Editorial

Beyond the liver in patients with non-alcoholic fatty liver disease (NAFLD)—cause for concern?

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Provenance: This is an invited Editorial commissioned by Editor-in-Chief Yilei Mao (Department of Liver Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China).

Comment on: Adams LA, Anstee QM, Tilg H, *et al.* Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. Gut 2017;66:1138-53.

Submitted Jan 14, 2018. Accepted for publication Jan 24, 2018.
doi: 10.21037/hbsn.2018.01.09
View this article at: http://dx.doi.org/10.21037/hbsn.2018.01.09

Non-alcoholic fatty liver disease (NAFLD) is a global public health problem and is the most common cause of chronic liver disease worldwide. The prevalence of NAFLD is approximately 30%, irrespective of ethnicity, and parallels the exponential rise of the obesity and diabetes epidemics. The active inflammatory and cell injury component of NAFLD, known as non-alcoholic steatohepatitis (NASH), increases the risk of liver-related mortality by 5 to 10 times; but this is largely dependent on the extent of fibrosis (1,2). Despite this, cardiovascular disease (CVD) and extra-hepatic malignancy remain the commonest causes of death in these cohorts. Therefore, non-surprisingly the last decade has seen the clinical focus switch from NAFLD as a solitary organ entity to a multi-systemic disease.

In the recent edition of *Gut* 2017, Adams and colleagues (3) provide an extensive overview of the relationship and clinical burden of NAFLD on extra-hepatic disease, with particular focus on the increasingly recognised risk of CVD. There is now a large body of evidence that demonstrates that NAFLD is associated with CVD, chronic kidney disease (CKD), type 2 diabetes (T2DM), osteoporosis, endocrinopathies and colorectal neoplasms (4). Indeed, those with NASH, and in particular fibrosis, appear to be at greater risk of extra-hepatic diseases than their counterparts with simple steatosis. It is important, however, to recognise the limitations of the current studies prior to introducing widespread screening protocols, preventative strategies and new treatments for the extra-hepatic complications of NAFLD. To this date, there remains marked heterogeneity between studies in study design (cross-sectional versus prospective; sample size; presence/absence of well-defined controls), population (ethnic diversity; community-based versus hospital-based cohorts), and method of NAFLD diagnosis (liver enzymes versus imaging versus biopsy) (4).

It is well known that NAFLD is closely associated with the metabolic syndrome and the established CVD risk factors that it encompasses; including central obesity, insulin resistance, dyslipidaemia, hypertension and the under recognised deficiencies of vitamin D and adiponectin. However, determining whether NAFLD truly confers an independent, additional risk of hard cardiovascular clinical events (i.e., myocardial infarction, ischaemic stroke) and/or death, above and beyond that of its existing metabolic phenotype remains a challenge. A plethora of subclinical data exists highlighting that biopsy-proven NAFLD (in particular NASH) exhibit endothelial dysfunction, impaired left ventricular diastolic dysfunction/energy metabolism, increased carotid intima-media thickness and show a higher prevalence of carotid atherosclerotic plaques (including calcium scores), independent of metabolic and CVD risk factors (5). What remains key is being able to understand

the future risk of significant clinical CVD outcomes and premature death, when identifying newly diagnosed patient with NAFLD +/– NASH in the clinical setting. However, to understand a true independent causal relationship between NAFLD and hard CVD events is reliant on prospective study (11 studies; 4–18 years follow-up), rather than retrospective analysis (9 studies; 8–26 years follow-up). To date, the aggregate prospective evidence provides strong evidence that individuals with image-defined NAFLD are at increased 'independent' risk of developing non-fatal and fatal CVD events (6). With the exception of an isolated Italian case-control study in 2016 (7), in which NAFLD conveyed a two-fold risk of non-fatal coronary events compared to age/sex-matched controls, there remains a distinct lack of biopsy-proven disease in any other prospective study. In the last 3 years, two long-term retrospective datasets (26–33 years follow-up), either side of the Atlantic, have concluded that stage of hepatic fibrosis (rather than NASH) is the only predictor of overall and disease-specific mortality (1,2). Therefore, it remains paramount that future prospective studies incorporate biopsy or validated non-invasive markers of fibrosis at baseline to determine which components of NAFLD predict additional risk of premature CVD and related-death, over and above the clinical metabolic phenotype. Understanding the independent role of fibrosis in this context will be instrumental in targeting therapy to reduce both liver and CVD-related death in the future.

Similarly to CVD, multiple large cohort studies have shown that ultrasound or CT-proven NAFLD incurs a mean 1.5- to 2-fold increased risk of developing T2DM within 5–10 years of diagnosis, after adjusting for other lifestyle and metabolic confounding factors (3). By the end of follow-up in these studies, which largely originated from Japan, China, South Korea and the US, the proportion of patients with newly diagnosed T2DM ranged from 1–14% (8-10). Of note, with resolution of NAFLD on imaging the risk of new-onset T2DM also diminished, but this largely coincided with weight loss and ultrasound alone is not accurate in assessing serial changes in hepatic lipid content. Data in non-South Asian populations remain sparse and only a solitary Swedish study has prospectively reviewed the risk of new-onset T2DM in patients with biopsy-proven NAFLD (11). The authors state an incident rate of T2DM as 58% over 13 years, however it is hard to be certain of this, as no diabetic screening tests were performed at baseline. With this limitation in mind, patients with NASH (and fibrosis) had a 3-fold risk of developing T2DM compared to those with simple steatosis. Future studies should clarify the severity of NAFLD and thoroughly screen for T2DM at baseline, whilst adjusting for family history of T2DM and baseline levels of insulin resistance, which have rarely been included. Even though further prospective studies are required, routine screening for T2DM in patients with underlying NAFLD is now mandatory (EASL–EASD–EASO guidelines 2016) (12).

Several studies have highlighted that NAFLD and in particular biopsy-proven NASH is associated with a greater prevalence of CKD (defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, abnormal albuminuria or overt proteinuria), with rates ranging from 20% to 55% (compared to 5–30% in controls). Importantly, in the majority of the reported cross-sectional studies this association remained after adjustment for key causal risk factors of CKD, including T2DM and hypertension (13). The most robust dataset to date is a meta-analysis of 33 studies (13 prospective), which highlighted a 2-fold incidence of CKD in NAFLD patients, after adjustment for appropriate risk factors. Furthermore, those with biopsy-proven NASH were 2.5 times more likely to develop CKD than their counterparts with simple steatosis. Even though this data is compelling, no studies utilised isotopic GFR or renal pathology to define CKD or rule out other causes of renal injury, respectively.

Malignancy is the second commonest cause of death in patients with NAFLD. Since 2010 a series of 10 cohort studies (n=127 to 26,540) have focused on the association of NAFLD with large bowel adenomas and carcinomas (3). The vast majority were cross-sectional in design and of the two cohort studies with 5–7 years follow-up, only one study ensured a negative baseline colonoscopy. Therefore, a true causal relationship cannot be assessed, but the two East Asian cohort studies reported increased cancer risk of 2–3 folds in patients with ultrasound-defined NAFLD (14,15). Due to the lack of well-designed prospective study it is too soon to recommend preferential colonoscopy in patients with NAFLD, outside that of current bowel screening guidelines. However, having a low threshold to investigate colonic symptoms in this cohort is paramount (*Table 1*).

Other putative extra-hepatic complications have been previously associated with NAFLD, but due to a paucity of biopsy-proven disease included, sample size and prospective study, understanding the relationship remains limited. Most notably, ultrasound defined NAFLD is associated with low bone mass density (independent of BMI), sleep apnoea (independent of age, sex and BMI),

Table 1 Screening modalities for extra-hepatic diseases in patients with NAFLD

Disease stage	Extra-hepatic manifestation	Recommendations	Frequency
Definite screening			
NAFLD (spectrum) ❖ Imaging modality ❖ Or biopsy	T2DM*	Serum HbA1c	Yearly
		Fasting glucose	
		OGTT (limited practice)	
	CKD	Urinalysis	Yearly
		Urine ACR (microalbuminuria)	
		eGFR	
	CVD*	Blood pressure	Yearly
		BMI/Waist circumference	
		Serum lipid profile	
		Assess and record: ❖ Smoking history ❖ Family history of CVD	
		Caution the use of CVD-risk calculators (until further data available in NAFLD populations)	
Greater clinical awareness			
NASH (+/– fibrosis) ❖ Biopsy ❖ Non-invasive marker (advanced fibrosis)	Colorectal cancer	Assess and record risk factors: ❖ Family history ❖ Smoking ❖ Diet (Inc. alcohol) ❖ BMI	Yearly
		Monitor bowel symptoms	
		Use current national guidelines on colorectal cancer screening	
	Hypothyroidism/PCOS	Serum thyroid function tests (yearly)	Yearly
		Lower threshold for ovarian USS and serum androgens in females of reproductive age with irregular menstruation, infertility, hirsutism etc.	
	Sleep apnoea	Awareness of symptoms (i.e., daytime somnolence)	At diagnosis
		Assess and document risk factors: ❖ Smoking ❖ BMI (Inc. neck circumference) ❖ Alcohol and sedative medications	
	Osteoporosis	Awareness of symptoms (i.e., lower back pain)	At diagnosis
		Screen in patients undergoing transplant assessment to prevent peri-/post-operative fracture	

BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HCC, hepatocellular carcinoma; T2DM, type 2 diabetes mellitus; USS, ultrasound. *, EASL Guidelines 2016 (12).

polycystic ovarian syndrome (independent of BMI), hypothyroidism (independent of metabolic risk factors) and other endocrinopathies (i.e., growth hormone deficiency, hypopituitarism) (4).

A detailed description of the pathogenesis involved in the development of NAFLD-associated extra-hepatic disease is beyond the scope of this editorial (1). Overall, a clear understanding of the biological and genetic pathways involved remains lacking because of the close relationships between NAFLD and central obesity, dyslipidemia and insulin resistance. A complex interplay between multiple organs (liver, adipose, heart, vasculature, gut), inflammatory mediators (TNF-α, IL-6), procoagulants, lipotoxicity (free fatty acids, MCP-1), western diet (high saturated fats, salts), gut microbiota and genetics (most notably PNPLA3 and TM6SF2) has been reported.

A proposed screening and clinical awareness strategy is described in *Table 1* (views of authors only). Screening for T2DM in patients with NAFLD should be easily performed in routine clinics and primary care, as per EASL 2016 guidelines (12). Two-hour oral glucose tolerance test (OGTT) is more sensitive at detecting T2DM and impaired glucose tolerance than fasting blood glucose, but if limited availability, then HbA1c measurements are recommended (greater than 6.5% or 48 mmols/mol). Quantifying the short-term and lifetime risk of CVD in patients with NAFLD remains a challenge [i.e., Framingham Risk Score (FRS), Q-Risk 2 score], but screening and evaluation of well-recognised CVD risk factors is now mandatory (12). These should include BMI, waist circumference (ideally), blood pressure, serum lipid profile, baseline electrocardiograph and ask with regards to smoking and family history of CVD.

The clinical burden of NAFLD is not restricted to liver-related morbidity, but is in fact related to its independent associations with CVD, T2DM, CKD and malignancy. Despite the current evidence being largely restricted to observational cohort studies, physicians and patients with NAFLD (in particular fibrosis) should be made aware of these increased risks. Greater emphasis should be placed on specific lifestyle modifications (i.e., smoking cessation, weight loss, physical activity) and aggressive pharmaceutical modification (i.e., lipid-lowering, insulin sensitizers) which may not only reduce the risk of progressive liver disease, but could also significantly impact on extra-hepatic disease and overall prognosis. With the evolution of non-invasive markers of fibrosis (i.e., transient elastography, ELF test, Fibrotest), future long-term prospective studies should attempt to clarify whether it is actually the severity of liver fibrosis that predicts extra-hepatic complications and not the earlier features of NAFLD.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Armstrong MJ, Haydon G, Syn WK. Beyond the liver in patients with non-alcoholic fatty liver disease (NAFLD)—cause for concern? HepatoBiliary Surg Nutr 2018;7(2):138-142. doi: 10.21037/hbsn.2018.01.09

