The changing face of hepatology

Marina Berenguer[1,2,*]

[1]Hepatology – Liver Transplantation Unit, Digestive Medicine Service, IIS La Fe and CIBER-EHD, Hospital Universitari i Politécnic La Fe, Valencia, Spain; [2]Department of Medicine, Universitat de València, Valencia, Spain

The typical profile of a patient attending a hepatology clinic has substantially changed in the last few years. As the number of HCV-infected patients decline, there has been a surge in the number of individuals diagnosed with non-alcoholic fatty liver disease (NAFLD); it is now the leading cause of chronic liver disease worldwide, affecting approximately 25% of the global population,[1] and it will soon become the primary indication for liver transplantation, as an increasing number of younger individuals are affected by the so-called "adipose wave effect".[2] The development of NAFLD is closely linked with underlying insulin resistance, with a rise in NAFLD that parallels that of type 2 diabetes mellitus (T2DM) and obesity. From a global health perspective, the increasing prevalence of these diseases[3] in the setting of unhealthy lifestyles, particularly unhealthy diet[4] and sedentarism[5] constitutes an evolving public health crisis, with increased healthcare-associated costs and resource utilization.[6] As stated in the conclusion of a recent modelling study,[7] "NAFLD represents a large and growing public health problem and efforts to understand this epidemic and to mitigate the disease burden are needed. Public health campaigns to increase awareness and diagnosis, and to promote diet and exercise can help manage the growth in future disease burden". In this issue, Hallsworth *et al.*[8] examine the evidence behind dietary changes, weight loss, physical activity and exercise in improving hepatic steatosis and liver histology in patients with NAFLD. A comprehensive review with well-designed figures highlights the complex and multi-faceted driving forces behind unhealthy lifestyle habits that can, however, be successfully combated to induce significant health benefits. Indeed, when successful, lifestyle changes leading to weight loss have been shown to be highly effective in reducing fibrosis and the necro-inflammatory changes of non-alcoholic steatohepatitis (NASH). Unfortunately, only 10–20% of individuals are able to lose ≥10% of their body weight over a 1- to 2-year period, which is the threshold associated with the greatest benefit. Furthermore, sustained lifestyle changes and weight loss are difficult to maintain. The authors identify potential barriers to adopting lifestyle changes and strategies to overcome these. The impact of different diets, the role of gut microbiome manipulation, the reality behind the Mediterranean diet, the role of alcohol, coffee, tea or micronutrients and the effects of physical activity and exercise, including aerobic and resistance training, are thoroughly dissected. This review underscores the need to tailor optimal lifestyle programme recommendations to the individual patient based on clinical characteristics, comorbidities, current fitness and patient preference and the importance of incorporating behaviour change techniques to encourage patients to take a level of responsibility for their own health.

In another original paper in this issue, Van Baar *et al.*[9] examine a novel method for improving the metabolic state of patients with underlying insulin resistance, the hydrothermal duodenal mucosal resurfacing (DMR), an endoscopic technique that has been designed to treat metabolic disease through ablation of the duodenal mucosa. Both animal and human data have shown that the duodenal mucosa is an important metabolic regulator determining systemic insulin sensitivity, with bypass of the duodenum after bariatric surgery leading to improvements in insulin sensitivity. Furthermore, improvement in NAFLD/NASH, including reversal of fibrosis, has been described after bariatric surgery. Unfortunately, this is limited as a population-wide treatment for metabolic disease by its invasiveness. Clinical data suggest that DMR is well tolerated and elicits an improvement in hyperglycaemia in patients with poorly controlled T2DM. In the current paper where data were pooled from 2 single arm, open-label studies primarily designed to determine safety and efficacy of DMR as a procedure to improve glycaemic endpoints in patients with T2DM,[10,11] the authors report the effects of DMR on hepatic metabolic indices. DMR was found to be a safe procedure that improves glycaemic and hepatic indices, with a metabolomic signature that suggests an insulin sensitising mechanism of action. While encouraging, the lack of an appropriate control, as well as the absence of imaging or histologic data, underscore the need for additional research to better understand and confirm the clinical utility of DMR, a minimally invasive endoscopic procedure, as an actual disease intervention for both T2DM and NAFLD.

A wide array of compounds focused on different mechanisms of action including metabolic, anti-inflammatory and anti-fibrotic targets are being intensively investigated to combat NAFLD. Lebeau *et al.*[12] examine the role of the proprotein convertase subtilisin/kexin type 9 PCSK9 in liver fat accumulation and injury in response to saturated fatty acids (FAs) in a variety of cultured hepatocytes and in a mouse model of diet-induced hepatic steatosis. PCSK9 is a circulating protein known to reduce the abundance of receptors on the surface of liver cells charged with the task of lipid uptake from the circulation. One such receptor is the fatty acid translocase, also known as CD36. In the liver, CD36 is known to contribute to the progression of

* Corresponding author. Address: Servicio de Medicina Digestivo, La Fe Hospital, Avda Fernando Abril Martorell 106 (Torre F-5), Valencia 46026, Spain; Tel.: +34 669869743.
E-mail address: marina.berenguer@uv.es (M. Berenguer).

NAFLD to NASH by promoting triglyceride accumulation and subsequent lipid-induced endoplasmic reticulum (ER) stress. In this study, the authors show that PCSK9 deficiency in cultured hepatocytes increases the uptake and accumulation of saturated and unsaturated FAs, resulting in lipid accumulation in cultured cells and mice. Further, and in contrast to normal dietary conditions, a high fatty metabolic challenge resulted in a significant increase in the expression of markers of ER stress, fibrosis, inflammation and apoptosis, as well as plasma levels of ALT in *Pcsk9* knockout mice. The inhibition of CD36 ablated the observed accumulation of lipid *in vitro* and *in vivo*, highlighting the role of CD36 as a strong contributor to steatosis and liver injury in the context of PCSK9 deficiency. Importantly, PCSK9 is also known to induce the degradation of the low-density lipoprotein (LDL) receptors (LDLR) once secreted from the liver. This discovery has led to the development of human anti-PCSK9 monoclonal antibodies capable of reducing circulating LDL levels by 60% in patients at high risk of cardiovascular disease.[13] Whether these antibodies could be utilized to protect against CD36-driven diseases like NAFLD and NASH remains to be determined, but these results highlight new possibilities for treating this rapidly expanding disease.

Five additional papers were published in this issue of *JHEP Reports* on different topics. The review by Morris Sherman[14] focuses on hepatocellular carcinoma (HCC), another increasing health burden, which is currently the fourth leading cause of cancer-related deaths worldwide and projected to become the third by 2030, surpassing breast, colorectal, and prostate cancers.[15] With a 5-year survival of 18%, HCC is the second most lethal tumor after pancreatic cancer and is the main cause of death in patients with cirrhosis. The stage of disease at the time of diagnosis largely determines the effectiveness of treatment. In developing countries, HCC often comes to medical attention when the tumors are at an advanced stage and curative therapies are of limited benefit. In developed countries, in contrast, at-risk populations of patients are often under close surveillance and, as a result, HCC is usually detected when tumors are small and treatment is more likely to be successful. Expert Society Guidelines recommend HCC surveillance every 6 months using ultrasound – with or without alpha-fetoprotein (AFP) – in at-risk individuals. Despite these recommendations, the effectiveness of HCC surveillance remains a subject of debate, largely related to concerns regarding the quality of existing evidence. Furthermore, the choice of surveillance modality must balance sensitivity to optimize early HCC detection, specificity to minimize surveillance-related harms, and costs to remain cost-effective. Although surveillance ultrasound and AFP tests have minimal direct harm, downstream harms from follow-up tests (over one-quarter of patients with cirrhosis experience physical harm for false-positive or indeterminate surveillance tests) must be weighed against surveillance benefits when determining the value of HCC screening programs, a circumstance that will likely increase with the obesity and NAFLD epidemics.[1] Less than 20% of patients with cirrhosis undergo surveillance in the US.[16] The underuse of HCC surveillance can be attributed to several failures in the process, including provider failure to identify either liver disease or the (silent) transition to cirrhosis, provider failure to order HCC surveillance, and patient failure to adhere to surveillance recommendations. Morris Sherman examines current evidence on HCC surveillance outcomes and proposes measures to overcome obstacles at every step of the process, from identification of cirrhosis in any patient known to have liver disease to defining the utility of risk scores, the role of biomarkers and/or of biopsy. The author underscores the importance of better education to improve the awareness of primary providers and the need to adequately test each new combination of surveillance tests prospectively. Given the obesity and NAFLD epidemic, the sensitivity of ultrasound may be reduced in this population.

One specific group in which surveillance of HCC is required is that of HCV-patients with bridging fibrosis or cirrhosis that remain at risk, albeit lower, of developing life-threatening complications such as HCC, despite a sustained virological response. Understanding that risk and whether there are subgroups in whom surveillance might be avoided (ie fibrosis 3) is a complex matter that clearly depends on being able to reliably stage fibrosis and estimate HCC risk in individual patients.[17] In this issue, Nahon and Ganne-Carrié[18] reviews the evidence regarding post-sustained virological response outcome and surveillance needs in HCV-patients with pre-therapeutic advanced liver fibrosis. Data regarding the risk of HCC, but also that of portal hypertension complications, extra-hepatic complications or liver failure are carefully dissected to improve risk stratification and refine screening strategies in this additional growing population.

In another review, Ramadori *et al.*[19] present a comprehensive review of platelet biology that defines their natural function in preventing bleeding, as well as their functional involvement in immunological contexts ranging from inflammation, bacterial and viral immune reactions, up to immunity against tumors and tumor metastases. The authors focus on interactions of platelets within the liver parenchyma,[20] their role in chronic liver diseases (chronic viral hepatitis, alcoholic and non-alcoholic steatohepatitis and HCC) and the potential benefit of anti-platelet therapy in these contexts, highlighting the pro-regenerative effect of platelets on hepatocytes, the role of platelets in the progression of liver fibrosis, their immunomodulatory role and their pro-metastatic role. Experimental data regarding anti-platelet therapy in chronic viral hepatitis (B and C), which is characterized by immune-mediated liver damage, showed a potential benefit. In metabolic liver diseases, platelets might also constitute a therapeutic target with recent experimental and clinical studies pointing towards a protective effect of anti-platelet therapy in both preventing the progression of liver fibrosis and the development of NASH-induced HCC. Finally, anti-platelet therapy has shown promise in reducing HCC development and liver metastases in experimental models. In the near future, new methodologies based on the proteomic and transcriptomic analysis of platelets might offer tools for the diagnosis and treatment of chronic liver disease.

Caballol *et al.*,[21] report on a case of hepatitis A virus-related fulminant hepatic failure complicated by Takotsubo syndrome, where standard volume plasma exchange was successfully used as a salvage therapy to initiate rapid liver and cardiac recovery. This case suggests that standard and not only high-volume plasma exchange can be an effective therapy for patients with fulminant hepatic failure and potential contraindications for liver transplantation.

The multicentre retrospective study by Ni Than *et al.*[22] reports on new therapies for autoimmune hepatitis (AIH), an *a priori* rare disease whose incidence seems to be on the rise with significant associated morbidity and mortality.[23] Despite the increase in incidence and potential impact on health outcomes, relatively few advances in therapy have been made in the last 4 decades, since the original landmark trials – corticosteroids in combination with azathioprine have remained the established therapy since the 1970s, in contrast to many other immune-

mediated diseases such as psoriasis, multiple sclerosis or inflammatory bowel disease in which steroid-based treatment regimens have not been used for years. Steroid-based therapies interrupt the adaptative immune process globally and are thus associated with significant side effects, while 10–20% of patients have an insufficient response that requires additional agents. Interestingly, while AIH has been traditionally classified as a T cell-mediated autoimmune disease, it is increasingly clear that B cells also play a role in its pathogenesis. Rituximab is a chimeric mouse-human monoclonal antibody that promotes depletion of B lymphocytes via binding to the CD20 antigen expressed on the surface of B cells. A few reports have indicated the potential benefit of this compound in AIH, findings confirmed in the present study. Data from 22 patients with "difficult-to-treat" AIH showed that rituximab improved aminotransferase and albumin values for up to 2 years. In addition, 71% of patients had no clinical disease flares during this period and a reduction of prednisolone dose was possible in 62% of cases, though never to below 10 mg, which would ensure lower rates of side effects. Although retrospective, this is the largest cohort of patients with AIH to be treated with rituximab, opening the door for further research. Only a better understanding of immune pathogenesis will pave the way for more effective and better tolerated therapies that will replace the non-specific immunosuppressive agents currently used; a phenomenal challenge for scientists and clinicians!

References

[1] Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73-84.

[2] Shingina A, DeWitt PE, Dodge JL, Biggins SW, Gralla J, Sprague D, et al. Future trends in demand for liver transplant: birth-cohort effects among patients with NASH and HCC. Transplantation 2019;103(1):140–148.

[3] Byrne CD, Targher G. NAFLD: a multisystem disease. J Hepatol 2015;62:S47–64.

[4] GBD 2016 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390:1345–1422.

[5] Guthold R, Stevens GA, Riley LM, Bull FC. Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1·9 million participants. Lancet Glob Health 2018;6:e1077–e1086.

[6] Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, et al. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med 2017;377:13–27.

[7] Estes C, Anstee QM, Arias-Loste MT, Bantel H, Bellentani S, Caballeria J, et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016–2030. J Hepatol 2018;69:896–904.

[8] Kate Hallsworth K, Leon A, Adams LA. Lifestyle modification in NAFLD/NASH: Facts and figures. JHEP Reports 2019;1:471–482.

[9] van Baar ACG, Beuers U, Wong K, Haidry R, Costamagna G, Hafedi A, et al. Endoscopic duodenal mucosal resurfacing improves glycaemic and hepatic indices in type 2 diabetes: 6-month multi-centre results. JHEP Reports 2019;1:430–437.

[10] Rajagopalan H, Cherrington AD, Thompson CC, Kaplan LM, Rubino F, Mingrone G, et al. Endoscopic duodenal mucosal resurfacing for the treatment of type 2 diabetes: 6-month interim analysis from the first-in-human proof-of-concept study. Diabetes Care 2016;39(12):2254–2261.

[11] van Baar ACG, Holleman F, Crenier L, Haidry R, Magee C, Hopkins D, et al. Endoscopic duodenal mucosal resurfacing for the treatment of type 2 diabetes mellitus: one year results from the first international, open-label, prospective, multicentre study. Gut 2019. https://doi.org/10.1136/gutjnl-2019-318349 [Epub ahead of print].

[12] Lebeau PF, Byun JH, Platko K, Al-Hashimi AA, Lhoták S, MacDonald ME, et al. PCSK9 knockout exacerbates diet-induced non-alcoholic steatohepatitis, fibrosis and liver injury in mice. JHEP Reports 2019;1:418–429.

[13] Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713–1722.

[14] Sherman M. How to improve HCC surveillance outcomes. JHEP Reports 2019;1:463–470.

[15] Foerster F, Galle PR. Comparison of the current international guidelines on the management of HCC. JHEP Reports 2019;1:114–119.

[16] Singal AG, Yopp A, S Skinner C, Packer M, Lee WM, Tiro JA. Utilization of hepatocellular carcinoma surveillance among American patients: a systematic review. J Gen Intern Med 2012;27:861–867.

[17] Ioannou GN, Beste LA, Green PK, Singal AG, Tapper EB, Waljee AK, et al. Increased risk for hepatocellular carcinoma persists up to 10 years after HCV eradication in patients with baseline cirrhosis or high FIB-4 scores. Gastroenterology 2019;157:1264–1278.e4.

[18] Nahon P, Ganne-Carrié N. Management of patients with pre-therapeutic advanced liver fibrosis following HCV eradication. JHEP Reports 2019;1:483–492.

[19] Ramadori P, Klag T, Malek NP, Heikenwalder M. Platelets in chronic liver disease, from bench to bedside. JHEP Reports 2019;1:451–462.

[20] Chauhan A, Lalor P, Watson S, Adams D. Role of CLEC-2-driven platelet activation in the pathogenesis of toxic liver damage. Lancet 2017;389:S33.

[21] Caballol B, Reverter E, Cid J, Hernández-Tejero M, Triolo M, Lozano M, et al. Fulminant hepatitis A complicated by Takotsubo syndrome successfully treated with standard volume plasma exchange. JHEP Reports 2019;1:447–450.

[22] Ni Than N, Hodson J, Schmidt-Martin D, Taubert R, Wawman RE, Botter M, et al. Efficacy of rituximab in difficult-to-manage Autoimmune Hepatitis: Results from the International Autoimmune Hepatitis Group. JHEP Reports 2019;1:438–446.

[23] Lohse AWCO, Dalekos G, Drenth J, Heneghan M, Hofer H, Lammert F, et al. EASL Clinical Practice Guidelines: Autoimmune hepatitis. J Hepatol 2015;63(4):971–1004.