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Viewpoint: Implementation of a liver health check in people with type 2 diabetes

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Abstract:	As morbidity and mortality related to potentially preventable liver diseases is on the rise globally, early detection of liver fibrosis offers a window of opportunity to prevent disease progression. Early detection of non-alcoholic fatty liver disease (NAFLD) allows for initiation and reinforcement of weight management guidance, risk stratification for advanced liver fibrosis and treatment optimisation of diabetes and other metabolic complications. Identification of alcohol-related liver disease provides the opportunity to support patients with detoxification and abstinence programmes. In all patient groups, identification of cirrhosis ensures that patients are enrolled in hepatocellular carcinoma (HCC) and portal hypertension surveillance programmes. When considering early detection strategies, success can be achieved from applying ad-hoc screening for liver fibrosis in established frameworks of care. Patients with type 2 diabetes (T2D) are an important group to consider case finding of (advanced) liver fibrosis and cirrhosis, as almost 70% have NAFLD and up to 19% have advanced fibrosis, which is 10-fold higher than the general population. Additionally, T2D patients with alcohol use disorders have the highest proportion of liver related morbidity. Patients with T2D receive an annual diabetes review as part of their routine clinical care, where the health of many organs are considered. Yet, liver health is seldom included in this review. This viewpoint argues that augmenting the existing risk stratification strategy with an additional “Liver Health Check” provides the opportunity to detect advanced liver fibrosis, thereby opening a window for early interventions to prevent end-stage liver disease and its complications, including HCC.

Editorial and reviewer comments:

In general, please substantially bolster the "barriers" section to provide more balance to the article.

Thank you for the additional comments. We have bolstered the “barriers” section as suggested.

In addition to the below points, please outline the key considerations/parameters around cost-effectiveness when you mention "Fundamentally, we need cost-effectiveness data for screening high risk groups with prospective cohorts such as during an annual diabetes review (61)". Eg, under what scenarios would this screening be/not be cost-effective?

Thank you for this comment. We have outlined key considerations/parameters as suggested.

Replies to reviewer 5

We agree that the false positive rate will be high, indeed in the pathway published in J Hepatol by Srivastava and co-aurthors, 30% of the referred patients had advanced fibrosis (therefore 70% of the high ELFs were false positive). However, using a combination of sequential non-invasive tests, we can arrive at a diagnosis of advanced fibrosis or cirrhosis with some certainty (Majumdar Hepatology 2020). If anything, the prevalence of advanced fibrosis in the diabetic population is at least 10%, therefore the pre-test probability is higher than that of unselected people with NAFLD. We clarify this in the text.

Please discuss this aspect in better detail, with examples, in the barriers section.

Thank you, we have expanded and clarified further.

...we acknowledge the limitations of the Fibroscan and mention them in the text.

Please discuss the limitations in full and give more detail to those already given; one line is not sufficient

We have expanded on this as suggested.

Please give more detail to the risk of ELF false positive rate in low-prevalence/inflammatory conditions

We have expanded on this as suggested.

Our view is that the anxiety will be short lived if a resolution is fast in terms of a diagnosis. On the other hand, 50% of patients presenting with decompensated cirrhosis never had a previous diagnosis of liver disease. Our argument is that incidental diagnosis of potentially preventable liver disease is not a good enough outcome.

Please address the variety of individual-level screening-related harms in more detail, and steps to mitigate these harms.

We have expanded as suggested.

Thank you, we mention available data in the pros section (refs 50-52). The largest study comes from Kjægaard et al, who presented outcomes of lifestyle modification on a prospective cohort of 2,764 individuals screened for liver fibrosis with TE, and reported positive behavioural change in both NAFLD and ARLD.

As noted/implied by the reviewer, is this generalisable to the population in diabetes clinics? If yes, please state; if not, please clarify and discuss.

We have now clarified in the text.

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Search strategy and selection criteria

We searched Medline (January 1, 2005–January 15, 2023) using the search term “diabetes” combined with the terms “NAFLD”, “cirrhosis”, “ALD”, “FIB-4”, “ELF”, or “Fibroscan” without language restrictions. We selected further relevant publications from the reference lists of articles identified by this search strategy. We largely selected publications from the past 5 years, but did not exclude highly relevant older publications. Review articles are cited to provide more details and references than this Viewpoint has room for.

Abstract

As morbidity and mortality related to potentially preventable liver diseases is on the rise globally, early detection of liver fibrosis offers a window of opportunity to prevent disease progression. Early detection of non-alcoholic fatty liver disease (NAFLD) allows for initiation and reinforcement of weight management guidance, risk stratification for advanced liver fibrosis and treatment optimisation of diabetes and other metabolic complications. Identification of alcohol-related liver disease provides the opportunity to support patients with detoxification and abstinence programmes. In all patient groups, identification of cirrhosis ensures that patients are enrolled in hepatocellular carcinoma (HCC) and portal hypertension surveillance programmes.

When considering early detection strategies, success can be achieved from applying ad-hoc screening for liver fibrosis in established frameworks of care. Patients with type 2 diabetes (T2D) are an important group to consider case finding of (advanced) liver fibrosis and cirrhosis, as almost 70% have NAFLD and up to 19% have advanced fibrosis, which is 10-fold higher than the general population. Additionally, T2D patients with alcohol use disorders have the highest proportion of liver related morbidity. Patients with T2D receive an annual diabetes review as part of their routine clinical care, where the health of many organs are considered. Yet, liver health is seldom included in this review. This viewpoint argues that augmenting the existing risk stratification strategy with an additional “Liver Health Check” provides the opportunity to detect advanced liver fibrosis, thereby opening a window for early interventions to prevent end-stage liver disease and its complications, including HCC.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is prevalent in over 30% of the global adult population (1) and is the main reason for referral to hepatology services. NAFLD is a spectrum ranging from isolated steatosis (non-alcoholic fatty liver, NAFL) to steatohepatitis (NASH) with or without fibrosis, with some patients ultimately progressing to cirrhosis and/or hepatocellular carcinoma (HCC). A systematic review using the Global Burden of Disease study data between 1990-2017 showed that NAFLD was the only liver condition where age-standardised death rates increased, with annual cases of cirrhosis deaths almost doubling, from approximately 61,900 cases in 1990 to 118,000 cases in 2017 (2). Modelling from Canada suggests that NAFLD will overtake ARLD as the major cause of cirrhosis by 2040 (3).

Currently, an estimated 5% of the adult global population have NASH (1). These patients are at significant risk of developing advanced fibrosis, which has been repeatedly associated with liver related morbidity and mortality (4). In the UK and US, NASH cirrhosis is now the second commonest indication for liver transplantation, after ARLD, and the leading indication in women (5, 6). There are further implications for transplant services as steatotic donor grafts are associated with poorer outcomes (7).

HCC incidence in patients with NASH cirrhosis ranges between 1-3% annually, with the number of new cases predicted to increase by 55% by 2040 (8). Importantly, HCC risk in patients with seemingly benign NAFL and no fibrosis is ten times higher than in the general population (9). Crucially, patients with NAFLD-related HCC tend to be older and have greater cardiovascular comorbidity. They also often present at a later stage because most are not under a HCC screening programme, are less likely to fulfil criteria for curative liver transplantation and, ultimately, have worse survival outcomes (10).

Despite this landscape of rising NAFLD-related morbidity and mortality, and a recent consensus for an international NAFLD public health agenda (11), awareness amongst clinicians and policy preparedness remains low. In a global survey with responses from 102 countries, no country had a national strategy for NAFLD and only 32 countries had national NAFLD clinical guidelines (12). In a cross-sectional survey of public health responses across

29 European countries, ten had national NAFLD guidelines, of which all recommended screening for NAFLD in type 2 diabetes (T2D) (13).

The rise in NAFLD prevalence parallels that of T2D, obesity and cardiovascular disease, which are all associated with insulin resistance. In the context of this interlinked pathophysiology between NAFLD, insulin resistance and T2D, almost 70% of T2D patients will have some degree of NAFLD, with an estimated 58% having NASH and up to 38% having advanced fibrosis (14, 15). The rate of hospitalization and death (not including HCC) due to liver disease in patients with T2D is 25.9 and 7 per 10,000 patients/years respectively and it is 2-3 times higher than the non-diabetic population (16, 17). Vice versa, lipotoxicity in NAFLD induces hepatic insulin resistance, generating uncontrolled gluconeogenesis and contributing to T2D (18). Indeed, patients with NAFLD have a two-fold higher incidence rate of T2D (19). This reflects the bidirectional relationship between these diseases.

It is worth acknowledging that not only NAFLD, but also ARLD co-exists with T2D. Mallet et al presented an 11-year French cohort study of 52,066 patients with T2D, 7.5% of whom had alcohol use disorders (20). The authors demonstrated that T2D patients with alcohol use disorders contributed to 55% of progression to liver-related complications, highlighting the interaction of alcohol with NAFLD (20). The overall prevalence of cirrhosis in T2D patients is not known but cross-sectional data from the US National Health and Nutrition Examination Survey (NHANES), involving liver stiffness measurement using transient elastography (TE) in 825 patients with T2D, found 7.7% had TE measurements equivalent with the presence of cirrhosis (21). These patients were predominantly in the 5^{th} or 6^{th} decade of their life.

The International Diabetes Federation estimates a global diabetes prevalence of 10.5% (equivalent to 537 million adults) in 2021, the majority with T2D (22). Every patient with T2D should have an annual diabetes review, advocated in guidelines from societies such as the UK National Institute for Health and Care Excellence (NICE), the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) (23-25). NICE and ADA have detailed list of complications of T2D that should be monitored for annually (Table 1). These include key indices of health and risk stratification for comorbidities and complications of T2D such as cardiovascular diseases, nephropathy, neuropathy and retinopathy, which are also relevant for the choice of the optimal pharmacological treatment. Annual reviews also offer the opportunity to provide behavioural change advice and support e.g. weight management and signposting to smoking cessation services.

One glaring omission from annual diabetes review recommendations has been until recently the assessment of patients for liver fibrosis (26). In this viewpoint we call for routinely including a liver health check to screen for advanced liver fibrosis as a 10th key care process within the existing framework of an annual diabetes review.

Proposal

We are proposing the inclusion of a "*Liver Health check*" into the existing diabetes annual review (Table 1). The primary aim of such an intervention would be to screen for advanced liver fibrosis, in order to further facilitate behavioural change, specialist input and pharmacological interventions. Currently, detection of liver disease in the community is based on ad-hoc testing by primary care practitioners or endocrinologists in patients suspected of liver disease, typically in response to abnormal liver blood tests or an incidental finding of fatty liver on an abdominal ultrasound performed for another indication such as unspecific abdominal discomfort. This is both inefficient, as it does not systemically assess liver fibrosis in this highly prevalent population, and costly in terms of missed cases, as demonstrated by the success of various community strategies to augment the detection of liver disease (27-29). Cost comparison modelling for detection of NAFLD has repeatedly showed that utilising an algorithm based on non-invasive tests (NITs) for liver fibrosis was superior to standard of care practices (30, 31). Markov modelling of comparative strategies for screening for NAFLD in T2D patients has shown that screening with liver blood tests and TE is the most cost-effective approach (32).

Furthermore, the use of abnormal liver blood tests alone is notoriously unreliable in patients with hepatic steatosis and insufficient to detect advanced liver disease. Liver enzymes show a poor correlation with fibrosis stage and are often normal in cirrhosis (33). For T2D, Kotronen et al. demonstrated that serum alanine aminotransferase did not correspond with the presence of steatosis amongst diabetic patients compared to non-diabetic patients with matched body mass index (BMI) (34). This was despite the T2D group having 80% more steatosis and 16% more visceral adiposity compared to the non-diabetic group (34). A high prevalence of NASH and cirrhosis was recently reported in people with T2D and normal ALT (14, 15).

Patients with T2D have a prevalence of advanced liver fibrosis of more than 10% in most studies (Table 2). A recent French study demonstrated that in a cohort of 330 patients with T2D, NAFLD and abnormal ALT (defined as >30 in males and >20 in females), the prevalence of biopsy-proven advanced fibrosis or cirrhosis was 38% (35). Screening directly for liver fibrosis in one-stop clinical assessments will likely contribute to improved linkage to care.

When screening for advanced fibrosis, we need to acknowledge that we are using non-invasive fibrosis tests validated in patients with chronic liver disease in the secondary care setting and applying them to a T2D population with a lower prevalence of advanced fibrosis. Using such tests liberally introduces spectrum bias and increases the risk of false positive results (36). To mitigate this, the index test must have a high sensitivity and negative predictive value, such as a Fibrosis-4 (FIB-4) cut-off of <1.3. This has a negative predictive value of >95% in low prevalence populations (30). This can also be used to rule out advanced fibrosis in patients with NAFLD, ARLD or viral hepatitis and does not require a confirmed diagnosis of liver disease prior to checking. By using FIB-4 in this setting, more than 50% of patients will have a low score and will not require further testing (37).

If a FIB-4 is greater than 1.3, a second test such as Enhanced Liver Fibrosis (ELF) test or TE should then be performed for further risk stratification for advanced fibrosis (Figure 1). A two-step risk stratification process is now supported by EASL (36), the American Association for the study of Liver Disease (AASLD) (38), the American Association of Clinical Endocrinology AACE (26) and the American Gastroenterology Association (39) and has been demonstrated to increase diagnostic accuracy for fibrosis detection in community screening strategies (27). Two-step risk stratification strategies are more cost-effective than the sole use of ELF, FibroScan® or standard of care (31). A strategy using FIB-4>1.3 followed by TE has a higher positive predictive value for significant fibrosis and leads to lower resource utilization and healthcare costs if applied in those with T2D as opposed to the general population (40). In the T2D population, the Edinburgh Type 2 Diabetes Study showed high negative agreement, i.e. ruling out fibrosis, but poor positive agreement between NITs, highlighting the importance of concordant NITs to rule in fibrosis (41, 42). These studies support the health and economic benefit of a Liver Health Check in people with T2D.

A FIB-4 test is not without limitations. The predictive performance of FIB-4 is suboptimal at the extremes of age, with low sensitivity in those age <35 years, and low specificity in those of age >65. McPherson et al showed that a higher low-threshold of 2.0 improved specificity in patients greater than 65 years (43). It does however have excellent diagnostic accuracy in ruling out advanced fibrosis, which is its intended use in the proposed algorithm. It is also questionable whether it is valuable to be diagnosing fibrosis stage 2 or 3 in unselected patients over the age of 75 years (44), particularly if these patients have suspected NAFLD. This is in the context that NAFLD fibrosis progression rates are relatively slow. Following a meta-analysis of paired-biopsy studies, Singh et al estimated that in patients with NASH it took seven years to progress between fibrosis stages (45). A pragmatic decision in this context to avoid overburdening primary and secondary care services would be to utilise the Charlson

comorbidity index (46) to exclude from screening anyone with a low 10-year survival probability. Finally, in patients with low FIB-4 and/or TE/ELF, re-testing could potentially happen every 2-3 years rather than annually. As effective pharmacological treatment gets approved, the diagnostic and therapeutic window for such patients may, however, change.

Pros

By embedding a "*Liver Health Check*" in an annual diabetes review (Figure 1), the awareness of liver disease and NAFLD amongst primary care practitioners and other specialists is expected to increase. This is important as NAFLD is an often-neglected component of the metabolic syndrome that also requires assessment and risk stratification, whereas alcohol use in T2D is commonly overlooked (47).

Such an approach would increase the detection of clinically relevant liver disease in a high-risk group for NAFLD and associated advanced fibrosis or cirrhosis. FIB-4 is inexpensive (in the UK, the estimated cost is £0.12) and easily accessible. Incorporating FIB-4 into an annual diabetes review has already been piloted by Mansour et al with the Gateshead Pathway. T2D patients were screened with age-based cut-offs. If the FIB-4 were elevated, patients were referred for a hospital-based TE assessment (48). The authors found almost 20% of T2D screened had an elevated FIB-4, with a fifth of patients referred to hepatology having evidence of cirrhosis on TE, while 50% had stiffness values <8 KPa (48). Furthermore, their TE clinic attendance rate was high at 93%, mainly through pragmatic screening of patients that were deemed appropriate for specialist input (48). This approach of FIB-4 followed by TE to screen for fibrosis is now being advocated in Europe and the US (26, 49).

Ongoing work is important in order to understand the acceptability and feasibility of community-based TE clinics, as this will also determine if TE is an appropriate second step confirmatory test. The Mid-Hampshire pilot, presented in the 2021 UK Lancet Liver Commission, made portable FibroScan® available to general practitioners (GP) in the UK, and reported that the cost of a community-based scan was half of that of an in-hospital scan. Importantly community TE clinics provided high patient and GP satisfaction (50). In the near future, the use of probes that can be connected to a smartphone or laptop and hence will not require a dedicated machine might make point-of-care testing easier.

Whilst lifestyle management of NAFLD and ARLD are not contingent on a diagnosis of liver disease, informing patients they have liver fibrosis can alter their behaviour. A meta-analysis exploring the effectiveness of adding advice based on liver injury biomarkers to patients with alcohol misuse showed that patients receiving advice had substantial reduction in weekly alcohol consumption, improvement in the γ-glutamyl transferase level and reduced mortality

(51). The same group are exploring prospectively if knowledge of liver fibrosis can affect high risk drinking behaviour in the KLIFAD randomised controlled trial (52). Kjægaard et al presented outcomes of lifestyle modification on a prospective cohort of 2,764 individuals screened for liver fibrosis with TE, and reported positive behavioural change in both NAFLD and ARLD (53). **Amongst individuals at risk of ARLD, 50% were abstinent or had reduced alcohol intake a week later and this effect was sustained at 6 months (53). A similarly significant response was seen amongst individuals informed about their risk of NAFLD, with 34% of them reporting they consumed less food and/or more healthy food. Patients in diabetes clinics are at risk primarily of NAFLD with or without ARLD, therefore the results of this study is generalizable to this setting.** However, outcomes for lifestyle advice provided to people with NAFLD is more contentious. The BALLETS prospective cohort study found that telling patients with NAFL to improve their weight resulted in mainly provoking short-term anxiety (54). Clearly, prospective research is required in order to better quantify the potential behavioural changes following non-invasive fibrosis investigations. Furthermore, the diagnosis of NAFLD with fibrosis has implications on the choice of anti-diabetic treatment as outlined in recent guidelines (26) and will also make patients eligible for future NASH-specific pharmacotherapy when approved.

Ultimately, in a landscape where the index presentation for over 70% of patients with new liver disease is acutely to hospital, with an inpatient mortality as high as 15% (55), early detection of liver disease can provide significant value to patients and health systems. Furthermore, it also allows for the identification of patients with cirrhosis that would benefit from HCC surveillance and portal hypertension screening.

Barriers

To embed such a change in an established annual review process requires engagement from stakeholders, specifically primary care specialists and diabetologists. Despite mounting evidence and support from EASL (49), EASD (56), ADA (57) and the AACE (26) to test T2D patients for liver fibrosis, adoption of this strategy has been suboptimal at the national level. In addition, gastroenterologists and hepatologists should accept that part of early detection of liver disease will involve better engagement and overall coordination with primary care services, endocrinology and cardiology clinics and effective strategies to cope with the large number of referrals that would result if all T2D patients were tested with NITs.

The potential harms of screening, including patient anxiety and/or difficulty in getting medical insurance should also be acknowledged. The anxiety caused by a positive first test can be mitigated provided there is a rapid resolution in terms of a final diagnosis. This will require efficient automated pathways with reflex testing. Information leaflets

on non-invasive testing and liver disease would also be helpful. A true positive diagnosis of advanced fibrosis or cirrhosis would ultimately be beneficial for patients and would outweigh potential harms.

The availability of NITs is also variable, whilst cut-off values for these tests remains unstandardised (58). **Individual NITs have well documented weaknesses**, **however in combination they can provide an accurate estimate of fibrosis in the majority of patients tested.** LSM requires training and the readings can be influenced by morbid obesity, **with data from a prospective study in NAFLD suggesting that the applicability is 97% (59). There is also a well-documented variation of elastography measurements of more than 20% in up to 50% of subjects that should be taken into account in the interpretation of results (60).** The ELF score can be false positive in people with extra-hepatic inflammatory conditions **as it is not liver specific or in advanced age**. **In a general population sample of 1,973 individuals and low prevalence of fibrosis, 12% had a high ELF value and the majority were false positives (61).** Therefore, a combination of sequential NITs might be required for a conclusive diagnosis. FIB-4 can be automatically calculated in laboratories similar to estimated glomerular filtration rate and reported with a traffic light system (green/amber/red) to facilitate interpretation and prompt further action from clinicians. Portable TE machines or shear-wave elastography modules in regular ultrasounds can be used in primary care but this will require the purchase and maintenance of relatively expensive equipment and is unlikely to be available in low-income settings. If community-based TEs become widespread, the physical capacity for an additional clinic is another logistical hurdle to consider for primary care practitioners. Alternatively, hospital TE clinic capacity would need to be increased. This would invariably require additional material investment and healthcare budget allocation.

Prevalence estimates for cirrhosis in the general population range between 0.1-1.7% (62). Screening for liver disease in the general population would most likely not meet the World Health Organization's adapted criteria from the original Wilson and Jungner statement (63). However, targeted screening in a high-risk group such as the diabetic population would be an acceptable practice (64). In a previously published pathway of non-invasive testing of unselected patients with NAFLD with a 5% prevalence of advanced fibrosis, 30% of the patients referred had advanced fibrosis or cirrhosis (27) and these data were replicated in a recent study on patients at risk for NAFLD or ARLD (61). **Assuming a prevalence of advanced fibrosis in the diabetic population of 10% and therefore a higher pre-test probability than unselected NAFLD, the expectation is that the false positive results will be lower.** Fundamentally, we need cost-effectiveness data for screening high risk groups with prospective cohorts such as during an annual diabetes review (64). **Such studies would**

provide data on the combination of risk factors that would make screening cost-effective, **optimal age cut-offs and frequency of re-testing. Cost-effectiveness data will also be influenced from the future availability of approved treatments for fibrotic NASH but also from the effectiveness of lifestyle modifications following non-invasive testing.** We also need prospective data to have clarity on which combination of NITs have greatest diagnostic accuracy whilst being most acceptable to patients (42). Currently those data are limited; however, ongoing studies will provide more information in the near future (65). Finally, we need to address the stigma related to the diagnosis of liver disease, which can lead to avoiding or delaying care and worse health outcomes (66).

Conclusion

In summary, patients with T2D are a high-risk group for clinically relevant liver disease, predominantly due to NAFLD. In the context of rising NAFLD-related morbidity and mortality, utilising the existing framework of annual diabetes reviews to screen this high-risk group is pragmatic and valuable. FIB-4 is an inexpensive, effective, widely available NIT that can be used as part of a Liver Health check index screening tool in regular health check-up of patients with T2D to detect advanced fibrosis.

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Table 1. Themes for annual assessment in patients with type 2 diabetes (adapted from NICE and ADA). (67, 68).

Ten key care processes to perform during annual diabetes review
1. Glycated haemoglobin (HbA1c) measurement, with a suggested target of 59 mmol/mol
2. Blood pressure (BP) measurement, with a suggested target of 140/80 mm Hg
3. Cholesterol level measurement, with a suggested target for total cholesterol (TC) of 5 mmol/L.
4. Assessment for retinopathy with retinal screening
5. Assessment for neuropathy with foot checks
6. Assessment for nephropathy with urinary albumin testing & serum creatinine testing
7. Atherosclerotic cardiovascular disease risk factors and 10-year risk assessment
8. Weight check and lifestyle management
9. Smoking status check
10. Liver Health Check: Case finding for liver fibrosis with FIB-4 measurement

Non-invasive Test(s)	Setting	T2D N (mean age)	Non-invasive test cut-off	Suspected fibrosis detection*	Definition of advanced fibrosis/cirrhosis	Advanced fibrosis/ cirrhosis detection
Transient elastography	**Diabetes clinic, secondary care, Taiwan, 2022 (69)**	226 (62.1 years)	TE (cut off > 7kPa)	22.1% (n=50/226)	-	-
	Gastroenterology clinic, secondary care, Romania 2022 (70)	424 (53.7 years)	TE (F2 cut off ≥8.2kPa)	31.1% (n=132/424)	TE ≥13.6kPa	10.7% (n=45/424)
	Primary care & Endocrinology clinic, USA, 2021 (71)	561 (60.0 years)	TE (F2 cut off ≥8.2kPa)	14.8% (n=83/561)	TE ≥13.6kPa	3.0% (n=17/361)
	Diabetic Clinic, Hong Kong, 2021 (72)	766 (59.4 years)	TE (F3 cut off ≥9.3kPa)	19.5% (n=149/766)	TE ≥11.5kPa (M probe) TE ≥11kPa (XL probe)	11.7% (n=90/766)
	NHANES cohort study, USA, 2021 (21)	825 (60.6 years)	TE (F2 cut off ≥8.2kPa)	21.7% (n=179/825)	TE ≥13.6kPa	6.3% (n=52/825)
	Diabetes Clinic, secondary care, India, 2021 (73)	250 (51.9 years)	TE (F2 cut off ≥7.1kPa)	62% (n=155/250)	TE ≥13.0kPa	18.4% (n=46/250)
	Diabetes clinics, secondary care, Italy 2019 (74)	394 (68 years)	TE (F2 cut off ≥7.0kPa with M probe; ≥6.2kPa with XL probe)	21% (n=83/394)	-	-
	Diabetes Clinic, secondary care, Malaysia, 2019 (75)	557 (61.4 years)	TE (F3 cut off ≥9.3kPa)	21.0% (117/557)	TE ≥11.5kPa (M probe) TE ≥11kPa (XL probe)	13.5% (n=75/557)
	Secondary care, China, 2018 (76)	629 (47 years)	TE (F2 cut off ≥10.6kPa)	36.7% (n=231/629)	-	-
	Diabetes clinic, secondary care, Hong Kong, 2016 (77)	1918 (60.6 years)	TE (F3 cut off ≥9.6kPa with M probe; ≥9.3kPa with XL probe)	17.4% (n=334/1918)	TE ≥11.5kPa (M probe) TE ≥11kPa (XL probe)	11.7% (n=224/1918)
	Primary care, UK, 2017 (78)	542 (64 years)	TE (F2 cut off ≥8.0kPa)	31.5% (n=171/542)	Hepatologist review (TE +/- histology, endoscopic	3.7% (n=20/542)

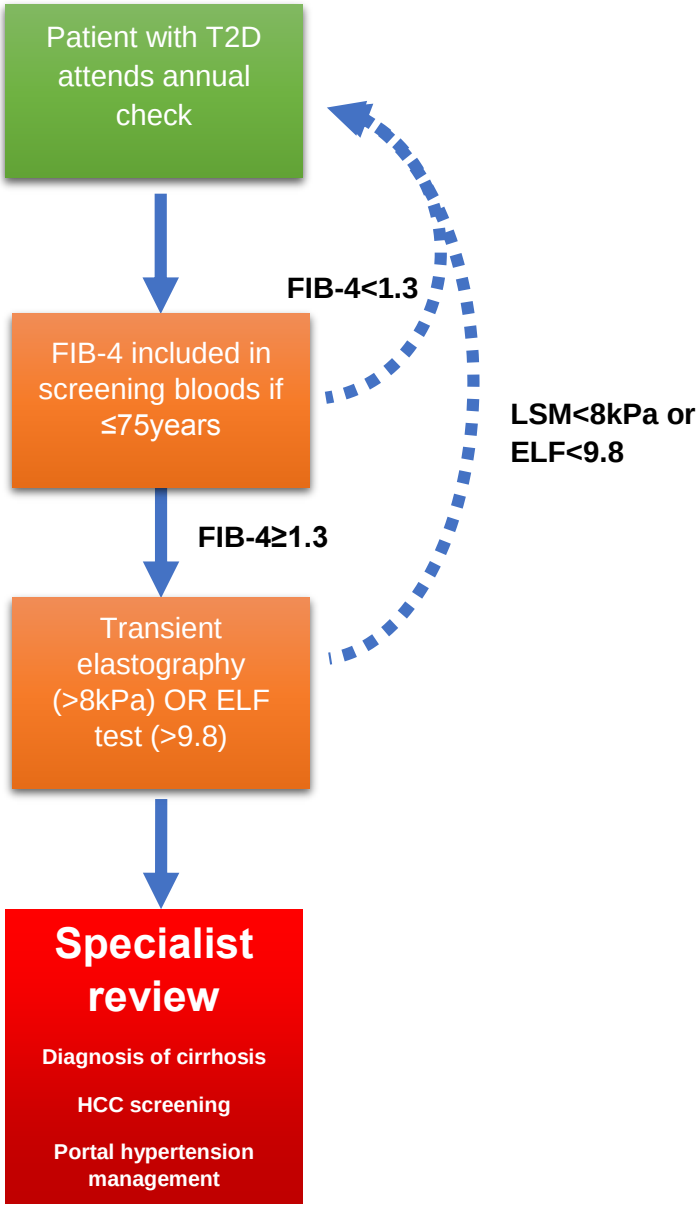
					and sonographic assessment)	
Transient elastography and Magnetic resonance elastogra	**Primary care & Endocrinology clinic, USA, 2022 (14)**	493 (64.4 years)	MRE (F3 cut off ≥3.63kPa) or TE (F3 cut off ≥8.8kPa)	14.0% (n=69/493)	MRE (F4 cut off ≥4.67kPa) or TE (F2 cut off ≥15kPa)	5.9% (n=29/493)
FIB-4 and Transient elastography	**Diabetes clinic, secondary care, Croatia, 2021 (79)**	454 (64.0 years)	TE (F2 cut off >7.9kPa) FIB-4 (≥2.67)	TE: 36.1% (n=164/454) FIB-4: 3.1% (n=14/454)	TE ≥11.5kPa	7.3% (n=33/454)
	Primary care, UK, 2021 (48)	466 (63.8 years)	FIB-4 (≥1·3 if 35– 65 years; ≥2·0 if >65 years) TE (F2 cut off ≥8kPa)	18.2% (n=85/466) had elevated FIB-4 43.1% had elevated TE (n= 25/58)†	TE ≥15kPa	22.4% (n=13/58)
Fibrosis-4 score	**Primary care, France, 2021 (80)**	214 (62 years)	FIB-4 (≥1.3 if <65 years; ≥2.0 if ≥65 years)	FIB-4: 15.0% (n=32/214)	-	-
	Diabetes clinics, secondary care, Italy, 2021 (81)	71285 (- †)	FIB-4 ≥1.3	66.8% (n=47584/71285)	FIB-4 > 2.67	20.9% (n=14888/71285)
	Diabetes clinics, secondary care, South Korea, 2021 (82)	1292 (60.8 years)	-	-	FIB-4 > 2.67	6.4% (n=83/1292)
	Diabetes clinics, secondary care, Italy, 2020	1429 (- †)	FIB-4 (≥1.3 if <65 years; ≥2.0 if ≥65 years) -	- 20.7% (n=295/1429)	FIB-4 > 2.67	5.3% (n=76/1429)
Fibrosis-4 score + NAFLD Fibrosis Score	**Rio-T2D Cohort Study, Brazil, 2021 (83)**	554 (60.3 years)	FIB-4 (≥1.3 if <65 years; ≥2.0 if ≥65 years) NFS (>-1.455 if <65 years; ≥0.12 if ≥65 years)	FIB-4: 13.9% (n=77/554) NFS: 54.2% (n=300/554)	NFS >0.676	12.8% (n=71/554)
Non-invasive tests & Liver biopsy	**QUID-NASH project, France, 2023 (15)**	330 (59 years)	Not specified; 1159 T2D patients from 4 diabetes clinics referred to liver clinics with suspected NAFLD	Median FIB-4 1.20 (IQR 0.90-1.69) Median LSM 8.3 (IQR 6.2-11.8)	Histological assessment (NASH CRN)	NASH: 58% ‡ F3: 28% F4: 10%

Table 2. Studies presenting fibrosis prevalence in T2D populations (without previously diagnosed liver disease) using NITs. Only studies with at least 200 participants are reported.

† - Mean age not reported. ‡ - *n* not reported

Abbreviations: CRN: Clinical Research Network; FIB-4: Fibrosis-4 score; NASH: Nonalcoholic steatohepatitis; NFS: NAFLD Fibrosis Score; TE: Transient elastography; T2D: Type 2 diabetes

Figure 1. Suggested pathway for use of non-invasive fibrosis tests incorporated into annual type 2 diabetes checks. Patients with a FIB-4 of ≥1.3, should have further testing with ELF or a Fibroscan, depending on local availability. If the ELF is >9.8 or the LSM is >8 KPa, then these patients should be evaluated in secondary care by a hepatologist. If the FIB4 is <1.3 in the first step of the algorithm or the ELF or LSM are <9.8 or <8 KPa respectively, then the patient does not require hepatological input and should be managed for his/her cardiovascular risk factors.



Footnote: ELF – Enhanced Liver Fibrosis test; FIB-4 – Fibrosis-4 score; LSM – liver stiffness measurement; T2D – type 2 diabetes mellitus

Viewpoint: Implementation of a liver health check in people with type 2 diabetes

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Search strategy and selection criteria

We searched Medline (January 1, 2005–January 15, 2023) using the search term “diabetes” combined with the terms “NAFLD”, “cirrhosis”, “ALD”, “FIB-4”, “ELF”, or “Fibroscan” without language restrictions. We selected further relevant publications from the reference lists of articles identified by this search strategy. We largely selected publications from the past 5 years, but did not exclude highly relevant older publications. Review articles are cited to provide more details and references than this Viewpoint has room for.

Abstract

As morbidity and mortality related to potentially preventable liver diseases is on the rise globally, early detection of liver fibrosis offers a window of opportunity to prevent disease progression. Early detection of non-alcoholic fatty liver disease (NAFLD) allows for initiation and reinforcement of weight management guidance, risk stratification for advanced liver fibrosis and treatment optimisation of diabetes and other metabolic complications. Identification of alcohol-related liver disease provides the opportunity to support patients with detoxification and abstinence programmes. In all patient groups, identification of cirrhosis ensures that patients are enrolled in hepatocellular carcinoma (HCC) and portal hypertension surveillance programmes.

When considering early detection strategies, success can be achieved from applying ad-hoc screening for liver fibrosis in established frameworks of care. Patients with type 2 diabetes (T2D) are an important group to consider case finding of (advanced) liver fibrosis and cirrhosis, as almost 70% have NAFLD and up to 19% have advanced fibrosis, which is 10-fold higher than the general population. Additionally, T2D patients with alcohol use disorders have the highest proportion of liver related morbidity. Patients with T2D receive an annual diabetes review as part of their routine clinical care, where the health of many organs are considered. Yet, liver health is seldom included in this review. This viewpoint argues that augmenting the existing risk stratification strategy with an additional “Liver Health Check” provides the opportunity to detect advanced liver fibrosis, thereby opening a window for early interventions to prevent end-stage liver disease and its complications, including HCC.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is prevalent in over 30% of the global adult population (1) and is the main reason for referral to hepatology services. NAFLD is a spectrum ranging from isolated steatosis (non-alcoholic fatty liver, NAFL) to steatohepatitis (NASH) with or without fibrosis, with some patients ultimately progressing to cirrhosis and/or hepatocellular carcinoma (HCC). A systematic review using the Global Burden of Disease study data between 1990-2017 showed that NAFLD was the only liver condition where age-standardised death rates increased, with annual cases of cirrhosis deaths almost doubling, from approximately 61,900 cases in 1990 to 118,000 cases in 2017 (2). Modelling from Canada suggests that NAFLD will overtake ARLD as the major cause of cirrhosis by 2040 (3).

Currently, an estimated 5% of the adult global population have NASH (1). These patients are at significant risk of developing advanced fibrosis, which has been repeatedly associated with liver related morbidity and mortality (4). In the UK and US, NASH cirrhosis is now the second commonest indication for liver transplantation, after ARLD, and the leading indication in women (5, 6). There are further implications for transplant services as steatotic donor grafts are associated with poorer outcomes (7).

HCC incidence in patients with NASH cirrhosis ranges between 1-3% annually, with the number of new cases predicted to increase by 55% by 2040 (8). Importantly, HCC risk in patients with seemingly benign NAFL and no fibrosis is ten times higher than in the general population (9). Crucially, patients with NAFLD-related HCC tend to be older and have greater cardiovascular comorbidity. They also often present at a later stage because most are not under a HCC screening programme, are less likely to fulfil criteria for curative liver transplantation and, ultimately, have worse survival outcomes (10).

Despite this landscape of rising NAFLD-related morbidity and mortality, and a recent consensus for an international NAFLD public health agenda (11), awareness amongst clinicians and policy preparedness remains low. In a global survey with responses from 102 countries, no country had a national strategy for NAFLD and only 32 countries had national NAFLD clinical guidelines (12). In a cross-sectional survey of public health responses across

29 European countries, ten had national NAFLD guidelines, of which all recommended screening for NAFLD in type 2 diabetes (T2D) (13).

The rise in NAFLD prevalence parallels that of T2D, obesity and cardiovascular disease, which are all associated with insulin resistance. In the context of this interlinked pathophysiology between NAFLD, insulin resistance and T2D, almost 70% of T2D patients will have some degree of NAFLD, with an estimated 58% having NASH and up to 38% having advanced fibrosis (14, 15). The rate of hospitalization and death (not including HCC) due to liver disease in patients with T2D is 25.9 and 7 per 10,000 patients/years respectively and it is 2-3 times higher than the non-diabetic population (16, 17). Vice versa, lipotoxicity in NAFLD induces hepatic insulin resistance, generating uncontrolled gluconeogenesis and contributing to T2D (18). Indeed, patients with NAFLD have a two-fold higher incidence rate of T2D (19). This reflects the bidirectional relationship between these diseases.

It is worth acknowledging that not only NAFLD, but also ARLD co-exists with T2D. Mallet et al presented an 11-year French cohort study of 52,066 patients with T2D, 7.5% of whom had alcohol use disorders (20). The authors demonstrated that T2D patients with alcohol use disorders contributed to 55% of progression to liver-related complications, highlighting the interaction of alcohol with NAFLD (20). The overall prevalence of cirrhosis in T2D patients is not known but cross-sectional data from the US National Health and Nutrition Examination Survey (NHANES), involving liver stiffness measurement using transient elastography (TE) in 825 patients with T2D, found 7.7% had TE measurements equivalent with the presence of cirrhosis (21). These patients were predominantly in the 5^{th} or 6^{th} decade of their life.

The International Diabetes Federation estimates a global diabetes prevalence of 10.5% (equivalent to 537 million adults) in 2021, the majority with T2D (22). Every patient with T2D should have an annual diabetes review, advocated in guidelines from societies such as the UK National Institute for Health and Care Excellence (NICE), the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) (23-25). NICE and ADA have detailed list of complications of T2D that should be monitored for annually (Table 1). These include key indices of health and risk stratification for comorbidities and complications of T2D such as cardiovascular diseases, nephropathy, neuropathy and retinopathy, which are also relevant for the choice of the optimal pharmacological treatment. Annual reviews also offer the opportunity to provide behavioural change advice and support e.g. weight management and signposting to smoking cessation services.

One glaring omission from annual diabetes review recommendations has been until recently the assessment of patients for liver fibrosis (26). In this viewpoint we call for routinely including a liver health check to screen for advanced liver fibrosis as a 10th key care process within the existing framework of an annual diabetes review.

Proposal

We are proposing the inclusion of a "*Liver Health check*" into the existing diabetes annual review (Table 1). The primary aim of such an intervention would be to screen for advanced liver fibrosis, in order to further facilitate behavioural change, specialist input and pharmacological interventions. Currently, detection of liver disease in the community is based on ad-hoc testing by primary care practitioners or endocrinologists in patients suspected of liver disease, typically in response to abnormal liver blood tests or an incidental finding of fatty liver on an abdominal ultrasound performed for another indication such as unspecific abdominal discomfort. This is both inefficient, as it does not systemically assess liver fibrosis in this highly prevalent population, and costly in terms of missed cases, as demonstrated by the success of various community strategies to augment the detection of liver disease (27-29). Cost comparison modelling for detection of NAFLD has repeatedly showed that utilising an algorithm based on non-invasive tests (NITs) for liver fibrosis was superior to standard of care practices (30, 31). Markov modelling of comparative strategies for screening for NAFLD in T2D patients has shown that screening with liver blood tests and TE is the most cost-effective approach (32).

Furthermore, the use of abnormal liver blood tests alone is notoriously unreliable in patients with hepatic steatosis and insufficient to detect advanced liver disease. Liver enzymes show a poor correlation with fibrosis stage and are often normal in cirrhosis (33). For T2D, Kotronen et al. demonstrated that serum alanine aminotransferase did not correspond with the presence of steatosis amongst diabetic patients compared to non-diabetic patients with matched body mass index (BMI) (34). This was despite the T2D group having 80% more steatosis and 16% more visceral adiposity compared to the non-diabetic group (34). A high prevalence of NASH and cirrhosis was recently reported in people with T2D and normal ALT (14, 15).

Patients with T2D have a prevalence of advanced liver fibrosis of more than 10% in most studies (Table 2). A recent French study demonstrated that in a cohort of 330 patients with T2D, NAFLD and abnormal ALT (defined as >30 in males and >20 in females), the prevalence of biopsy-proven advanced fibrosis or cirrhosis was 38% (35). Screening directly for liver fibrosis in one-stop clinical assessments will likely contribute to improved linkage to care.

When screening for advanced fibrosis, we need to acknowledge that we are using non-invasive fibrosis tests validated in patients with chronic liver disease in the secondary care setting and applying them to a T2D population with a lower prevalence of advanced fibrosis. Using such tests liberally introduces spectrum bias and increases the risk of false positive results (36). To mitigate this, the index test must have a high sensitivity and negative predictive value, such as a Fibrosis-4 (FIB-4) cut-off of <1.3. This has a negative predictive value of >95% in low prevalence populations (30). This can also be used to rule out advanced fibrosis in patients with NAFLD, ARLD or viral hepatitis and does not require a confirmed diagnosis of liver disease prior to checking. By using FIB-4 in this setting, more than 50% of patients will have a low score and will not require further testing (37).

If a FIB-4 is greater than 1.3, a second test such as Enhanced Liver Fibrosis (ELF) test or TE should then be performed for further risk stratification for advanced fibrosis (Figure 1). A two-step risk stratification process is now supported by EASL (36), the American Association for the study of Liver Disease (AASLD) (38), the American Association of Clinical Endocrinology AACE (26) and the American Gastroenterology Association (39) and has been demonstrated to increase diagnostic accuracy for fibrosis detection in community screening strategies (27). Two-step risk stratification strategies are more cost-effective than the sole use of ELF, FibroScan® or standard of care (31). A strategy using FIB-4>1.3 followed by TE has a higher positive predictive value for significant fibrosis and leads to lower resource utilization and healthcare costs if applied in those with T2D as opposed to the general population (40). In the T2D population, the Edinburgh Type 2 Diabetes Study showed high negative agreement, i.e. ruling out fibrosis, but poor positive agreement between NITs, highlighting the importance of concordant NITs to rule in fibrosis (41, 42). These studies support the health and economic benefit of a Liver Health Check in people with T2D.

A FIB-4 test is not without limitations. The predictive performance of FIB-4 is suboptimal at the extremes of age, with low sensitivity in those age <35 years, and low specificity in those of age >65. McPherson et al showed that a higher low-threshold of 2.0 improved specificity in patients greater than 65 years (43). It does however have excellent diagnostic accuracy in ruling out advanced fibrosis, which is its intended use in the proposed algorithm. It is also questionable whether it is valuable to be diagnosing fibrosis stage 2 or 3 in unselected patients over the age of 75 years (44), particularly if these patients have suspected NAFLD. This is in the context that NAFLD fibrosis progression rates are relatively slow. Following a meta-analysis of paired-biopsy studies, Singh et al estimated that in patients with NASH it took seven years to progress between fibrosis stages (45). A pragmatic decision in this context to avoid overburdening primary and secondary care services would be to utilise the Charlson

comorbidity index (46) to exclude from screening anyone with a low 10-year survival probability. Finally, in patients with low FIB-4 and/or TE/ELF, re-testing could potentially happen every 2-3 years rather than annually. As effective pharmacological treatment gets approved, the diagnostic and therapeutic window for such patients may, however, change.

Pros

By embedding a "*Liver Health Check*" in an annual diabetes review (Figure 1), the awareness of liver disease and NAFLD amongst primary care practitioners and other specialists is expected to increase. This is important as NAFLD is an often-neglected component of the metabolic syndrome that also requires assessment and risk stratification, whereas alcohol use in T2D is commonly overlooked (47).

Such an approach would increase the detection of clinically relevant liver disease in a high-risk group for NAFLD and associated advanced fibrosis or cirrhosis. FIB-4 is inexpensive (in the UK, the estimated cost is £0.12) and easily accessible. Incorporating FIB-4 into an annual diabetes review has already been piloted by Mansour et al with the Gateshead Pathway. T2D patients were screened with age-based cut-offs. If the FIB-4 were elevated, patients were referred for a hospital-based TE assessment (48). The authors found almost 20% of T2D screened had an elevated FIB-4, with a fifth of patients referred to hepatology having evidence of cirrhosis on TE, while 50% had stiffness values <8 KPa (48). Furthermore, their TE clinic attendance rate was high at 93%, mainly through pragmatic screening of patients that were deemed appropriate for specialist input (48). This approach of FIB-4 followed by TE to screen for fibrosis is now being advocated in Europe and the US (26, 49).

Ongoing work is important in order to understand the acceptability and feasibility of community-based TE clinics, as this will also determine if TE is an appropriate second step confirmatory test. The Mid-Hampshire pilot, presented in the 2021 UK Lancet Liver Commission, made portable FibroScan® available to general practitioners (GP) in the UK, and reported that the cost of a community-based scan was half of that of an in-hospital scan. Importantly community TE clinics provided high patient and GP satisfaction (50). In the near future, the use of probes that can be connected to a smartphone or laptop and hence will not require a dedicated machine might make point-of-care testing easier.

Whilst lifestyle management of NAFLD and ARLD are not contingent on a diagnosis of liver disease, informing patients they have liver fibrosis can alter their behaviour. A meta-analysis exploring the effectiveness of adding advice based on liver injury biomarkers to patients with alcohol misuse showed that patients receiving advice had substantial reduction in weekly alcohol consumption, improvement in the γ-glutamyl transferase level and reduced mortality

(51). The same group are exploring prospectively if knowledge of liver fibrosis can affect high risk drinking behaviour in the KLIFAD randomised controlled trial (52). Kjægaard et al presented outcomes of lifestyle modification on a prospective cohort of 2,764 individuals screened for liver fibrosis with TE, and reported positive behavioural change in both NAFLD and ARLD (53). Amongst individuals at risk of ARLD, 50% were abstinent or had reduced alcohol intake a week later and this effect was sustained at 6 months (53). A similarly significant response was seen amongst individuals informed about their risk of NAFLD, with 34% of them reporting they consumed less food and/or more healthy food. Patients in diabetes clinics are at risk primarily of NAFLD with or without ARLD, therefore the results of this study is generalizable to this setting. However, outcomes for lifestyle advice provided to people with NAFLD is more contentious. The BALLETS prospective cohort study found that telling patients with NAFL to improve their weight resulted in mainly provoking short-term anxiety (54). Clearly, prospective research is required in order to better quantify the potential behavioural changes following non-invasive fibrosis investigations. Furthermore, the diagnosis of NAFLD with fibrosis has implications on the choice of anti-diabetic treatment as outlined in recent guidelines (26) and will also make patients eligible for future NASH-specific pharmacotherapy when approved.

Ultimately, in a landscape where the index presentation for over 70% of patients with new liver disease is acutely to hospital, with an inpatient mortality as high as 15% (55), early detection of liver disease can provide significant value to patients and health systems. Furthermore, it also allows for the identification of patients with cirrhosis that would benefit from HCC surveillance and portal hypertension screening.

Barriers

To embed such a change in an established annual review process requires engagement from stakeholders, specifically primary care specialists and diabetologists. Despite mounting evidence and support from EASL (49), EASD (56), ADA (57) and the AACE (26) to test T2D patients for liver fibrosis, adoption of this strategy has been suboptimal at the national level. In addition, gastroenterologists and hepatologists should accept that part of early detection of liver disease will involve better engagement and overall coordination with primary care services, endocrinology and cardiology clinics and effective strategies to cope with the large number of referrals that would result if all T2D patients were tested with NITs.

The potential harms of screening, including patient anxiety and/or difficulty in getting medical insurance should also be acknowledged. The anxiety caused by a positive first test can be mitigated provided there is a rapid resolution in terms of a final diagnosis. This will require efficient automated pathways with reflex testing. Information leaflets on non-invasive testing

and liver disease would also be helpful. A true positive diagnosis of advanced fibrosis or cirrhosis would ultimately be beneficial for patients and would outweigh potential harms.

The availability of NITs is also variable, whilst cut-off values for these tests remains unstandardised (58). Individual NITs have well documented weaknesses, however in combination they can provide an accurate estimate of fibrosis in the majority of patients tested. LSM requires training and the readings can be influenced by morbid obesity, with data from a prospective study in NAFLD suggesting that the applicability is 97% (59). There is also a well-documented variation of elastography measurements of more than 20% in up to 50% of subjects that should be taken into account in the interpretation of results (60). The ELF score can be false positive in people with extra-hepatic inflammatory conditions as it is not liver specific or in advanced age. In a general population sample of 1,973 individuals and low prevalence of fibrosis, 12% had a high ELF value and the majority were false positives (61). Therefore, a combination of sequential NITs might be required for a conclusive diagnosis. FIB-4 can be automatically calculated in laboratories similar to estimated glomerular filtration rate and reported with a traffic light system (green/amber/red) to facilitate interpretation and prompt further action from clinicians. Portable TE machines or shear-wave elastography modules in regular ultrasounds can be used in primary care but this will require the purchase and maintenance of relatively expensive equipment and is unlikely to be available in low-income settings. If community-based TEs become widespread, the physical capacity for an additional clinic is another logistical hurdle to consider for primary care practitioners. Alternatively, hospital TE clinic capacity would need to be increased. This would invariably require additional material investment and healthcare budget allocation.

Prevalence estimates for cirrhosis in the general population range between 0.1-1.7% (62). Screening for liver disease in the general population would most likely not meet the World Health Organization's adapted criteria from the original Wilson and Jungner statement (63). However, targeted screening in a high-risk group such as the diabetic population would be an acceptable practice (64). In a previously published pathway of non-invasive testing of unselected patients with NAFLD with a 5% prevalence of advanced fibrosis, 30% of the patients referred had advanced fibrosis or cirrhosis (27) and these data were replicated in a recent study on patients at risk for NAFLD or ARLD (61). Assuming a prevalence of advanced fibrosis in the diabetic population of 10% and therefore a higher pre-test probability than unselected NAFLD, the expectation is that the false positive results will be lower. Fundamentally, we need cost-effectiveness data for screening high risk groups with prospective cohorts such as during an annual diabetes review (64). Such studies would provide data on the combination of risk factors that would make screening cost-effective, optimal age cut-offs and frequency of re-testing. Cost-effectiveness data will also be

influenced from the future availability of approved treatments for fibrotic NASH but also from the effectiveness of lifestyle modifications following non-invasive testing. We also need prospective data to have clarity on which combination of NITs have greatest diagnostic accuracy whilst being most acceptable to patients (42). Currently those data are limited; however, ongoing studies will provide more information in the near future (65). Finally, we need to address the stigma related to the diagnosis of liver disease, which can lead to avoiding or delaying care and worse health outcomes (66).

Conclusion

In summary, patients with T2D are a high-risk group for clinically relevant liver disease, predominantly due to NAFLD. In the context of rising NAFLD-related morbidity and mortality, utilising the existing framework of annual diabetes reviews to screen this high-risk group is pragmatic and valuable. FIB-4 is an inexpensive, effective, widely available NIT that can be used as part of a Liver Health check index screening tool in regular health check-up of patients with T2D to detect advanced fibrosis.

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Table 1. Themes for annual assessment in patients with type 2 diabetes (adapted from NICE and ADA). (67, 68).

Ten key care processes to perform during annual diabetes review
1. Glycated haemoglobin (HbA1c) measurement, with a suggested target of 59 mmol/mol
2. Blood pressure (BP) measurement, with a suggested target of 140/80 mm Hg
3. Cholesterol level measurement, with a suggested target for total cholesterol (TC) of 5 mmol/L.
4. Assessment for retinopathy with retinal screening
5. Assessment for neuropathy with foot checks
6. Assessment for nephropathy with urinary albumin testing & serum creatinine testing
7. Atherosclerotic cardiovascular disease risk factors and 10-year risk assessment
8. Weight check and lifestyle management
9. Smoking status check
10. Liver Health Check: Case finding for liver fibrosis with FIB-4 measurement

Non-invasive Test(s)	Setting	T2D N (mean age)	Non-invasive test cut-off	Suspected fibrosis detection*	Definition of advanced fibrosis/cirrhosis	Advanced fibrosis/ cirrhosis detection
Transient elastography	**Diabetes clinic, secondary care, Taiwan, 2022 (69)**	226 (62.1 years)	TE (cut off > 7kPa)	22.1% (n=50/226)	-	-
	Gastroenterology clinic, secondary care, Romania 2022 (70)	424 (53.7 years)	TE (F2 cut off ≥8.2kPa)	31.1% (n=132/424)	TE ≥13.6kPa	10.7% (n=45/424)
	Primary care & Endocrinology clinic, USA, 2021 (71)	561 (60.0 years)	TE (F2 cut off ≥8.2kPa)	14.8% (n=83/561)	TE ≥13.6kPa	3.0% (n=17/361)
	Diabetic Clinic, Hong Kong, 2021 (72)	766 (59.4 years)	TE (F3 cut off ≥9.3kPa)	19.5% (n=149/766)	TE ≥11.5kPa (M probe) TE ≥11kPa (XL probe)	11.7% (n=90/766)
	NHANES cohort study, USA, 2021 (21)	825 (60.6 years)	TE (F2 cut off ≥8.2kPa)	21.7% (n=179/825)	TE ≥13.6kPa	6.3% (n=52/825)
	Diabetes Clinic, secondary care, India, 2021 (73)	250 (51.9 years)	TE (F2 cut off ≥7.1kPa)	62% (n=155/250)	TE ≥13.0kPa	18.4% (n=46/250)
	Diabetes clinics, secondary care, Italy 2019 (74)	394 (68 years)	TE (F2 cut off ≥7.0kPa with M probe; ≥6.2kPa with XL probe)	21% (n=83/394)	-	-
	Diabetes Clinic, secondary care, Malaysia, 2019 (75)	557 (61.4 years)	TE (F3 cut off ≥9.3kPa)	21.0% (117/557)	TE ≥11.5kPa (M probe) TE ≥11kPa (XL probe)	13.5% (n=75/557)
	Secondary care, China, 2018 (76)	629 (47 years)	TE (F2 cut off ≥10.6kPa)	36.7% (n=231/629)	-	-
	Diabetes clinic, secondary care, Hong Kong, 2016 (77)	1918 (60.6 years)	TE (F3 cut off ≥9.6kPa with M probe; ≥9.3kPa with XL probe)	17.4% (n=334/1918)	TE ≥11.5kPa (M probe) TE ≥11kPa (XL probe)	11.7% (n=224/1918)
	Primary care, UK, 2017 (78)	542 (64 years)	TE (F2 cut off ≥8.0kPa)	31.5% (n=171/542)	Hepatologist review (TE +/- histology, endoscopic	3.7% (n=20/542)

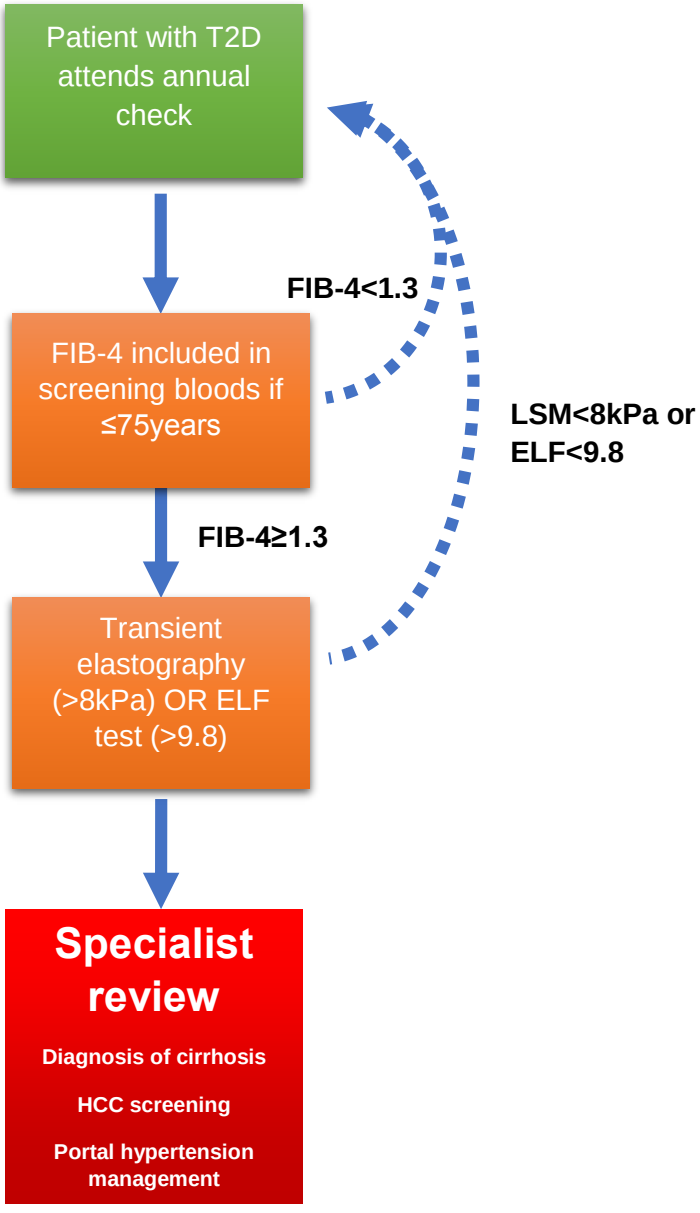
					and sonographic assessment)	
Transient elastography and Magnetic resonance elastogra	**Primary care & Endocrinology clinic, USA, 2022 (14)**	493 (64.4 years)	MRE (F3 cut off ≥3.63kPa) or TE (F3 cut off ≥8.8kPa)	14.0% (n=69/493)	MRE (F4 cut off ≥4.67kPa) or TE (F2 cut off ≥15kPa)	5.9% (n=29/493)
FIB-4 and Transient elastography	**Diabetes clinic, secondary care, Croatia, 2021 (79)**	454 (64.0 years)	TE (F2 cut off >7.9kPa) FIB-4 (≥2.67)	TE: 36.1% (n=164/454) FIB-4: 3.1% (n=14/454)	TE ≥11.5kPa	7.3% (n=33/454)
	Primary care, UK, 2021 (48)	466 (63.8 years)	FIB-4 (≥1·3 if 35– 65 years; ≥2·0 if >65 years) TE (F2 cut off ≥8kPa)	18.2% (n=85/466) had elevated FIB-4 43.1% had elevated TE (n= 25/58)†	TE ≥15kPa	22.4% (n=13/58)
Fibrosis-4 score	**Primary care, France, 2021 (80)**	214 (62 years)	FIB-4 (≥1.3 if <65 years; ≥2.0 if ≥65 years)	FIB-4: 15.0% (n=32/214)	-	-
	Diabetes clinics, secondary care, Italy, 2021 (81)	71285 (- †)	FIB-4 ≥1.3	66.8% (n=47584/71285)	FIB-4 > 2.67	20.9% (n=14888/71285)
	Diabetes clinics, secondary care, South Korea, 2021 (82)	1292 (60.8 years)	-	-	FIB-4 > 2.67	6.4% (n=83/1292)
	Diabetes clinics, secondary care, Italy, 2020	1429 (- †)	FIB-4 (≥1.3 if <65 years; ≥2.0 if ≥65 years) -	- 20.7% (n=295/1429)	FIB-4 > 2.67	5.3% (n=76/1429)
Fibrosis-4 score + NAFLD Fibrosis Score	**Rio-T2D Cohort Study, Brazil, 2021 (83)**	554 (60.3 years)	FIB-4 (≥1.3 if <65 years; ≥2.0 if ≥65 years) NFS (>-1.455 if <65 years; ≥0.12 if ≥65 years)	FIB-4: 13.9% (n=77/554) NFS: 54.2% (n=300/554)	NFS >0.676	12.8% (n=71/554)
Non-invasive tests & Liver biopsy	**QUID-NASH project, France, 2023 (15)**	330 (59 years)	Not specified; 1159 T2D patients from 4 diabetes clinics referred to liver clinics with suspected NAFLD	Median FIB-4 1.20 (IQR 0.90-1.69) Median LSM 8.3 (IQR 6.2-11.8)	Histological assessment (NASH CRN)	NASH: 58% ‡ F3: 28% F4: 10%

Table 2. Studies presenting fibrosis prevalence in T2D populations (without previously diagnosed liver disease) using NITs. Only studies with at least 200 participants are reported.

† - Mean age not reported. ‡ - *n* not reported

Abbreviations: CRN: Clinical Research Network; FIB-4: Fibrosis-4 score; NASH: Nonalcoholic steatohepatitis; NFS: NAFLD Fibrosis Score; TE: Transient elastography; T2D: Type 2 diabetes

Figure 1. Suggested pathway for use of non-invasive fibrosis tests incorporated into annual type 2 diabetes checks. Patients with a FIB-4 of ≥1.3, should have further testing with ELF or a Fibroscan, depending on local availability. If the ELF is >9.8 or the LSM is >8 KPa, then these patients should be evaluated in secondary care by a hepatologist. If the FIB4 is <1.3 in the first step of the algorithm or the ELF or LSM are <9.8 or <8 KPa respectively, then the patient does not require hepatological input and should be managed for his/her cardiovascular risk factors.



Footnote: ELF – Enhanced Liver Fibrosis test; FIB-4 – Fibrosis-4 score; LSM – liver stiffness measurement; T2D – type 2 diabetes mellitus