly linked to disease development and progression for both NASH and alcoholic liver disease, other genes have recently been identified, such as the TM6SF2 gene that can modulate the phenotype of fatty liver disease. An intriguing hypothesis has emerged that this gene may differentially determine the risk for cardio-metabolic disease versus liver disease. These aspects are reviewed by Drs Quentin M. Anstee, Devanshi Seth and Christopher P. Day (pages 1728–1744).[11] The next paper by Drs Naga S. Betrapally, Patrick M. Gillevet, and Jasmohan S. Bajaj (pages 1745–1755) focuses on the rapidly growing field of the microbiome in fatty liver disease and the literature linking the microbiome to altered bile acid biology, systemic and gut inflammation and altered neurobiology.[12] Drs Laura E. Nagy, Wen-Xing Ding, Gail Cresci, Paramananda Saikia, and Vijay H. Shah (pages 1756–1768) connect the dots between the multiple pathways implicated in the development of alcoholic liver disease to provide a conceptual framework for disease development and how disease pathogenesis is associated with disease phenotypes, particularly the development of alcoholic hepatitis.[13] Drs Mariana Verdelho Machado and Anna Mae Diehl (pages 1769–1777) provide a similar analysis of the field for NASH.[14] It is hoped that these back-to-back reviews will allow readers to gain perspective on overlapping versus distinct mechanisms of disease development which will inform strategies to target pure NASH versus alcoholic steatohepatitis (ASH) and also those where risk factors for both types of liver disease are present.

The literature on the burden of alcoholic and nonalcoholic fatty liver disease is an important one. Drs Zobair Younossi and Linda Henry (pages 1778–1785) begin the third section by summarizing the published work to date and highlighting the major public health importance of these conditions.[15] It is hoped this will help policy makers to make decisions about resource allocation for funding and also health care access and delivery related to these conditions. Drs Suthat Liangpunsakul, Paul Haber and Geoffrey McCaughan (pages 1786–1797) follow this with an extensive and critical review of the literature summarizing what is known and what is not known about the clinical aspects of alcoholic liver disease where many of the existing paradigms are based on studies performed over forty years ago.[16] There is a need to revisit these in the context of the changing profile of individuals with alcohol-related liver disease, both in terms of demographics and comorbidities. This review will allow interested readers to focus in on the key questions in the field. Drs Valerio Nobili, Anna Alisi, Kimberly P. Newton, and Jeffrey B. Schwimmer (pages 1798–1810) address the topic of pediatric fatty liver disease, a matter of great public health concern.[17] The clinical profile of the disease in children has several features that are distinct from adults with NASH, and adult data on disease progression can’t be legitimately transposed on children with the disease.

The fourth and last section of this special issue deals with the bedside management of patients with alcoholic and nonalcoholic fatty liver disease, which will be of interest for all clinicians involved in the care of patients with these conditions and also serve as a general review for basic scientists to enhance their awareness of clinical aspects of these diseases. Over 60% of the adult population consumes alcohol at some level, and over two thirds of the population is overweight (BMI > 25-29.9) or obese (BMI≥ 30). These statistics underscore the need for simple point of care tests for the initial evaluation of patients at risk and triage of those where the disease is identified. There has been an explosion of recent literature on the use of circulating biomarkers and imaging methods such as ultrasound or magnetic resonance elastography which are reviewed by Drs Pierre Bedossa and Keyur Patel (pages 1811–1822) who relate these to traditional histological disease progression end points.[18] Drs Mark Thursz and Timothy R. Morgan (pages 1823–1834) follow this with a state of the art summary of the success and limitations of existing therapeutics for alcoholic hepatitis including the growing literature showing a lack of efficacy of pentoxyfyline and the high risk of sepsis in those with severe alcoholic hepatitis.[19] Drs Guillaume Lassailly, Robert Caiazzo, François Pattou, and Philippe Mathurin (pages 1835–1848) provide a similar summary of the growing and exciting field of therapeutics for NASH.[20] The final review by Drs M. Shadab Siddiqui and Michael Charlton (pages 1849–1862) provides a detailed discussion on best practices in the management of patients who have undergone a liver transplant and highlight the issues of recidivism for alcohol-related liver disease and disease recurrence for NASH.[21]

Together, it is hoped that this compilation of commentaries and reviews will allow those who are involved in liver research, or who take care of patients with liver disease or are involved in policy-making to gain an overview of where the overlapping fields of alcoholic and nonalcoholic fatty liver disease stand and where it needs to go. We thank all the authors for contributing their valuable commentaries and reviews, and we hope that the readership will find the content a valuable part of the literature they refer to.

Biographies

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References

1. Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. Proc Natl Acad Sci U S A 2015;112:15078–15083. [PubMed: 26575631]
2. Bedogni G, Miglioli L, Masutti F, et al. Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. Hepatology 2005;42:44–52. [PubMed: 15895401]
3. Crabb DW, Bataller R, Chalasani NP, et al. Standard definitions and common data elements for clinical trials in patients with alcoholic hepatitis: recommendation from the NIAAA Alcoholic Hepatitis Consortia. Gastroenterology 2016;150:785–790. [PubMed: 26921783]
4. Sanyal AJ, Friedman SL, McCullough AJ, et al. Challenges and opportunities in drug and biomarker development for nonalcoholic steatohepatitis: findings and recommendations from an American Association for the Study of Liver Diseases-U.S. Food and Drug Administration Joint Workshop. Hepatology 2015;61:1392–1405. [PubMed: 25557690]
5. Sookoian S, Pirola CJ. How safe is moderate alcohol consumption in overweight and obese individuals? Gastroenterology 2016;150:1698–1703. [PubMed: 26775630]
6. Gao B, Tsukamoto H. Inflammation in alcoholic and nonalcoholic fatty liver disease: friend or foe? Gastroenterology 2016;150:1704–1709. [PubMed: 26826669]
7. Goossens N, Hoshida Y. Is hepatocellular cancer the same disease in alcoholic and nonalcoholic fatty liver diseases? Gastroenterology 2016;150:1710–1717. [PubMed: 26784140]
8. Bruix J, Reig M, Sherman M. Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. Gastroenterology 2016;150:835–853. [PubMed: 26795574]
9. Serfaty L Clinical implications of concomitant alcohol use, obesity, and viral hepatitis. Gastroenterology 2016; 150:1718–1722. [PubMed: 26873400]
10. Sanyal AJ, Miller V. Regulatory science and drug approval for alcoholic and nonalcoholic steatohepatitis. Gastroenterology 2016;150:1723–1727. [PubMed: 26924092]
11. Anstee QM, Seth D, Day CP. Genetic factors that affect risk of alcoholic and nonalcoholic fatty liver disease. Gastroenterology 2016;150:1728–1744. [PubMed: 26873399]
12. Betrapally NS, Gillevet PM, Bajaj JS. Changes in the intestinal microbiome and alcoholic and nonalcoholic liver diseases: causes or effects? Gastroenterology 2016; 150:1745–1755. [PubMed: 26948887]
13. Nagy LE, Ding W-X, Cresci G, et al. Linking pathogenic mechanisms of alcoholic liver disease with clinical phenotypes. Gastroenterology 2016;150:1756–1768. [PubMed: 26919968]
14. Machado MV, Diehl AM. Pathogenesis of nonalcoholic steatohepatitis. Gastroenterology 2016;150:1769–1777. [PubMed: 26928243]
15. Younossi Z, Henry L. Contribution of alcoholic and nonalcoholic fatty liver disease to the burden of liver-related morbidity and mortality. Gastroenterology 2016; 150:1778–1785. [PubMed: 26980624]
16. Liangpunsakul S, Haber P, McCaughan G. Alcoholic liver disease in Asia, Europe, and North America. Gastroenterology 2016;150:1786–1797. [PubMed: 26924091]
17. Nobili V, Alisi A, Newton KP, et al. Comparison of the phenotype and approach to pediatric vs adult patients with nonalcoholic fatty liver disease. Gastroenterology 2016;150:1798–1810. [PubMed: 27003600]
18. Bedossa P, Patel K. Biopsy and noninvasive methods to assess progression of nonalcoholic fatty liver disease. Gastroenterology 2016;150:1811–1822. [PubMed: 27003601]

19. Thursz M, Morgan TR. Treatment of severe alcoholic hepatitis. Gastroenterology 2016;150:1823–1834. [PubMed: 26948886]

20. Lassailly G, Caiazzo R, Pattou F, et al. Perspectives on treatment for nonalcoholic steatohepatitis. Gastroenterology 2016;150:1835–1848. [PubMed: 26971824]

21. Siddiqui MS, Charlton M. Liver transplantation for alcoholic and nonalcoholic fatty liver disease: pretransplant selection and post-transplant management. Gastroenterology 2016;150:1849–1862. [PubMed: 26971826]