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From the Editor's Desk

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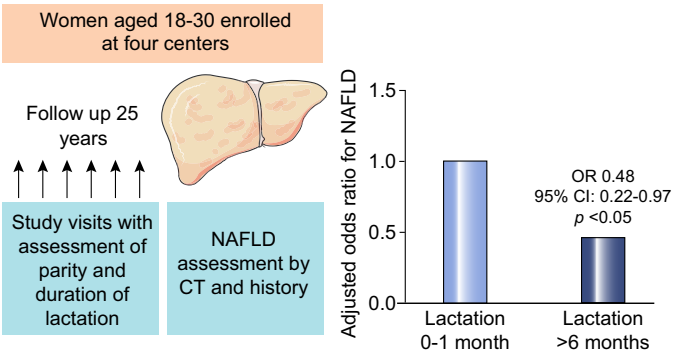
SELECTION OF THE MONTH

Longer lactation reduces NAFLD prevalence in the mother

Identifying environmental factors associated with the development of non-alcoholic fatty liver disease (NAFLD) is a matter of intense research. Lactation has been shown to exert beneficial effects in both the child and the mother. Among its beneficial effects, lactation is known to lower triglycerides and to increase insulin sensitivity. In this issue of the *Journal*, Ajmera *et al.* studied if longer duration of lactation is associated with a lower prevalence of NAFLD in women. The study included a large cohort of young women who delivered one post-baseline birth or more and were followed for 25 years. **In unadjusted logistic regression, the risk of NAFLD at 25 years was significantly reduced by 52% in women with a lactation duration of 6 months compared to those with a lactation duration of 0 to 1 month;** and the statistical significance remained after adjustment for typical confounders. This effect was less evident in women with shorter lactation periods. This important epidemiological study proves another potential beneficial effect of prolonged lactation in mothers. Further prospective studies should confirm this important finding.



Ajmera *et al.*, 2018.
Longer lactation reduces NAFLD prevalence.

HEPATOCYTE REPROGRAMMING

Back to the future

The development of new cell sources for clinical therapy using cell fate conversion approaches by small molecules is an active field of research. Direct lineage reprogramming to a progenitor state has been reported in terminally differentiated rodent hepatocytes, but not yet in human hepatocytes. Kim *et al.* addressed this question by using human hepatocytes isolated from healthy and diseased donor livers and reprogrammed into progenitor cells by 2 small molecules, A83-01 and CHIR99021, in the presence of epidermal growth factor and hepatocyte growth factor. They show for the first time **reprogramming of human hepatocytes to a population of proliferating bipotent cells with regenerative potential.** They conclude that "Human chemically-derived hepatic progenitors may provide a novel tool that permits expansion and genetic manipulation of patient-specific progenitors to study regeneration and the repair of diseased livers."

LIVER INFLAMMATION

A role for miR-378 in inflamed livers with NASH

In mouse, livers with steatosis have increased expression of a microRNA (miRNA, *i.e.*, a short (20–24 nucleotide) non-coding RNA), called miR-378. MiR-378 is embedded in the first intron of *Ppargc1b* encoding peroxisome proliferator activated receptor γ coactivator 1-beta (PGC-1-beta); this protein being thought to be involved in fat oxidation and non-oxidative glucose metabolism and in the regulation of energy expenditure. There is evidence that miR-378 can promote liver steatosis and insulin resistance. However, its role in the progression of steatosis to non-alcoholic steatohepatitis (NASH) was unknown. Using livers from obese mice and patients with NASH, Zhang *et al.* now show that, in this context, **miR-378 overexpression plays a key role in the development of liver inflammation and fibrosis by facilitating the NF-κB-tumor necrosis factor α axis**. These findings suggest that miR-378 may be a target for novel therapeutic approaches for NASH.

NAFLD

Magnetic resonance-based hepatic imaging

Another field with important advances is the non-invasive diagnosis of NAFLD. In this issue, Jayakumar *et al.* analysed data from several prospective clinical trials to evaluate the utility of magnetic resonance (MR)-based hepatic imaging measures for the assessment of liver histology in patients with NASH. Among patients with MR elastography (MRE) and biopsies at baseline and week 24 after specific interventions, one-third had fibrosis improvement (≥1-stage reduction). The AUROC of **MRE-stiffness to predict fibrosis improvement was 0.62 with 48% positive predictive value (PPV) and 79% negative predictive value (NPV)**. Among patients with MR imaging-estimated proton density fat fraction (MRI-PDFF) and biopsies at baseline and week 24, **the performance of MRI-PDFF to predict steatosis response was 0.70, with 39% PPV, and 92% NPV**. These results indicate that the performance of MRE-based techniques to detect changes in fibrosis and steatosis is acceptable, yet future studies should be

performed to optimise this performance and to completely avoid liver biopsies in randomised trials.

GENETIC LIVER DISEASES

Factors influencing genetic haemochromatosis, factors influencing prevalence of lysosomal acid lipase

The natural history and modifiers of genetic haemochromatosis are largely unknown. Genetic haemochromatosis is mainly related to homozygosity for the *HFE* p.Cys282Tyr (C282Y) mutation, leading to hepcidin deficiency. **Its low penetrance strongly suggests the involvement of environmental factors modulating its expressivity and the resulting disease phenotypes**. In this issue, Deugnier *et al.* studied the progression, markers of iron burden, and risk factors according to the year of diagnosis in a cohort of 2,050 C282Y homozygotes and 542 relatives. The study revealed that over the analysed period, genetic testing has not modified the age at diagnosis, which contrasts with the dramatic decrease in iron burden in both sexes. Interestingly, cigarette smoking could be involved in the extent of iron loading. Besides HFE testing, which allowed the diagnosis of minor forms of the disease, **the reduction of alcohol consumption and changes in the frequency of weight excess may have played a role in the diminution of iron burden in the long term, likely by improving hepcidin production**. This large study reveals that lifestyle-related factors (mainly smoking, alcohol consumption and diet) are important modifiers of the penetrance of hereditary haemochromatosis.

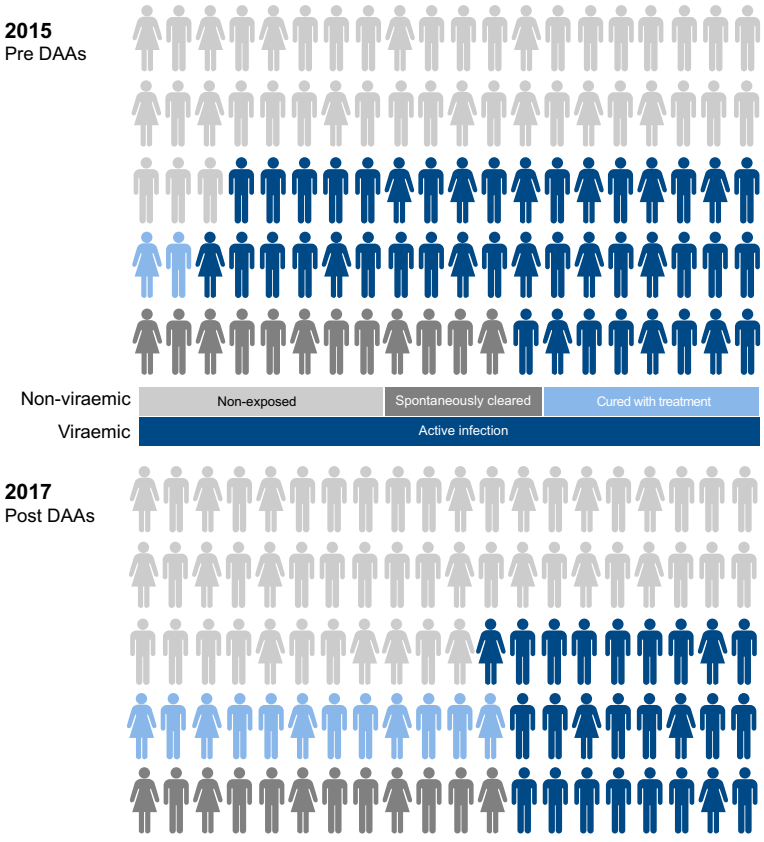
The prevalence of lysosomal acid lipase deficiency (LAL-D), an autosomal recessive cholesteryl ester storage disease that mimics NAFLD, especially among patients diagnosed with NAFLD, is not well known. In this issue, Carter *et al.* performed a meta-analysis of existing genetic studies. **The estimated prevalence of LAL-D was 1 per 160,000**. Almost 100 previously reported disease variants in the lysosomal acid lipase gene (official symbol: *LIPA*) were identified, of which one-third were present in Genome Aggregation Data Base (known as gnomAD). When this was combined with 22 previously unreported major functional variants in lysosomal acid lipase identified in humans the pooled prevalence of LAL-D was 1 per 177,452 with a carrier frequency of 1 per 421. **Interestingly, prevalence was lowest in those of East Asian, South Asian, and Finnish ancestry.** This large systematic study concludes that LAL-D is an ultra-rare disorder. However, given the therapeutic capability of sebelipase alpha, **LAL-D testing might be included in second-line metabolic screening in NAFLD, especially in non-obese patients**.

HEPATITIS C VIRUS (HCV) INFECTION

Microelimination becomes reality, real-world news from Veterans Affairs facilities

To first eliminate HCV among certain high-risk sub-populations has been proposed as a way forward to promote global WHO HCV elimination goals. People who inject drugs (PWID) have been recognised in most high-income countries as a priority population for these microelimination strategies, given the high HCV prevalence and risk of HCV transmission in this population. To evaluate the impact of unrestricted access to direct-acting antiviral (DAA) therapy in this key population, Iversen *et al.* examined treatment uptake and estimated HCV prevalence among PWID attending the Australian national needle syringe programmes between 2015 and 2017. Compared to the pre-DAA HCV treatment era, **an 8-fold increase in treatment-induced HCV clearance among Australian PWID could be achieved, and HCV prevalence among the overall population significantly declined from 43% to 25%**. This study provides evidence that relatively high rates of HCV treatment can be achieved among PWID when DAA therapy is made available without restrictions, and provides proof of concept that eliminating HCV as a public health threat through HCV treatment as prevention is feasible.

The study by Belperio *et al.* represents one of the largest real-world cohorts evaluating the effectiveness of 2 different DAA treatment regimens in HCV type 2- and 3-infected patients, and thus a patient group that was often underrepresented in clinical trials. This observational intent-to-treat cohort analysis used the Veterans Affairs (VA) HCV Clinical Case Registry to follow 5,763 patients (2,939 infected with HCV type 2, and 2,824 with type 3) who initiated daclatasvir plus sofosbuvir ± ribavirin or velpatasvir plus sofosbuvir ± ribavirin at 128 VA facilities. **The overall SVR rates were approximately 94% for genotype 2 patients and 90% for genotype 3 patients with no significant differences observed between both regimens**. Being treatment-experienced and having advanced fibrosis were the most important predictors of



Iversen *et al.*, 2018.
Decline in viraemic prevalence in PWIDs in Australia.

treatment outcome, especially for patients with type 3 infection. The study also provides important information on how adding ribavirin and/or extending treatment duration affects the SVR rates.

HEPATITIS B VIRUS (HBV) INFECTION

The economic burden of chronic HBV infection

Although chronic HBV infection currently affects approximately 240 million individuals worldwide, including 2 million individuals within the United States, little is known about healthcare utilisation and costs associated with this chronic infection. This retrospective, observational study by Nguyen *et al.* represents one of the first studies to quantify the healthcare utilisation and costs by disease severity and payer type of an aging HBV-infected population within the United States, using data from a large, diverse, and nationally representative sample of 27,949 patients with chronic HBV infection and 86,072 matched non-HBV-infected controls. Although, as expected, decompensated cirrhosis, hepatocellular carcinoma (HCC), or a liver transplant incurred the highest annual costs and utilisation of healthcare resources, **even patients with compensated liver disease had 3 times the cost of the non-HBV-infected controls**. The study describes for the first time the economic burden related to chronic HBV infection in the United States and provides important background information to be used when making decisions about covering treatments and interventional approaches in order to prevent infection and advanced liver disease.

CIRRHOSIS

Brain glymphatics are deranged in experimental cirrhosis

Many lines of investigation suggest that metabolically active waste accumulates in the interstitial fluid in the brain of cirrhotic patients, which contributes to the severity of hepatic encephalopathy. Traditionally, this has been thought to result from metabolic disturbance of cirrhosis. Recently, a new drainage system of the interstitial fluid, referred to as 'the glymphatic system' has been described. **Hadjihambi *et al.* describe for the first time, abnormalities of the glymphatic system in the brain of animals with experimental cirrhosis and the location of the abnormalities in different brain regions correlates with observed functional disturbances.** They go on to show that these abnormalities are likely due to altered expression and function of aquaporins. These data provide novel insights into the pathophysiological mechanisms underlying the pathogenesis of hepatic encephalopathy, which will allow development of new therapies.

TRANSPLANTATION

HOPE for liver transplantation recipients

Organ shortages lead to the death of many patients on the liver transplant waiting list. This has led to the widespread use of organs from deceased donors (DCD). Unfortunately, the outcomes of patients transplanted with DCD organs are significantly worse that those transplanted with organs from brain dead donors (DBD). One of the ways to try and improve the outcome of DCD organs is to use hypothermic oxygen perfusion (HOPE) of the DCD organs. **Schlegel *et al.* describe the long-term results of using HOPE for DCD organs in a real-world setting. Their data show that the HOPE-treated DCD organs had 5-year graft survival rates that were similar to those transplanted with DBD organs.** Graft loss was significantly lower in the HOPE-treated patients compared with loss in those that were transplanted with untreated DCD organs. Their data argue strongly for introduction of HOPE into clinical practice.

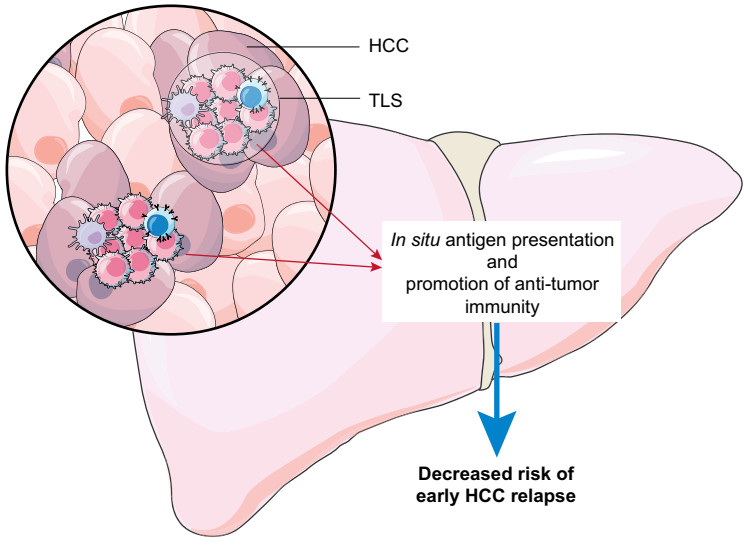
HCC

Ketoconazole promotes mitophagy and apoptosis in HCC

The antifungal drug, ketoconazole, may be a therapeutic option against cancer. However, its mechanisms of action are still elusive. Chen *et al.* aimed to evaluate the effects of ketoconazole on HCC and investigate the underlying mechanisms of action. For this, they examined the antitumor effect of ketoconazole on HCC cells, cell line-derived xenografts, and a patient-derived xenograft model. They show that **ketoconazole induces apoptosis in HCC cells by triggering mitophagy through inhibition of cyclooxygenase-2,** providing preclinical proof of concept for the use of ketoconazole in HCC treatment.

Protective role of intra-tumoral tertiary lymphoid structures (TLSs), DAAs do not promote HCC recurrence

TLSs provide a local and critical microenvironment for generating anti-tumour cellular and humoral immune responses, and are associated with improved clinical outcomes in several solid tumours. Because the role of TLSs is debated in the context of HCC, Calderaro *et al.* studied the



Calderaro *et al.*, 2018.
Intra-tumoral TLSs reduce risk of early HCC relapse

associations of histopathological intra-tumoral and non-tumoral TLSs with clinical outcomes in a series of 273 patients with HCC treated by surgical resection in Henri Mondor University Hospital, France. **Their findings show that intra-tumoral TLSs are associated with a lower risk of early relapse.**

It has been suggested that DAAs, while curing hepatitis C infection, may accelerate the recurrence of hepatitis C-related HCC. Kinoshita *et al.* aimed to evaluate HCC recurrence after DAA treatment for chronic hepatitis C. For this, they enrolled patients with a history of successful radiofrequency ablation treatment for hepatitis C-related HCC who received DAAs (147 patients) or interferon (IFN)-based therapy (156 patients). Here, **they show that the HCC recurrence rates at 1 and 2 years were, respectively, 39% and 61% among patients who received IFN therapy, and 39% and 60% among those who received DAAs.**

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