Editorial Commentary

Advancing towards accurate phenotyping based on metabolic and fibrosis risk in metabolic-dysfunction associated steatotic liver disease: one step closer to personalized care

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Relevance of liver fibrosis amongst diabetic patients with metabolic-dysfunction associated steatotic liver disease (MASLD) and knowledge gaps

Insulin resistance is paramount in the crosstalk between intrahepatic and extrahepatic pathophysiological mechanisms leading to MASLD (1), hence gaining special relevance in patients diagnosed with type 2 diabetes (T2D). MASLD is the term that was recently endorsed by an international multidisciplinary consensus panel to replace non-alcoholic fatty liver disease [as non-alcoholic steatohepatitis (NASH) was replaced by metabolic dysfunction-associated steatohepatitis (MASH)] (2).

Liver fibrosis has been extensively proven as the main predictor of disease progression and complications in MASLD, including cardiovascular events, renal complications, non-hepatic neoplasms and liver events (3). Nonetheless, the diagnosis and staging of liver fibrosis is a current matter of controversy, with important developments during recent years. In particular, the potential replacement of liver biopsy by non-invasive tests (NITs) to assessing the severity of fibrosis in patients with MASLD/MASH is at the core of many endeavors and discussions in the liver disease community.

Screening and staging of liver fibrosis is particularly relevant amongst patients with T2D, as they constitute a large proportion of adult patients diagnosed with MASLD and present higher rates of advanced fibrosis (4). Moreover, T2D is as an independent predictor of hepatic decompensation and hepatocellular carcinoma in MASLD patients (5). International practice guidelines recommend systematic screening for advanced fibrosis in T2D patients (6,7), but the best methods and screening strategy remain to be elucidated (8,9). In addition, the bulk of evidence available on the intricacies of MASLD amongst T2D patients comes from hospital cohorts, often from clinical trials participants. Thus, data from the primary care setting are lacking to complete the epidemiological and

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clinical picture of T2D-MASLD. An additional limitation of most studies published to date, generally conducted by endocrinologists, is the focus on steatosis rather than fibrosis as the backbone of any screening and staging strategy.

The study by Ajmera *et al.* (10) greatly contributes to filling several important gaps, i.e., prospective data, a cohort of patients enrolled in primary care and endocrinology clinics, detailed data on NITs, and strong focus on assessing fibrosis and liver events. In brief, after excluding those with potentially harmful alcohol consumption and other potential causes of liver disease, the investigators recruited 501 T2D patients 50–80 years old and studied them with magnetic resonance imaging (MRI) techniques, i.e., MRI-derived proton density fat fraction (PDFF) to diagnose MASLD and means of magnetic resonance elastography (MRE) to assess fibrosis [or vibration-controlled transient elastography (VCTE) when MRE was not available]. Major findings included a prevalence of MASLD, advanced fibrosis and cirrhosis of 65.3%, 14% and 6% respectively, and obesity and insulin use were associated with increased likelihood of advanced fibrosis.

Although massively common, patients with T2D constitute a "special population" within the steatotic liver disease spectrum

The authors found higher rates of advanced liver fibrosis than in a previous study by the same group, in which they estimated the MASLD and advanced fibrosis prevalence among T2D patients on a primary care setting (11). The study was conducted in a much smaller cohort (N=100) also by MRI-PDFF and MRE, resulting on MASLD and advanced fibrosis prevalence of 65% and 7.1%, respectively (11). Only in individuals ≥65 years the prevalence of advanced fibrosis reached the rates reported in Ajmera's study (13.3% and 14%). These figures are consistent with those reported in recent systematic reviews and meta-analyses (12).

Nonetheless, there is the suspicion amongst the scientific community that the actual rates of advanced fibrosis might be higher and are growing in recent years in certain settings, likely because of the synergistic effects of the concomitant epidemics of T2D, obesity and sedentarism. For instance, Castera *et al.* studied 713 outpatients with T2D, 330 of whom had available liver biopsies and they found a prevalence of advanced fibrosis and cirrhosis of 38% and 10%, respectively (4). When compared to the rates of advanced fibrosis and cirrhosis found in the general population, the differences are dismal. For instance, Calleja *et al.* (13) estimated the prevalence of significant fibrosis and cirrhosis in Spain based on a population-based cohort of 12,246 individuals and a biopsy-proven MASH cohort of 501 patients, finding that the estimated prevalence of significant fibrosis and cirrhosis due to MASH in the Spanish adult population was respectively 1.33% [95% confidence interval (CI): 0.29–5.98%] and 0.70% (95% CI: 0.10–4.95%). Consequently, data from the Ajmera *et al.* (10), Castera *et al.* (4) and other (8) studies call for a specific strategy to screen for MASH and particularly fibrosis in the T2D population. Though systematic screening is already recommended by some scientific societies (6,7), how (with which tools) and how often remain unanswered questions.

There is a striking finding regarding the relationship between MASLD and advanced fibrosis in the study at issue that prompts further questions, namely the lack of significant differences in mean values of MRE and VCTE between the MASLD and non-MASLD groups. One potential explanation is already given by the authors, i.e., some MASLD patients might have been incorrectly identified as non-MASLD because of the lack of steatosis in advanced stages ("burned MASH"), and this group has a higher likelihood of having advanced fibrosis. Yet, further elaboration on the potential causes of this finding in the discussion section would probably have been welcomed by the readership.

Data on NITs to assess the presence and severity of MASLD and liver fibrosis

Ajmera and colleagues (10) proposed to lower the fibrosis-4 (FIB-4) cut-off point of 1 to improve the sensitivity to detect advanced fibrosis in this population. Current guidelines recommend a threshold of 1.3 in patients younger than 65 years and 2.0 in those older (6,7). However, current evidence suggests that the positive predictive value of such FIB-4 thresholds might be far from ideal. For instance, Boursier *et al.* reported that around a third of T2D patients with FIB-4 <1.30 had significant or advanced fibrosis in the liver biopsy (8). More recently, Poynard *et al.* analyzed the accuracy of several tests and scores to detect advanced fibrosis amongst 402 patients with T2D and found that FIB-4 displayed a significantly lower area under the receiver operating characteristic curve (AUROC) than its comparators (i.e., FibroTest-T2D, VCTE and share-

wave elastography) (9). In the Ajmera *et al.* study, 22.4% of patients with advanced fibrosis had FIB-4 values lower than 1.3 (10). It seems reasonable, therefore, that at least T2D with obesity and/or requiring insulin (or other signs of severity or poor glycemic control) undergo a second test to rule out fibrosis [e.g., enhanced liver fibrosis (ELF), VCTE, MRE].

The context of use is paramount to assess the cost-effectivity of the tools to detect MASLD and liver fibrosis

Multiple scores and tests have been tested to optimize the referral pathways of T2D placing liver fibrosis at the core of the strategy. There are at least four key aspects to consider before issuing a general recommendation for its use. First, feasibility. In primary care, since general practitioners and non-liver specialists manage a wide arrange of non-liver pathologies, it is often more convenient to utilize a score based on serum biomarkers that are easily determined in routine lab analyses, especially if automatically calculated. Performing VCTE in primary care might not be possible for the lack of devices' availability or personnel. In some settings, general practitioners (GPs) cannot order VCTE or MRE, and need to refer the patient to a liver specialist first. Moreover, it might be difficult for GPs or other health providers to interpret the results and decide whether to refer the patient to a liver specialist. Second, the prevalence of a certain condition/disease in a particular setting affects the pre-test likelihood and its general accuracy, e.g., it is not the same to interpret a value of FIB-4 of 1.4 in the primary care setting than in the liver clinic. Third, the prior considerations and others should be assessed through cost-effectiveness studies and cost-equity analyses before and after the implementation of a certain strategy. And fourth, the context of use also determines the utility of certain tests assessing fibrosis, e.g., various tests have been validated for both fibrosis detection and prognosis (mostly regarding liver-related outcomes, but in some cases also for cardiovascular events and other).

Interestingly, the analysis of accuracy for detecting advanced fibrosis by NITs in the Ajmera *et al.* study (10) showed an AUROC of 0.84 for MRE, higher than that of VCTE. This is of special interest in patients with morbid obesity, in whom VCTE has been shown to have overall low accuracy. The MRE AUROC reported was similar than the reported by the LITMUS Consortium, being of 0.92 in the overall cohort, and of 0.87 in T2D patients (14). Additionally, a recent cost-effectivity study supports this strategy, at least in specialized U.S. settings (15). Using a magnetic resonance-based strategy, either combined with serum tests or VCTE, seems a promising avenue, but further data are warranted on different contexts of use outside specialized centers of reference.

Open research questions

Data from the Ajmera *et al.* study add to that from other recent studies showing the potential of various NITs not only to identify individuals at risk of fibrosis, but also to predict clinical outcomes (8,16,17), which might have a profound impact in both how MASH is diagnosed and how patients are enrolled and efficacy assessed in clinical trials, thus replacing liver biopsy and histologic surrogate endpoints as the preferred tool. Future studies should compare the accuracy of MRE with other NITs including VCTE at predicting clinical events beyond hepatocellular carcinoma in patients with T2D. Other areas of interest in the field include, amongst other, the detailed characterization of MASLD versus MetALD (overlap of metabolic-induced and alcohol-related steatotic liver disease) (2) in T2D patients, and how dynamic changes in metabolic control affect the disease progression and the ability of NITs including those based on magnetic resonance to capture such changes.

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