‘Identification of individuals at risk of HCC: screening for clinically significant liver fibrosis in patients with T2DM’

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Cancer is a leading cause of premature mortality in patients with type 2 diabetes mellitus (T2DM)[1] and T2DM is strongly associated with site-specific cancers including hepatocellular carcinoma (HCC)[2]. In 2020, 830,200 people died from HCC and the incidence of HCC is expected to increase by 55% in the next 20 years[3]. HCC is now the fastest growing indication for liver transplantation[4] and is predicted to become the third most common cause of cancer death world-wide by 2030[5]. HCC has a very poor prognosis with a 5-year survival of just ~20%; however, if cases are identified at an early-stage, curative treatments are available which include surgical resection, liver transplant or tumour ablation[6].

A major risk factor for the increasing numbers of HCC is the increasing global prevalence of T2DM[3, 5, 7]. T2DM is strongly associated with central obesity, insulin resistance (IR) and other features of the metabolic syndrome; and of these linked risk factors, IR in particular is strongly linked with the development of liver steatosis, inflammation, fibrosis and liver cirrhosis. When insulin resistance is present, in the absence of excess alcohol consumption, it is most likely that NAFLD is responsible for the development of chronic liver disease. Importantly, patients with NAFLD-related cirrhosis have a risk of developing HCC at least similar to[8] that reported for patients with cirrhosis occurring from other aetiologies.

There is a high prevalence of all chronic liver diseases in people living with T2DM compared to the general population[9]. All stages of NAFLD occur with T2DM [10, 11, 12, 13], and we now know that there is a bi-directional causality between NAFLD and T2DM[14, 15]. A recent study of 561 patients from the United States showed a high prevalence of liver fibrosis and cirrhosis in patients with T2DM

leading to the authors advocating the need for screening[11]. This study showed that in patients with T2DM significant fibrosis was present in 6% and severe fibrosis or cirrhosis in 9% of patients[11].

NAFLD represents a spectrum of liver conditions that begins with hepatic steatosis and progresses to non-alcoholic steatohepatitis (NASH), liver fibrosis and cirrhosis. Occasionally hepatic steatosis occurs without changes in easily measured concentrations of liver enzymes such as alanine aminotransferase (ALT) that is commonly measured in primary care. However, it is important to recognise that increases in ALT concentration does not parallel the stages of liver disease and serum concentrations of ALT occurring within the laboratory normal range, may occur in NAFLD. Sometimes patients with NAFLD may have ALT concentrations below laboratory upper limits of normal and consequently, people living with T2DM may have undiagnosed NAFLD. With that in mind, the American College of Gastroenterology (ACG) suggests that current upper limits of normal are too high and that there should be sex-specific thresholds for the upper limits of normal. The ACG recommend ALT upper limits of normal of 33 U/L for men and 25 U/L for women, respectively, and that individuals with enzyme catalytic activity concentrations above these upper limits should be further investigated[16]. Despite uncertainty as to what level of ALT should trigger further investigations, concern has also been expressed about the assays used for measurement of ALT concentration[17]. Nevertheless, it seems likely that many laboratories' current upper limit of normal of 40 U/L is probably too high, and a lower threshold for defining a normal ALT result should be used.

Understanding how sex influences NAFLD is important for risk stratification and management of the disease, particularly as there is a disparity between men and women in the prevalence and severity of NAFLD[18]. We know that women with prior gestational diabetes mellitus are more prone to metabolic syndrome[19, 20] and have a higher risk of NAFLD compared with women without a history of gestational diabetes mellitus[21, 22]. Moreover, the presence of gestational diabetes and NAFLD, synergistically increases the risk of developing diabetes[23]. Indeed, NAFLD was initially considered a female disease[24], however, studies have shown that NAFLD is as common in men as in women[25]. A recent systematic review concluded that women have a lower risk of NAFLD than men[18], but once NAFLD is established the risk of progressing to advanced fibrosis is higher in women[18].

When patients have cirrhosis they are considered at high risk of developing HCC and surveillance (for detecting HCC) is relatively simple with liver ultrasound. International guidance recommends biannual surveillance in these patients; yet despite that, less than one third of incident cases of HCC are identified via surveillance in patients with T2DM [26]. This is important as cancers that are identified via surveillance have better outcomes[27]. Accordingly, the NHS England Cancer alliance have recently incorporated the early detection of HCC into its success metrics as it strives to achieve the objectives of the NHS long-term plan.

To engage patients with T2DM into HCC surveillance, it is necessary to first identify patients with cirrhosis. In the past liver disease was hard to identify because it usually progresses without signs or symptoms. However, several approaches have now been validated in patients with T2DM to identify asymptomatic disease. These include panels of blood tests, including FIB-4[28] and the Enhanced Liver Fibrosis (ELF™) test[29], and a simple scan of the liver which uses vibration controlled-transient elastography (VCTE) to assess liver stiffness[28, 30, 31] as a marker of liver fibrosis. In recent years, thresholds of liver stiffness measurements (expressed in kPa) have been established to correspond to the likelihood of a given fibrosis stage. These thresholds have been validated against liver histology assessment of liver fibrosis[32].

The 2021 Korean Clinical Practice Guidelines for Diabetes Mellitus recommend evaluating adults with T2DM for NAFLD[33]. Additionally, the American Diabetes Association updated their guidelines to recommend that patients with T2DM and pre-diabetes are tested for NAFLD[34]. However, routine screening of liver disease in patients with T2DM is not currently recommended by the National Institute for Health and Care Excellence (NICE)[35, 36] or the European Association for the Study of

Diabetes[37]. This is despite the high background prevalence of liver disease in patients with T2DM[11, 13], the availability of validated diagnostic tests for detecting high probability of advanced liver fibrosis, and recent calls for screening for liver fibrosis in patients with T2DM[11]. In 2021, NICE highlighted a lack of evidence in this area and called for further research. Existing NICE guidance[38] recommends that targeted testing for liver disease should be restricted to patients with T2DM *and* a fatty liver on ultrasound (detecting liver steatosis) *or* harmful alcohol consumption *or* abnormal liver function tests[38]. However, routine measurement of liver function tests are not recommended in the NICE guidelines for people with diabetes[39], which means people with diabetes will not, as a matter of routine care, access diagnostic pathways for liver disease from their annual diabetes reviews (unless measurements of liver enzymes are undertaken for another clinical reason).

Community liver pathways are being developed in the UK to help guide primary care physicians through standardized and evidence based processes that deal with the risk factors associated with liver disease. These pathways could help screen people to identify patients with T2DM who have evidence of potentially progressive liver disease, and who are at high risk of HCC[40, 41]. However, currently it is important to recognize that these primary care-focussed pathways reflect NICE guidance by only testing patients with abnormal liver function tests or who have abnormal ultrasound imaging[38]. This is a sub-optimal pathway for detecting liver disease in patients with T2DM. Moreover, liver function tests are not part of the routine annual diabetes review and half of patients with liver disease who are at risk of HCC have normal liver function tests[42]. Consequently, relying on abnormal liver enzyme concentrations to trigger further investigation of potential liver disease is fraught with problems for people living with T2DM. By virtue of having T2DM these people are already in a high risk group for liver fibrosis, cirrhosis and HCC. Rather, it is important to consider whether screening all patients with T2DM for evidence of liver fibrosis should be implemented. It is now evident that NAFLD is not only associated with increased risk of adverse liver disease outcomes such as cirrhosis and end stage liver disease, but NAFLD is also associated with increased risk of CVD[43], heart failure[44] and CKD[45].

Given that VCTE scanning is now increasingly becoming available in many communities within primary care settings, it should be possible for all patients to undergo liver fibrosis biomarker blood testing together with VCTE, to determine whether they have evidence of liver fibrosis. Since the early stages of NASH are potentially amenable to the benefits of lifestyle changes, and there are now incretin receptor agonist drugs, that are licensed for both the treatment of T2DM and weight loss, (that can also benefit liver disease in NAFLD[46]), there is a powerful argument in 2023 supporting the detection of NASH. If the early stages of NAFLD are diagnosed, agents such as GLP-1 receptor agonists could be prescribed in patients with T2DM.

Since thresholds for each of the liver fibrosis stages have now been validated in a large series of patients who have undergone liver biopsy as the gold standard for staging liver fibrosis[32], there is a case to suggest that all people with T2DM should undergo liver fibrosis biomarker testing and VCTE. That said, whether such an approach in routine care is cost effective and how often patients should be tested for liver fibrosis is uncertain. Additionally, whether VCTE and liver biomarkers can be used to monitor progression or amelioration of liver fibrosis over time is uncertain[47, 48, 49]. Nevertheless, considerable progress is being made in this area for people living with diabetes and it is likely that these issues can be resolved in the near future.

In conclusion, the balance of evidence is now shifting in favour of screening all patients with T2DM for liver fibrosis with a combination of liver fibrosis biomarkers and VCTE. Detecting low stage fibrosis would facilitate targeting patients towards lifestyle measures and certain treatments and detecting cirrhosis would enable patients to be referred for HCC surveillance (Figure 1). Generating good evidence of cost effectiveness from randomized-controlled trials comparing such an approach, with a control arm that uses contemporaneous usual care as a comparator arm is crucial; and hopefully it will soon be difficult for policy makers not to recommend screening of all people living with T2DM for liver fibrosis.

<u>Figure 1:</u> Screening for clinically significant liver fibrosis in patients with type 2 diabetes
The figure illustrates key risk factors for liver fibrosis, and the use of biomarkers and vibration-controlled transient elastography for the detection of clinically significant fibrosis and cirrhosis. The figure highlights that: a) patients with low stage fibrosis should be targeted towards lifestyle measures proven to be clinically effective for amelioration of early liver disease in NAFLD, and treatment with GLP-1 receptor agonists to facilitate weight loss, treat hyperglycaemia and decrease risk of cardiovascular disease; and b) patients with cirrhosis should be referred for HCC surveillance.

≥F2, clinically significant fibrosis; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus; ≥F3, advanced fibrosis; HCC, hepatocellular carcinoma; ELF™, enhanced liver fibrosis; FIB-4, fibrosis-4; LFTs, liver function tests; GLP-1, glucagon-like peptide-1; CKD, chronic kidney disease; CVD, cardiovascular disease.

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