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COMMENTARY

Assessing liver fibrosis in all patients with type 2 diabetes and fatty liver disease: It's time to act now

Non-alcoholic fatty liver disease (NAFLD) consists of a range of hepatic disorders from isolated hepatic steatosis or non-alcoholic fatty liver, to non-alcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis and the development of hepatocellular carcinoma. Of the various stages within this spectrum, liver fibrosis is the major determinant of adverse long-term prognosis. In the latest and most contemporary meta-analysis involving more than 4,000 individuals with biopsy-confirmed NAFLD, it was found that liver fibrosis, irrespective of the presence of NASH, was a significant predictor of all-cause mortality, liver-related mortality and morbidity. Importantly, these risks appeared to be incremental with advancing stages of liver fibrosis[1]. However, most of the evidence was derived from retrospective studies, and was limited by spectrum bias, insufficient adjustments for key confounders and the lack of a protocol-driven assessment for development of adverse outcomes.

The recent study by Sanyal *et al.*[2], published in the *New England Journal of Medicine*, was the first prospective study that evaluated both hepatic and extrahepatic outcomes of 1,773 adult patients with NAFLD based on a protocol-mandated approach with adjustments of covariates in the analyses. All participants were recruited from the NASH Clinical Research Network and included the full histological spectrum of NAFLD. Over a median follow-up period of 4 years, the incidence of all-cause mortality, liver-related mortality and any hepatic decompensation events, which included clinically apparent ascites, overt encephalopathy and variceal hemorrhage, increased progressively with higher fibrosis stages from F0–2 (no, mild or moderate fibrosis), F3 (bridging fibrosis) to F4 (cirrhosis). Furthermore, the development of any new hepatic decompensation event was independently associated with a more than sixfold increase in the risk of all-cause mortality, even after adjustments for confounders, such as age, sex, presence of type 2 diabetes, NASH and fibrosis stage at baseline. Collectively, these prospective findings provide compelling clinical support to the conventional notion derived from retrospective studies, that liver fibrosis is indeed an important prognostic indicator in NAFLD patients.

However, among the large number of individuals with NAFLD that constitute one-quarter of the global adult population, who are the ones that will develop progression leading to advanced fibrosis, cirrhosis and ultimately, mortality? Interestingly, a recent study using the long-term follow-up data of the Third National Health and Nutrition Examination Survey (NHANES III) of the USA showed that the association between NAFLD and all-cause mortality was significant only among those with evidence of metabolic dysfunction, including type 2 diabetes, obesity or central adiposity, dyslipidemia and hypertension. In other words, NAFLD on its own was not a significant predictor of mortality if adjusted for the presence of metabolic risk factors[3]. In another recent meta-analysis involving over 24 million individuals globally, among those with NAFLD, type 2 diabetes more than doubled their risks of developing severe liver disease, namely, cirrhosis, hepatic decompensation and liver-related mortality. Notably, type 2 diabetes elevated this risk to a much larger extent than that brought by other metabolic risk factors, such as obesity, hypertension and dyslipidaemia[4]. As hepatic steatosis is also highly prevalent in type 2 diabetes patients, it seems that patients with type 2 diabetes who also have co-existing fatty liver disease will probably derive the greatest benefits, among the NAFLD population, from fibrosis assessments for hepatic risk stratification.

In contrast, NAFLD has been regarded as a multisystem disorder that is also associated with cardiovascular disease, chronic kidney disease and extrahepatic cancers, such as colorectal malignancy. However, in contrast to all-cause mortality and liver-related outcomes, Sanyal *et al.*[2] did not observe significant associations between fibrosis stage and the incidence of cardiovascular disease or non-hepatic cancers, although F4 fibrosis independently increased the risk of developing a >40% decline in estimated glomerular filtration rate compared with those with F0–2 fibrosis[2]. Similarly, the recent study of the USA NHANES III database showed that the association between NAFLD and cardiovascular mortality became insignificant after adjustments for demographic and lifestyle factors, whereas that with cancer mortality was also attenuated after adjustments for metabolic risk factors[3].

In the prospective study by Sanyal *et al.*[2], type 2 diabetes, obesity and hypertension were present in 42, 73 and 61% of the participants with NAFLD, respectively. Although all regression

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models for mortality and incident clinical events in the study had been stratified according to the presence of type 2 diabetes at baseline, further information about the differences in long-term prospective outcomes of NAFLD patients with and without metabolic risk factors, in particular type 2 diabetes, would be helpful to derive more insights into the impact of metabolic dysfunction on the overall prognosis of NAFLD.

Nevertheless, given the strong prognostic importance of liver fibrosis in NAFLD, as shown by previous retrospective cohorts and the recent prospective study by Sanyal *et al.*[2], together with the reported high prevalence of clinically significant fibrosis in patients with type 2 diabetes, the American Diabetes Association has already started to recommend screening for advanced fibrosis in those with elevated serum alanine aminotransferase levels or hepatic steatosis detected on imaging studies[1,5]. A clinical care pathway has also been proposed by a multidisciplinary team of experts consisting of gastrohepatologists, endocrinologists and primary care physicians, highlighting the key steps in screening, diagnosis and treatment of NAFLD[5]. According to this pathway, all patients with type 2 diabetes should be screened for fatty liver disease. For those who are screened positive for hepatic steatosis, a comprehensive evaluation through history, physical examination and laboratory investigations should be carried out to screen for other common causes of chronic liver diseases, such as excessive alcohol intake and chronic hepatitis B infection. Notably, the latter is of extreme importance, especially in regions such as South-East Asia, given its high prevalence and the availability of effective antiviral treatment. Other tests, including antibody against hepatitis C virus, anti-nuclear antibody, anti-mitochondrial antibody and anti-smooth muscle antibody, should also be considered if there is clinical suspicion. Although NASH is a histological diagnosis requiring liver biopsy, fibrosis assessment can be carried out non-invasively with high accuracy. The clinical care pathway recommends a two-tier sequential testing for fibrosis, which involves the initial use of the Fibrosis-4 index, a non-invasive serum-based fibrosis score based on age, platelet count, alanine aminotransferase and aspartate aminotransferase levels. For those who are determined to be at intermediate risk on the Fibrosis-4 index, vibration-controlled transient elastography or other elastographic techniques should be carried out for liver stiffness measurements or be referred to hepatologists for further evaluation.

The prospective study by Sanyal *et al.*[2] was mainly carried out in the USA, and with study populations being predominantly white. Therefore, whether the findings could be generalized to the

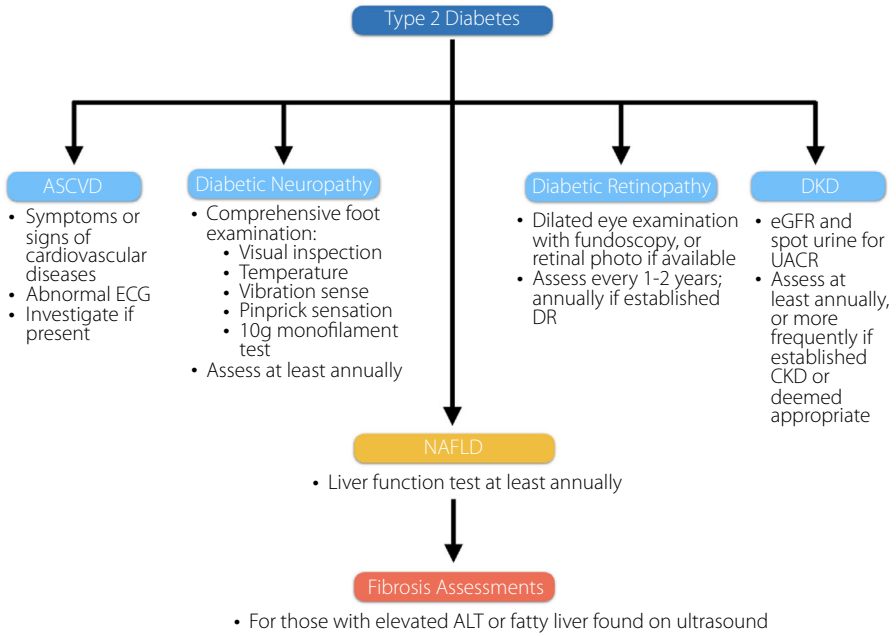

Figure 1 | Systematic evaluation for diabetes complications including non-alcoholic fatty liver disease (NAFLD). In patients with type 2 diabetes, NAFLD, especially in the presence of clinically significant fibrosis, should be viewed as an important diabetes complication, and be systematically evaluated as for the other classic diabetes complications, such as atherosclerotic cardiovascular diseases, diabetic kidney disease, retinopathy and neuropathy. ALT, alanine aminotransferase; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DKD, diabetic kidney disease; DR, diabetic retinopathy; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; UACR, urine albumin : creatinine ratio.

global population is a major limitation. Similar prospective studies in other regions of the world with diverse ethnicity and sociocultural background are necessary for further validation of the findings.

Despite the multitude of studies confirming the mutually detrimental relationship between NAFLD and type 2 diabetes, NAFLD as an emerging diabetes complication, especially in the presence of clinically significant fibrosis, has not been widely recognized, unlike the classic diabetes complications, such as cardiovascular disease and chronic kidney disease. Several recent clinical studies have already shown clear beneficial hepatic effects of pioglitazone, liraglutide, semaglutide and, potentially, sodium glucose cotransporter 2 inhibitors in reducing hepatic steatosis, as well as markers of liver injury and liver fibrosis. Therefore, it is high time for all diabetes care providers to make a concerted effort in managing NAFLD and systematically evaluate all patients with type 2 diabetes who also have fatty liver disease for the presence of clinically significant liver fibrosis (Figure 1).

DISCLOSURE

Approval of the research protocol: Not applicable. Informed consent: Not applicable. Registry and the registration no. of the study/trial: Not applicable. Animal studies: Not applicable.

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