Fat, cancer, the gut-liver axis and rare liver diseases

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Non-alcoholic fatty liver disease (NAFLD) is a rapidly growing cause of chronic liver disease and could soon become the leading cause of cirrhosis requiring liver transplantation. This trend mirrors the increasing global incidence of obesity and the metabolic syndrome.[1] While lifestyle modifications and weight loss remain the cornerstone of management,[2] promising new pharmacotherapies are being developed that will enter the clinical arena in the next decade. In this issue of *JHEP Reports*, a potential new therapeutic approach for liver steatosis and insulin resistance is discussed.[3] The authors investigate the role and mechanism of a star strand miRNA (miR-192-3p) in regulating hepatic steatosis and insulin signalling in the livers of diabetic mice and mice fed a high-carbohydrate diet. While functional loss of miR-192-3p in the liver exacerbated hepatic steatosis and insulin resistance in both mouse models, liver-specific overexpression of miR-192-3p halted hepatic steatosis and ameliorated insulin resistance.

In addition, establishing the burden of disease in the real world is paramount to address public health policies.[1] Indeed, in regulatory trials, patients are highly selected using liver histology to define inclusion, whereas real-world data on NAFLD epidemiology is largely unknown. In this issue, Hofmann *et al.* describe the results of the Fatty Liver Assessment in Germany (FLAG) study, an observational real-world study in patients with NAFLD that aimed to assess disease burden and standard of care.[4] The authors found that approximately 10% of patients in their cohort had advanced fibrosis and they anticipate that every sixth patient could be eligible for pharmacotherapy once approved. Unfortunately, the low uptake and frequency of lifestyle interventions (physical reported by only 6% of those with advanced fibrosis, nutritional counselling provided to only 25% of patients), highlight the urgent need for a systematic health agenda in these patients.[1]

In fact, in a subsequent epidemiological study, Golabi *et al.*, using the National Health and Nutrition Examination Survey (NHANES) 1999–2004 with Linked Mortality file, demonstrate the independent contribution of sarcopenia and physical inactivity to mortality in people with NAFLD.[5] Patients with NAFLD have been reported to have an increased prevalence of sarcopenia, which in turn has been shown to be independently associated with an increased risk of advanced fibrosis. The authors report a 78% increase in all-cause mortality and a 320% increase in cardiac-specific mortality in those with sarcopenia. Of note, sarcopenia was significantly and inversely related to an increase in physical activity level with 63% of deaths among people with NAFLD and sarcopenia occurring in the inactive population.

Altogether the findings from these 2 studies highlight the relevance of physical exercise[6] and the need to optimally manage sarcopenia in patients with NAFLD.

Although it is not clear whether paediatric and adult NAFLD are 2 different pathologic entities or just age-dependent manifestations of the same disease, children and adolescents are an extremely relevant target population.[7] During recent decades, the worldwide prevalence of obesity, and thus of NAFLD, has markedly increased in the paediatric population. As in the adult population, there is growing evidence that children with NAFLD are at increased risk of cardiometabolic complications, while those with non-alcoholic steatohepatitis and advanced fibrosis are also at risk of significant liver-related morbidity. These high rates of obesity and NAFLD among younger individuals have prompted efforts to identify a cardiometabolic risk factor profile in these individuals. In adults, remnant lipoprotein cholesterol (RLP-C), the cholesterol contained in very low-density lipoproteins, is associated with incident coronary heart disease. Using a large well-characterised cohort of adolescents, Chin *et al.*[8] found a significant association between RLP-C and NAFLD beyond traditional risk factors of adiposity and insulin resistance. Furthermore, adolescents with NAFLD and serum RLP-C levels in the highest quartile compared with the lowest quartile, had higher cardiometabolic profile (higher serum leptin, HOMA-IR, hsCRP, low-density lipoprotein cholesterol, triglycerides, body mass index, subcutaneous and visceral adipose thickness, systolic blood pressure and arterial stiffness), findings that may help to identify adolescents at future risk of cardiovascular disease who could benefit from risk reduction measures.

Despite the large-scale use of effective antiviral agents against HCV and HBV, the incidence of hepatocellular carcinoma (HCC) continues to rise, particularly in the context of NAFLD epidemics. The definitive treatment for HCC remains challenging, with 2 potentially curative options (hepatic resection and liver transplantation) for those in whom the cancer is detected at early stages.[9] In this issue, 4 different papers report on improvements in the management of HCC, with a focus on antiviral therapy against HBV,[10] predictive models of HCC risk,[11] the use of optimal imaging modalities[12] and optimised surgical approaches.[13]

In a retrospective territory-wide cohort study,[10] the authors show that the secular trend of nucleoside analogue (NA) treatment uptake has increased over time among patients with HCC. Importantly, the benefits of NA treatment in patients with HBV-related HCC were observed regardless of time of NA

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initiation, either before or after HCC diagnosis. A significant reduction in the risk of death was consistently reported in NA-treated patients, including those receiving curative or palliative HCC treatments.

In the second study,[11] the authors develop a deep learning-based model to predict the risk of HCC development. There has been considerable research into identifying high-risk HBV-infected patients, with several risk-scores developed both in Asia and the West.[14] In the current study,[11] a novel model was created for patients with HBV-related cirrhosis on potent antiviral therapy (80% undetectable HBV DNA level) using the residual learning framework of the ResNet architecture. The C-statistic of the model was markedly better than several standard validated models. While an important step forward, additional validation studies will be needed in non-Asian cohorts and cohorts with advanced fibrosis before cirrhosis.

The third study[12] summarises the diagnostic part of the SORAMIC trial, a prospective, phase II, randomised, controlled trial in HCC consisting of 3 parts: a diagnostic study and 2 therapeutic studies with either curative ablation or palliative Y90-radioembolisation combined with sorafenib. The authors report on the diagnostic cohort study that aimed to compare the accuracy of gadoxetic acid-enhanced MRI, including hepatobiliary phase (HBP) imaging features, to contrast-enhanced CT. Importantly, and in contrast to other studies that focus on lesion count, the primary objective was improving therapeutic decision making, *i.e*., the accuracy of treatment decisions stratifying patients to curative or palliative (non-ablation) treatment. In comparison to state-of-the-art contrast-enhanced multislice CT, HBP-MRI including dynamic MRI improved the accuracy of treatment decisions.

In the fourth HCC study in this issue,[13] the authors evaluated the impact of surgical approach and quality of resection on the probability of cure in a homogeneous population of patients with early stage HCC, occurring on compensated cirrhosis, in 5 French hepatopancreaticobiliary centres. The laparoscopic approach was associated with improved quality of surgical care as measured using the "textbook outcome", a combination of 6 criteria (including R0, no transfusion, no complication, short length of stay, no readmission, and no mortality) representing ideal hospitalisation. Furthermore, a strong and independent association was observed between the quality of surgical care and long-term prognosis. Despite the fact that the study was not randomised, and should thus be interpreted under the assumption of an inherent bias, the findings suggest that the quality of surgery is a relevant prognostic parameter to consider along with histo-prognostic factors, supporting the curative role of mini-invasive treatments for early stage HCC.

The microbiota has emerged as a key player in a variety of liver diseases.[15] In turn, the liver impacts, and communicates with, the microbiota through liver mediators, such as bile acids or inflammatory signals. In a pilot study published in this issue of *JHEP Reports*, the authors study the links between iron depletion through venesection, gut iron content and the gut microbiome.[16] They show that removing iron from patients leads to a significant reduction in faecal iron content and that this reduced faecal iron content, in turn, promotes bacterial species that are associated with a healthier gut microbiome profile. This new and interesting approach is the first study showing a convenient and easy way to manipulate the gut microbiome through iron metabolism. Of note, the results are supported by those of an iron supplementation study where an opposite approach, *i.e.* iron supplementation, was associated with a reduction of the same bacterial species.

In a second study by Riva *et al.*,[17] the authors investigate the use of novel techniques, such as profiling of cytokines and gut-barrier integrity markers in faeces, to study differences in gut inflammation in patients with stable and acutely decompensated cirrhosis; they also investigate how these relate to conventional plasma markers. An association was found between acute decompensation and a highly inflamed and damaged gut barrier, with faecal cytokine and gut-barrier integrity marker profiles appearing to be T-cell driven, unlike the classical and innate-like features of systemic inflammation in cirrhosis. While a more extensive longitudinal study is needed to assess the predictive value of faecal cytokines for clinical endpoints (*i.e*. infection, acute-on-chronic liver failure, death or re-hospitalisation), this study provides new insights into gut-specific immune disturbances that predispose to complications of cirrhosis and emphasises that a better understanding of the gut-liver axis is necessary to develop better targeted therapies.

The increasing use of large databases has improved our knowledge of different diseases, particularly those considered rare. In the study by Suwabe *et al.*,[18] the authors use the Rochester Epidemiology Project and Radiology databases of Mayo Clinic and Olmsted Medical Center to ascertain the incidence and point prevalence of autosomal dominant polycystic liver disease (ADPLD) in Olmsted county. While the study confirms that clinically significant isolated ADPLD is a rare disease with a prevalence <1:10,000 population, incident rates were found to be much higher when adding possible cases, mainly identified through Radiology databases, particularly in recent years and in older patients due to the increased utilisation of imaging studies. These findings suggest that the overall prevalence of ADPLD, while to a large extent not clinically significant, is likely much higher and closer to the reported genetic prevalence. In addition, the incidence of ADPLD was similar in females and males, but the cystic disease appeared to be more severe and symptomatic in females, highlighting the need to address gender specificities in liver diseases.[19]

In summary, I am pleased to introduce the new of issue of *JHEP Reports*, which covers the hot topics of "fat, cancer, the gut-liver axis and rare liver diseases".

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Author names in bold designate shared co-first authorship

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