Editorial

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NAFLD: The evolving landscape

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Non-alcoholic fatty liver disease (NAFLD) comprising non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH), together with their complications of cirrhosis, liver failure and liver cancer will be the predominant liver disease for the conceivable future. Traditionally, viral hepatitis has been the focus of basic and clinical research, and the bread and butter for clinicians in the field. However, with the advent of therapies that suppress hepatitis B virus replication and the shift in standard of care for the treatment of hepatitis C to highly effective direct acting antivirals, the focus of clinical practice and research has altered. For hepatitis C, the goal has moved to elimination strategies and the massive treatment scale up required to achieve this outcome. For hepatitis B, lifelong antiviral therapy for those that require it, as well as cancer surveillance for at-risk groups, has established a relatively easy to follow management algorithm, as we transition to global hepatitis B eradication through immunisation and development of strategies to achieve a functional cure.

While these achievements are a highlight for the speciality, NAFLD has now replaced viral hepatitis as the mainstay of clinical hepatology. Not only does NAFLD and its many variations comprise an ever-increasing number and proportion of referrals to specialists, but it also represents a challenge for primary care physicians managing the early and intermediate stages of the disease. In this respect, disease due to fatty liver is a relative late comer to the limelight in Hepatology, compared to the consequences of the same systemic metabolic derangements to other organ systems including type 2 diabetes, cardiovascular and cerebrovascular disease, and chronic kidney disease.

As we move towards a world where the glimmer of viral hepatitis elimination is becoming a possibility and NAFLD related disease increases, it is appropriate that the Journal commissioned this supplement. Together with my co-editors and the Senior Editors, we focus on four main themes of relevance to both clinicians and researchers. While the topics selected for in-depth review are by no means exhaustive, they cover the broad themes of disease models, pathogenesis, clinical diagnosis and clinical controversies. These were selected from a range of over 20 topics suggested to the Editors, cognizant of recent reviews on various aspects of NAFLD published recently in the *Journal*. These include articles in areas as diverse as basic pathobiology (2015),[1] the acid sphingomyelinase-ceramide system in steatohepatitis (2015)[2] and the metabolic interplay between white, beige and brown adipocytes with the liver (2016),[3] to MRI/MRE-based assessment of hepatic steatosis and fibrosis (2016),[4] clinical aspects including lifestyle intervention strategies (2017),[5] emerging pharmacotherapies (2015)[6] and liver transplantation for NAFLD (2016).[7] Looking back, the field has moved ahead rapidly, particularly in reaching a critical threshold for understanding the basic pathophysiology of this disease. Coupled with increased interest in developing non-invasive biomarkers that reflect disease stage and grade, there has been an explosion of interest both in academia and more importantly from Pharma for developing new therapies.

To reflect this growing interest in all aspects of NAFLD, the Editor in Chief and Senior Editors commissioned this set of up-to-date reviews on key aspects of NAFLD. The complexities and controversies surrounding the biological rationale for various clinical trial endpoints, histologic and biomarker endpoints, trial enrollment and trial design in the context of NASH, as well as an updated list of phase II and III trials currently being undertaken, is reviewed in-depth by Harrison and colleagues[8] and Ratziu.[9] At the other end of the spectrum, everyone accepts, and current guidelines recommend lifestyle intervention with diet modulation and physical activity as first line management for NAFLD/NASH. Unfortunately, while large scale trials in cardiovascular and metabolic diseases demonstrate clear benefits, practicing physicians are either skeptical of its efficacy in clinical practice or are not sufficiently resourced to provide effective interventions. In this context, the review by Simpson and colleagues[10] is timely, bringing advances in concepts from nutritional science to the clinic. They introduce the concept of the Geometric Framework for Nutrition (GFN), a novel overarching theoretical foundation to integrate key aspects of nutritional systems (nutrients, foods, diets, appetites and nutritional homeostatic physiology) and to map the relationship between nutrient intakes, physiology and health outcomes. While studies to date in liver disease have not utilised the GFN, they propose that GFN offers a framework for future studies of the causes and treatment of NAFLD.

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For the clinician awaiting the approval of new and effective therapies, a key challenge is understanding the spectrum of liver disease in the context of a disrupted systemic metabolic milieu consequent to relative over nutrition and reduced physical activity. From this perspective, type 2 diabetes mellitus, hypertension and cardiovascular disease are the most frequent comorbidities, present in a high proportion of patients with NAFLD. As Lonardo and colleagues[11] conclude, emerging high-quality evidence suggests that the interaction between these metabolic syndrome components and NAFLD is complex and importantly, bi-directional. Thus, evidence from cross sectional and longitudinal studies favours the idea that both the presence of NAFLD and its severity may precede and/or promote the development of metabolic comorbidities. Concomitantly, this relationship is bi-directional with the systemic metabolic milieu impacting both incident and prevalent fatty liver disease. In the same vein, both in terms of bi-directionality and complexity, is the relationship of NAFLD to alcoholic liver disease (ALD). While clinical and small animal research has sought to dichotomise NAFLD and ALD for reasons of scientific purity, this is rarely so at the bedside. As Boyle and colleagues illustrate,[12] both alcohol and metabolic cofactors co-exist, and perhaps do so in a majority of patients. This interaction drives and potentially accelerates the ultimate phenotypic expression of liver disease. In turn, the concept of "dual-aetiology fatty liver disease" they suggest should be considered as a useful and distinct diagnostic category, requiring its own future research agenda.

A final controversy that we cover is the vexed issue as to whether we undertake hepatocellular carcinoma (HCC) surveillance in NAFLD. As Younes and Bugianesi[13] conclude, there is reasonable epidemiological cohort data to recommend surveillance in patients with NASH cirrhosis. However, implementing an effective program at population level in a disease that is largely asymptomatic, perhaps even in the majority of patients with cirrhosis, is a mammoth logistic challenge. At the opposite end of the spectrum, a significant burden of HCC arises in non-cirrhotic NAFLD, where currently the low absolute incidence would suggest that screening is not cost effective until better algorithms are developed to identify and stratify the at-risk population.

The large number of pharmacotherapies currently being trialled for NASH and advanced forms of the disease suggests that at least some of these therapies will become available for clinical use. However, given the costs involved in research and development, the new therapies are likely to be costly, at least in the short term for payers. In the scenario of roll out of the new therapies, the current gold standard of liver biopsy will be an impractical and costly approach to identify patients suitable for treatment. Thus, in parallel with drug development, there has been a push to develop non-invasive tools to stage and grade the severity of metabolic liver disease. Of the tools available, imaging based technologies are perhaps the most advanced for day to day practice, while MRI and MRE techniques have the best performance. The latter are however, still predominantly clinical research tools given cost considerations, as reviewed by Dr. Loomba.[14] Blood-based biomarkers for staging and grading NAFLD are particularly attractive for population level disease screening, providing they have high sensitivity and specificity. The current 'state of the art' in the field is reviewed by Vilar-Gomez and Chalasani,[15] including clinical prediction rules, as well as a discussion of what is on the horizon in terms of next generation 'omic' technologies.

Compared to diseases with a single aetiology, such as viral hepatitis, alcohol or drug induced liver injury, metabolic liver disease as exemplified by NAFLD is significantly more difficult to reverse. This is particularly so because multiple interacting stimuli lead to the clinical manifestations. The outcome in the broadest possible terms, is a composite of gene $\times$ gene, environment $\times$ environment and gene $\times$ environment interactions. Thus, our present understanding of NAFLD/NASH as a single conglomerate disease is perhaps overly simplistic. There are likely multiple subtypes and drivers of various intensity that operate in any single individual leading to his or her final phenotype. For example, why does one person remain with persistent fatty liver while another progresses, or why does one patient develop a predominant liver phenotype, while the next develops cardiovascular predominant disease? Viewed from this angle, the single therapies currently being trialled may have suboptimal effects compared to combination therapies. Moreover, a single agent may be most effective if it targets the predominant driver of the disease in a particular patient. Clearly answers to these questions can only be garnered through further fundamental research. For NAFLD, this requires preclinical models that reflect pathogenesis in humans as reviewed by Santhekadur and colleagues[16] and a detailed understanding of the drivers of disease progression and regression. The latter is reviewed in all its complexity by Schuppan and colleagues,[17] who highlight the key roles of hepatocyte lipoapoptosis, the cellular composition of the fibrotic milieu and the non-cellular pathological extracellular matrix, which has been shown to have functional modulatory effects. While disease pathogenesis in its totality is beyond the scope of this supplement, lipotoxicity and the gut-liver axis have come to the forefront both as drivers of disease, but also as targets for therapeutic intervention. Mara and Svegliati-Baroni[18] discuss both aspects, focussing on the role of toxic lipid subclasses including free fatty acids, cholesterol, lysophosphatidylcholine and ceramides, and their downstream effects. In the second part of their review, the authors discuss the role of the microbiota, bile acids, nuclear receptors, gut hormones and the system of gut-liver cross talk. Finally, no current review of NAFLD would be complete without an examination of the enormous increases in understanding of how host genetic variation influences disease phenotype. The era of host genomics and its contribution to NAFLD was heralded by the identification of the I148M *PNPLA3* variant as the major common genetic determinant of NAFLD. Subsequent genome wide and candidate gene studies have identified and characterised several other variants with moderate effect size, including variants in *TM6SF2*, *MBOAT7* and *GCKR*. Together with the potential to identify additional variants and other types of genetic variation that contribute to NAFLD through the interrogation of well annotated clinical cohorts, we are at the cusp for developing polygenic risk scores for clinical decision making, as reviewed by Eslam and colleagues.[19]

As stated at the outset, this supplement does not seek to cover in its entirety, the current state of play in the field of NAFLD/NASH. Rather, if we have provided a comprehensive and up-to-date review of the unresolved controversies and clinical research questions in the field, the supplement will have achieved its goal.

References

[1] Pawlak M, Lefebvre P, Staels B. Molecular mechanism of PPARalpha action and its impact on lipid metabolism, inflammation and fibrosis in non-alcoholic fatty liver disease. J Hepatol 2015;62:720–733.

[2] Garcia-Ruiz C, Mato JM, Vance D, Kaplowitz N, Fernandez-Checa JC. Acid sphingomyelinase-ceramide system in steatohepatitis: a novel target regulating multiple pathways. J Hepatol 2015;62:219–233.
[3] Scheja L, Heeren J. Metabolic interplay between white, beige, brown adipocytes and the liver. J Hepatol 2016;64:1176–1186.
[4] Dulai PS, Sirlin CB, Loomba R. MRI and MRE for non-invasive quantitative assessment of hepatic steatosis and fibrosis in NAFLD and NASH: Clinical trials to clinical practice. J Hepatol 2016;65:1006–1016.
[5] Romero-Gomez M, Zelber-Sagi S, Trenell M. Treatment of NAFLD with diet, physical activity and exercise. J Hepatol 2017;67:829–846.
[6] Ratziu V, Goodman Z, Sanyal A. Current efforts and trends in the treatment of NASH. J Hepatol 2015;62:S65–S75.
[7] Pais R, Barritt AS, Calmus Y, Scatton O, Runge T, Lebray P, et al. NAFLD and liver transplantation: Current burden and expected challenges. J Hepatol 2016;65:1245–1257.
[8] Konerman MA, Jones J, Harrison S. Pharmacotherapy for NASH: Current and emerging. J Hepatol 2017. https://doi.org/10.1016/j.jhep.2017.10.015.
[9] Ratziu V et al. Clinical and biological rationale of current end-points for therapy. J Hepatol 2017.
[10] Simpson S, Raubenheimer D, Cogger VC, Macia L, Solon-Biet SM, Le Couteur DG, et al. The nutritional geometry of liver disease including non-alcoholic fatty liver disease. J Hepatol 2017. https://doi.org/10.1016/j.jhep.2017.10.005.
[11] Lonardo A, Nascimbeni F, Mantovani A, Targher G. Hypertension, diabetes, atherosclerosis and NASH: Cause or consequence? J Hepatol 2017. https://doi.org/10.1016/j.jhep.2017.09.0021.
[12] Boyle M, Masson S, Anstee QM. The bidirectional impacts of alcohol consumption and the metabolic syndrome: Cofactors for progressive fatty liver disease. J Hepatol 2017. https://doi.org/10.1016/j.jhep.2017.11.006.
[13] Younes R, Bugianesi E. Should we undertake surveillance for HCC in patients with NAFLD. J Hepatol 2017. https://doi.org/10.1016/j.jhep.2017.10.006.
[14] Loomba R. Role of imaging-based biomarkers in NAFLD: Recent advances in clinical application and future research directions. J Hepatol 2017. https://doi.org/10.1016/j.jhep.2017.11.028.
[15] Vilar-Gomez E, Chalasani N. Non-invasive assessment of non-alcoholic fatty liver disease: clinical prediction rules and blood-based biomarkers. J Hepatol 2017. https://doi.org/10.1016/j.jhep.2017.11.013.
[16] Santhekadur PK, Kumar DP, Sanyal AJ. Preclinical models of non-alcoholic fatty liver disease. J Hepatol 2017. https://doi.org/10.1016/j.jhep.2017.10.031.
[17] Schuppan D, Surabattula R, Wang XY. Determinants of fibrosis progression and regression in NASH. J Hepatol 2017. https://doi.org/10.1016/j.jhep.2017.11.012.
[18] Marra F, Svegliati-Baroni. Lipotoxicity and the gut-liver axis in NASH pathogenesis. J Hepatol 2017. https://doi.org/10.1016/j.jhep.2017.11.014.
[19] Eslam M, Valenti L, Romeo S. Genetics and epigenetics of NAFLD and NASH: Clinical impact. J Hepatol 2017. https://doi.org/10.1016/j.jhep.2017.09.003.