Liver fibrosis testing in patients with type II diabetes – the time is now

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Running title: Liver fibrosis testing in type II diabetes

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A study by Caussy and co-authors has looked at the outcomes of non-invasive fibrosis testing in patients with type II diabetes and metabolic-dysfunction associated steatotic liver disease (MASLD)[1]. MASLD is the most prevalent liver disease in western countries, affecting up to 30% of the general adult population[2]. The prevalence is even higher in people with metabolic comorbidities, such as obesity or type II diabetes, where it is estimated to be higher than 50%[2]. People with MASLD are either asymptomatic or have subtle non-specific symptoms, such as tiredness or low grade right upper quadrant pain, therefore the diagnosis is often incidental, following abnormal liver blood tests or an abdominal ultrasound performed for different indications[3].

Recent guidelines from learned societies recommend case finding of liver fibrosis in patients with risk factors for MASLD, particularly those with type II diabetes or obesity with at least one cardiometabolic risk factor[4,5]. This recommendation has not been widely applied in clinical practice to date, due to a combination of factors including limited awareness, limited non-

invasive testing availability in non-hepatology settings, a perceived lack of interventions for MASLD and concerns regarding testing capacity[6].

In an interim analysis of a prospective study in France, Caussy and co-authors present the results of non-invasive fibrosis testing in 654 patients with MASLD on a background of either type II diabetes or obesity[1]. Non-invasive testing included indirect fibrosis markers (FIB-4, NAFLD fibrosis score, MAF5), patented serum tests (ELF, Fibrotest, Fibrometer) and liver stiffness measurement with Fibroscan, shear wave elastography and MR elastography in a subset of patients. The authors used a pragmatic and well-constructed hierarchical risk stratification for assessing the diagnostic performance of the various NITs, mirroring clinical practice where liver biopsy is indicated and/or available for only minority of patients.

They subsequently examined the performance of the recommended two-step risk stratification algorithms (FIB-4 followed by ELF or Fibroscan), to understand the burden of referrals to hepatology clinics and the prevalence of advanced

fibrosis in at-risk populations. Using the two-step algorithm would result in a referral rate of 14-18% and a positive predictive value of 39-62% depending on the combination used, with a negative predictive value of 88-91%. Overall, 17.6% and 9.3% of patients had an intermediate/high risk and a high risk of advanced fibrosis respectively. There are several important messages from this paper that are worth discussing in more detail.

Firstly, 98.4% of patients at high risk of advanced fibrosis had type II diabetes, while high BMI in isolation was not an independent risk factor for advanced fibrosis. This observation validates the recent EASL/EASD/EASO recommendation to target for fibrosis testing those with obesity and an additional cardiometabolic risk factor (and not those with obesity in isolation)[4]. As case finding does not currently occur in routine clinical practice, it is important to start from those at higher risk of significant liver disease. The diabetic population, with a risk of advanced fibrosis of over 9% (also confirmed in other studies[7,8]), is the logical cohort to start from. A liver health check

can be incorporated in the annual diabetic review as recently highlighted[9].

Secondly, FIB-4 performed significantly better that the other available indirect serum tests as the first step of risk stratification. MAF5, designed for testing the general population, cannot be used in this context of relatively high prevalence of advanced liver disease. The age-adapted FIB-4 cut-off of >2.0 in those older than 65 years is probably not fit for purpose, as it would result in suboptimal diagnostic accuracy. The Camden & Islington pathway previously showed suboptimal sensitivity of the 2.0 cut-off[10] and this study confirms that until better tests become available in this age group, we should continue to use the 1.3 cut-off and accept a higher number of referrals.

Thirdly, the ELF test had a numerically higher AUROC compared to the Fibrometer and the Fibrotest and until proven otherwise should be considered the patented serum test of choice in the MASLD population. The study confirmed that the 7.7 ELF cut-off is too low and not fit for clinical use. It also

confirmed that a cut-off of 9.6-9.8 is optimal in deciding which patients should be referred to secondary care and therefore externally validated the findings of the Camden and Islington pathway[10].

The results of this study indicate that there is a significant burden of advanced fibrosis in patients with type II diabetes. The licensing of medications with an indication for fibrotic MASLD[11] invalidates previous arguments on the lack of interventions for identified patients. Therefore, establishing frameworks for non-invasive liver fibrosis testing as part of the routine clinical care of patients with type II diabetes is important going forward. A two-step algorithm (FIB-4 followed by either ELF or transient elastography based on local availability) seems to work well based on the results of this study (Figure 1). The next steps are to increase awareness in non-hepatology settings and create the capacity required for testing these patients. Multi-morbidity care models will need to be co-designed from hepatologists and diabetologists with metrics of effectiveness and cost-effectiveness incorporated into them[12].

What is abundantly clear is that we cannot ignore the presence of significant liver disease in patients with type II diabetes any longer.

Acknowledgments:

Professor E. Tsochatzis is the guarantor of this article.

Funding: None

Conflicts of interest: EAT has participated in advisory boards for Boehringer, Siemens, NovoNordisk, Madrigal and MSD and received speaker fees from NovoNordisk, Boehringer, Echosens, Gilead and AstraZeneca. MZ has no COIs to report.

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Figure 1. Proposed two-step non-invasive liver fibrosis risk stratification in patients with type II diabetes.