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Prevalence and severity of non-alcoholic fatty liver disease are underestimated in clinical practice: impact of a dedicated screening approach at a large university teaching hospital

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What's new?

- The prevalence and severity of non-alcoholic fatty liver disease (NAFLD) in patients with diabetes are currently underestimated by diabetes specialists.
- Informative, non-invasive scoring algorithms to stage NAFLD more accurately can be easily integrated into clinical practice in secondary/tertiary care.
- A total of 17.9% of people with diabetes who were attending diabetes clinics in a secondary/tertiary care setting were identified as either at indeterminate or high risk of advanced fibrotic NAFLD, and required additional investigation.
- A total of 63.6% of people with Type 2 diabetes requiring secondary/tertiary care, who were identified as at indeterminate or high risk of advanced NAFLD on screening, had elevated liver stiffness evaluations. This equates to 13.1% of the people with Type 2 diabetes who needed hospital-based care.

Abstract

Aims To define the attitudes and current clinical practice of diabetes specialists with regard to non-alcoholic fatty liver disease and, based on the results, implement an evidenced-based pathway for non-alcoholic fatty liver disease assessment.

Methods An online survey was disseminated to diabetes specialists. Based on findings from this survey, we sought a local solution by launching an awareness campaign and implementing a screening algorithm across all diabetes clinics at a secondary/tertiary referral centre.

Results A total of 133 diabetes specialists responded to the survey. Fewer than 5% of responders correctly assessed the prevalence and severity of advanced fibrotic non-alcoholic fatty liver disease in people with diabetes as 50–75%. Whilst most clinicians performed liver function tests, only 5.7% responded stating that they would use, or had used, a non-invasive algorithm to stage the severity of non-alcoholic fatty liver disease. Implementing a local non-alcoholic fatty liver disease awareness

campaign and screening strategy using pre-printed blood request forms, we ensured that 100% ($n=395$) of all people with Type 1 and Type 2 diabetes mellitus attending secondary/tertiary care diabetes clinics over a 6-month period were appropriately screened for advanced fibrotic non-alcoholic fatty liver disease using the Fib-4 index; 17.9% required further investigation or assessment.

Conclusions The prevalence and severity of non-alcoholic fatty liver disease are underestimated among diabetes specialists. The Fib-4 index can easily be incorporated into clinical practice in secondary/tertiary care to identify those individuals at risk of advanced fibrosis who require further assessment and who may benefit from a dedicated multidisciplinary approach to their management.

Introduction

The prevalence of non-alcoholic fatty liver disease (NAFLD) has increased in parallel with the global epidemic of obesity and diabetes; by 2020, NAFLD is predicted to become the commonest cause of liver failure and transplantation worldwide [1]. In Western populations, prevalence of NAFLD is estimated at up to 30% [2], rising to 90% in morbidly obese individuals[3]. It is a spectrum of disease extending from simple steatosis through to inflammation (non-alcoholic steatohepatitis) and subsequent fibrosis that can lead to cirrhosis as well as predispose to the development of hepatocellular carcinoma. Importantly, NAFLD is associated with increased mortality, particularly in the advanced fibrotic stages of the disease [4]. Whilst there is liver-associated mortality and morbidity, the majority of excess mortality is attributed to cardiovascular causes [5].

Type 2 diabetes and NAFLD are closely associated; the prevalence of NAFLD in people with Type 2 diabetes is estimated at ~70% using ultrasonography techniques [6]; however, this may underestimate its true prevalence because ultrasonography has a poor sensitivity to detect liver steatosis below 33%. The relationship between Type 1 diabetes and NAFLD is less clear-cut, but prevalence estimates based on ultrasonography data range from 44.4% to 50.2% [7,8]. Furthermore, there is evidence to

suggest that the presence of NAFLD not only carries an increased mortality risk, but may be associated with worse complications of diabetes [8,9].

Despite the prevalence of NAFLD amongst populations with diabetes and its associated adverse outcomes, there has been a perceived reluctance to identify people with NAFLD, perhaps fuelled by the current lack of availability of disease-modifying medications. In addition, isolated liver biochemical measurements are very poor at identifying those with most advanced disease. Indeed, in ~50% of people with advanced fibrotic NAFLD, circulating alanine aminotransferase (ALT) measurements are normal [10]

Liver biopsy remains the current 'gold standard' clinical assessment tool, but it is an invasive procedure with associated morbidity, and samples only a very small fraction of the liver. Furthermore, scoring of the histological tissue obtained is subject to significant inter-observer variability. Several non-invasive scoring systems have been developed to help identify the presence of the advanced stages of NAFLD, including aspartate aminotransferase (AST)/ALT ratio, AST to platelet ratio index, Fib-4 score and NAFLD fibrosis score [11,12], as well as specific serum biomarker tests including the enhanced liver fibrosis panel and transient elastography to measure liver stiffness. Many studies have validated the use of these markers in people with biopsy-proven NAFLD. The use of some of these tools has recently been advocated in joint guidelines published by the European Association for the Study of Diabetes (EASD), European Association for the Study of the Liver (EASL) and the European Association for the Study of Obesity (EASO) [13], as well as recently published guidance from the UK National Institute for Health and Care Excellence (NICE)[14]. Whilst the most recent NAFLD guidance from NICE does suggest a pathway for the assessment of NAFLD severity and highlights the association with Type 2 diabetes, it stops short of recommending case finding in people with diabetes, contrasting with the European guidance. Specifically with regard to people with diabetes, NICE currently recommends annual health checks in primary care for those with Type 2 diabetes and lists specific Quality and Outcomes Framework indicators, which include assessment of

BMI, blood pressure, HbA_{1c}, dyslipidaemia, smoking status, renal function and foot examination, but no assessment of NAFLD.

Given that Type 2 diabetes and NAFLD are highly prevalent diseases which commonly co-exist and act in concert to drive adverse outcomes, we aimed to: define the attitudes and current clinical practice of diabetes specialists towards NAFLD across the UK; implement an evidence-based pathway for the assessment of NAFLD in all patients attending diabetes outpatient clinics at a large teaching hospital/NHS Trust; and estimate the proportions of people with Type 1 and Type 2 diabetes attending outpatient clinics who are at risk of advanced hepatic fibrosis.

Patients and Methods

Assessing the current clinical approach to NAFLD by diabetes specialists

To determine current attitudes towards NAFLD and the clinical approach to its investigation and management, we designed an anonymous online survey that was disseminated via email to diabetes specialists across the UK. The survey was conducted between 1 October 2015 and 1 November 2015, prior to the publication of European and NICE guidance. As part of the survey, we emphasized that our aim was to understand what currently happens in day-to-day routine clinical practice. The questions that were asked as part of the survey are provided in Table S1. Based on the findings of this survey, key areas were identified that were felt to be amenable to intervention that would allow more appropriate staging and stratification of liver disease in people with diabetes, with the aim of enhancing their clinical care. This was formulated into the 'Think NAFLD' campaign.

'Think NAFLD'

Based on findings from this survey, which highlighted areas where the clinical approach, notably with regard to the assessment of stage and severity of NAFLD could be enhanced, we instituted a local 'Think NAFLD' campaign in the secondary care setting of the Oxford Centre for Diabetes,

Endocrinology and Metabolism (OCDEM) and the diabetes outpatient clinics at Oxford University Hospitals NHS Foundation Trust.

Our aim was firstly to raise awareness amongst healthcare professionals with respect to the prevalence of NAFLD (including that of advanced fibrotic disease) in people with diabetes. Information was targeted at clinic doctors, nurses and administrative staff via circulated email bulletins, presentations at departmental meetings, printed material and posters in clinic rooms. All these methods aimed to highlight the prevalence of NAFLD in people with diabetes and its adverse impact on outcomes. Secondly, we aimed to screen all people with diabetes attending outpatient diabetes clinics within OCDEM for the presence of advanced hepatic fibrosis using the validated non-invasive Fib-4 index. This was achieved through use of pre-printed blood forms to include specific measurement of all the variables necessary to calculate the Fib-4 index.

The Fib-4 index was calculated using the following equation:

$$[\text{Age (years)} \times \text{AST (iu/L)}] / [\text{platelet count} (\times 10^9/\text{L}) \times \sqrt{\text{ALT (iu/L)}}]$$

Online Fib-4 calculators were uploaded onto all diabetes clinic computers at OCDEM, alongside guidance on further investigation and management of patients stratified by the Fib-4 index. Scores of <1.3 were regarded as suggestive of a low risk of advanced fibrotic NAFLD and individuals were reassured. Scores between 1.3 and 2.67 were classified as indeterminate and scores >2.67 were classified as high risk [15]. Information on gamma-glutamyltransferase was not requested because of its poor specificity. Importantly, gamma-glutamyltransferase does not form part of any of the currently used non-invasive algorithms to assess the stage and severity of NAFLD. Further investigations, including a comprehensive liver screen for alternative aetiologies of liver disease as well as hepatic elastography and imaging (ultrasonography) were requested in individuals with indeterminate or high risk scores. Routine imaging was not requested in all screened patients because of the poor sensitivity of ultrasonography in identifying levels of steatosis below 33% and based on

the assumption that, in the presence of a low-risk Fib-4 score, the ultrasonography results were unlikely to influence clinical management.

Transient elastography of the liver was performed using Fibroscan[®] (Echosens, France). Only valid liver stiffness measurements were recorded in keeping with manufacturer's guidance (10 readings, interquartile range <30% of the median LSE, success rate >60%). A threshold of >7.9kPa was selected as being indicative of significant fibrosis (greater than histological stage F1) and would also capture those with advanced fibrotic NALFD (greater than histological stage F2).

Data were collected using electronic medical records from all individuals attending an outpatient diabetes appointment and therefore entering the screening programme for 6 months after launch, including demographics, weights, liver chemistry and full blood count, comorbidities and medications. Liver biochemistry, electrolytes, urea, creatinine, cholesterol, triglycerides and full blood counts were measured using standard laboratory methods (Roche Modular system, Roche Ltd, Lewis, UK). Blood tests were taken in the non-fasting state.

Results

Assessing the current clinical approach to NAFLD by diabetes specialists

A total of 133 responses to the survey were returned over a period of 4 weeks during 2015. The majority of responders were diabetes consultants (52%), followed by specialist registrars (23%), diabetes specialist nurses (12%), general practitioners with a specialist interest in diabetes (11%) and associate specialists (2%).

The responses to specific questions are shown in Figs 1 and 2. The majority of responders were not only concerned about missing a diagnosis of advanced NAFLD, but also felt that a diagnosis of advanced NAFLD would have a significant impact on the patients that they treat (Fig.1a). Both the prevalence of NAFLD (Fig. 1b) and that of advanced fibrotic NAFLD (Fig. 1c) were underestimated by responders. Most clinicians recognized the significance of a diagnosis of NAFLD in their patients;

61.5% responded that they would treat this group more aggressively. The remaining 38.5% of responders, however, reported that making a diagnosis of NAFLD would have no impact on the way they would manage their patients (Fig. 1d).

Interestingly, clinicians checked liver chemistry in the majority of their patients (>75%; Fig. 2a). ALT was the most common liver test requested. AST assessment was requested in 56% of cases and a platelet count in 39% (Fig. 2b). Faced with abnormal liver blood tests, most clinicians would screen for other underlying causes, request an ultrasound scan and consider repeating the test after an appropriate interval. A small number of responders (10%) would consider direct referral to a hepatologist (Fig. 2c). Only 5.7% responded to say that they would use a non-invasive scoring system to determine severity of disease. A large proportion of responders were not aware of any non-invasive scoring systems to help stage NAFLD (47%), therefore, unsurprisingly, 68% had not used them within the last 12 months (Fig. 2d).

Assessing the impact of a ‘think NAFLD’ campaign and dedicated screening approach

The ‘Think NAFLD’ campaign and screening programme were implemented in November 2015. In the 6 months prior to this (May to October 2015), no individual attending routine diabetes outpatient clinics at Oxford University Hospitals was risk-assessed for the presence of advanced fibrotic NAFLD using a non-invasive scoring system. This was exclusively attributable to the lack of measurement of AST and platelets as part of their clinical assessment. During the 6 months of implementation (November 2015 to April 2016), all individuals [$n=395$; Type 1 diabetes ($n=254$) and Type 2 diabetes ($n=141$)] attending diabetes clinics were appropriately screened and risk-stratified using the Fib-4 index. Three individuals with Type 1 diabetes were subsequently excluded because of heavy alcohol use. No individual had any comorbid viral, genetic or autoimmune causes of chronic liver disease. Specific comorbidities and current medications are shown in Tables S2 and S3.

A total of 322 (82.1%) individuals had a low Fib-4 index (<1.3) and could be reassured pending repeat scoring at 1 year; 70 (17.9%) had an indeterminate or high Fib-4 index, and clinicians were encouraged to arrange outpatient transient elastography (alongside a dedicated liver screen and imaging) as the next investigations before considering referral to a dedicated metabolic hepatology clinic (Fig. 3).

The clinical characteristics of those screened according to type of diabetes are shown in Table 1 (see also Tables S2 and S3). Elevated ALT levels were found more commonly in people with Type 2 diabetes compared with Type 1 diabetes using both local reference ranges (26.2% vs 7.2%) and the more stringent ALT criteria proposed by Prati *et al.* [16] (46.8% vs 22.7%). Indeterminate/high Fib-4 scores were recorded in 16.3% of people with Type 1 diabetes and in 20.6% of people with Type 2 diabetes.

In all, 30.3% of people with Type 2 diabetes and an indeterminate/high Fib-4 index had a normal ALT level, as determined by local reference ranges (Fig. 4a). A measurement of ALT used in isolation, would therefore have failed to identify 19.2% of individuals with Type 2 diabetes at risk of advanced fibrotic liver disease. Using the more stringent ALT criteria recommended by Prati *et al.*, 11.6% of those with Type 2 diabetes and an indeterminate/high Fib-4 index had a normal ALT level, and, even using these thresholds, an isolated measurement of ALT would have missed 14.7% of individuals at risk of advanced fibrotic NAFLD (Fig. 4b). In people with Type 1 diabetes, a normal ALT alone would have missed 14.6% of those at risk using local ALT criteria and 13.4% using the criteria of Prati *et al.* (Fig. 4c and d)

Although appointments were offered to all individuals with indeterminate or high Fib-4 scores, transient elastography was performed in 41% of these people at higher risk. Of these, 7/11 (63.6%) people with Type 2 diabetes had a liver stiffness measurement >7.9 kPa, suggestive of significant hepatic fibrosis, contrasting with 2/18 (11.1%) of people with Type 1 diabetes. Individual transient elastography measurements are shown in Table S4. Assuming that the prevalence of LSE >7.9 kPa

was similar in those individuals who did not attend for transient elastography, 13.1% of all those with Type 2 diabetes and 1.8% of those with Type 1 diabetes attending this secondary/tertiary care setting would have been identified as having evidence of advanced fibrotic NAFLD.

Discussion

The results of our survey show that the magnitude and severity of NAFLD amongst people with diabetes are underestimated by the diabetes specialists managing their care. In addition, it suggests that there is a heavy reliance on standard liver biochemical analysis (principally ALT) for screening of NAFLD, rather than non-invasive scores and algorithms, to inform clinical practice. Finally, we have shown that with simple measures to raise awareness, together with requesting appropriate routinely available biochemical and haematological tests, a more informative assessment of NAFLD stage can be made. On the basis of our screening algorithm, 17.9% of individuals required additional assessment, and our estimates suggest the presence of advanced fibrotic NAFLD in 13.1% and 1.8% of people with Type 2 and Type 1 diabetes, respectively.

The association between NAFLD and Type 2 diabetes is strong; an individual's risk of developing diabetes increases up to fivefold if they have a diagnosis of NAFLD [17,18] . Currently, we are unable to predict which individuals with NAFLD will subsequently develop diabetes; therefore, joint European hepatology, diabetes and obesity guidelines advocate regular screening for diabetes in those with NAFLD using HbA_{1c} or oral glucose tolerance testing [13]. A reciprocal risk relationship also exists. Cross-sectional analysis of 99 969 apparently healthy, Korean individuals without diabetes, were found to have an increased risk of NAFLD (determined by ultrasonography) with increasing levels of HbA_{1c} and insulin resistance, independently of obesity [19]. Cross-sectional studies have also shown an association between Type 1 diabetes and NAFLD diagnosed on ultrasonography, with prevalence estimates of up to 44%. No study, however, has applied risk stratification tools to identify those at risk of advanced hepatic fibrosis in this population. Our estimates, from applying Fib-4 and

transient elastography do suggest a small burden of advanced fibrosis in people with Type 1 diabetes (1.8%); however, the small numbers and also the lack of validation of these non-invasive tools in individuals with Type 1 diabetes limit interpretations.

The presence of NAFLD with advanced hepatic fibrosis is associated with increased mortality. The most common cause of death is cardiovascular disease, followed by non-liver cancer, complications of cirrhosis and hepatocellular carcinoma [5]. In addition to the identification of appropriately staged NAFLD in order to reduce liver specific morbidity and mortality (as well as identifying individuals at particularly high cardiovascular risk), NAFLD is also associated with an increased risk of micro- and macrovascular complications in those with both Type 2 diabetes [20,21] and Type 1 diabetes [7,8], and doubles the risk of death in Type 2 diabetes [22,23]. Furthermore, paired liver biopsy studies have also shown that diabetes is the most significant predictor of NAFLD progression [24], with recent data showing that, among those without diabetes and with simple steatosis at baseline, 80% of those who had fibrosis progression had developed Type 2 diabetes by the time of their follow-up biopsy [25].

Screening for NAFLD in asymptomatic populations remains controversial owing to uncertainties in diagnostic tools, limited disease interventions and cost-effectiveness, and is not currently recommended in American NAFLD guidelines [26]. The recent EASL–EASD–EASO clinical practice guidelines, however, do recommend screening for NAFLD in people with Type 2 diabetes because these people carry a high risk of disease progression [13]. The most clinically significant hallmark of progression is the development of fibrosis, which is the strongest predictor for overall and disease-specific mortality in NAFLD [5,27]. In primary and secondary care populations with Type 2 diabetes, advanced fibrotic NAFLD may be present in ~10%, with an increasing prevalence in older and more obese patients [28,29]. The identification of these individuals with advanced fibrosis would allow a more targeted allocation of resources but poses a significant clinical challenge given the vast majority are asymptomatic and have normal liver function tests. Although NAFLD is often diagnosed after finding mildly abnormal liver function tests, more than two thirds of individuals will have

normal aminotransferase levels [30] and the entire histological spectrum of NAFLD can be found in those with normal ALT values [31].

Current standards of 'normal' liver enzymes, however, were defined nearly 30 years ago in populations that included subclinical liver disease, including NAFLD and chronic viral hepatitis [32]. Prati et al. [16] redefined ALT limits using blood donors at low risk for NAFLD and without hepatitis B virus or hepatitis C virus. They advocated reducing the upper limit of normal for ALT from the widely used standard of >40 U/L to >30 U/L and >19 U/L in men and women, respectively. Applying these revised ALT thresholds to those screened in our outpatient diabetes clinics increased the proportion of abnormal liver function tests fourfold in Type 1 diabetes and twofold in Type 2 diabetes. Whilst using updated thresholds may help to unmask the true prevalence of NAFLD in people with diabetes, the majority (52%) with increased risk of advanced fibrosis had normal ALT levels despite revised ALT criteria, reinforcing the need to use validated tools for risk stratification tools, such as Fib-4.

The Fib-4 index is an easy-to-use scoring system, with readily accessible online calculators, that combines age with three standard biochemical variables: ALT, AST and platelet count. Declining platelet count correlates closely with the increased portal pressures derived from liver fibrosis. The Fib-4 index allows individuals to be categorized as being at low (<1.3), indeterminate (≥ 1.3 – 2.67) or high risk (>2.67) of advanced fibrosis and, in NAFLD, a Fib-4 threshold score of 1.3 carries a 85% sensitivity, 65% specificity and 95% negative predictive value for diagnosis of severe disease [11]. This high negative predictive value allows individuals with a low score to be reassured they are very unlikely to have advanced fibrosis, which was the case in 82% of people with diabetes screened in the present study. The positive predictive value of a score >1.3 , however, is less robust, at 50% [11], requiring these individuals to be further investigated, typically with a LSE or the use of the enhanced liver fibrosis serum panel recently advocated by NICE [14]. There is, however, a note of caution in that non-invasive scoring systems, including the Fib-4 index, may be influenced by age. They perform relatively poorly in individuals aged <35 years, which may have been a confounding factor in the

present study population. In this cohort, 44.6% of people with Type 1 diabetes and 14.9% with Type 2 diabetes were aged <35 years. In addition, alternative thresholds have been suggested for those aged > 65 years [33]; 26.2% of our participants with Type 2 diabetes were aged >65 years.

The present study has several limitations. It was conducted within a large secondary/tertiary care referral centre which was likely to be managing individuals with more advanced diabetes, with a higher burden of complications including NAFLD (perhaps reflected by the relatively young age of our cohort of individuals with Type 2 diabetes). The findings are therefore not generalizable to primary care, or indeed other secondary care settings. Factors such as ethnicity also need to be considered; the catchment area for referral to our clinic has a predominantly white demographic (78%) and the increased prevalence of NAFLD in some South-Asian populations is well described [34]. Any extrapolation, therefore, to other centres or care settings needs to be made with caution and the data should be validated as part of dedicated studies.

The number of transient elastography assessments that were performed in those with an indeterminate or high Fib-4 index was disappointing (41% of those identified as requiring transient elastography). Ideally, this procedure could be performed within the context of the diabetes clinic as a point-of-care assessment; however, in this pilot study, the necessary equipment was not available locally and the transient elastography assessment had to be performed in the hepatology department located at a different hospital site and necessitating a separate dedicated appointment. It is highly likely that this will have had a significant negative impact on the uptake of the transient elastography assessments.

In conclusion, the associations between NAFLD, diabetes and adverse outcome are clear. The currently adopted approaches to staging NAFLD in people with diabetes are likely to falsely reassure clinicians and fail to identify many individuals who have advanced fibrotic NAFLD, and this may have driven the underestimates of severity and prevalence that we observed in our survey. Adopting a non-invasive scoring algorithm, such as the Fib-4, should be considered in addition to current surveillance for complications for people with diabetes to identify those with particularly high risk of cardiovascular, as well as liver-related, morbidity and mortality.

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Competing interests

None declared.

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Supporting Information

Table S1 Dedicated survey designed to assess the current attitudes and approach to NAFLD amongst diabetes specialists.

Table S2 Comorbidities among a secondary/tertiary care cohort of people with diabetes screened for the stage and severity of NAFLD as part of the 'Think NAFLD' campaign.

Table S3 Prescribed medication amongst a secondary/tertiary care cohort of people with diabetes screened for the stage and severity of NAFLD as part of the 'Think NAFLD' campaign.

FIGURE 1 Current attitudes towards non-alcoholic fatty liver disease (NAFLD) in diabetes specialists (a and b). Estimates of the prevalence of NAFLD (c) and advanced liver fibrosis (d) in people with diabetes made by diabetes specialists.

FIGURE 2 The frequency (a) and spectrum (b) of liver function tests (LFTs) that are requested by diabetes specialists for patients under their care. Ultrasonography, screening for alternative aetiologies and repeating blood tests are commonly performed in patients with diabetes and abnormal liver chemistry (c). There is a poor awareness of non-invasive algorithms that can be used to assess the risk of advanced fibrotic non-alcoholic fatty liver disease (NAFLD) and these are use infrequently (d). AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyltransferase; FBC, full blood count; INR, international normalized ratio; BARD score, BMI + AST:ALT ratio + diabetes score; APRI, AST to platelet ratio index.

FIGURE 3 Flow diagram showing screening pathway for advanced hepatic fibrosis using Fib-4 in all those attending outpatient clinics in a large secondary/tertiary care setting. AST, aspartate aminotransferase; ALT, alanine aminotransferase; NAFLD, non-alcoholic fatty liver disease.

FIGURE 4 Number of individuals with Type 2 diabetes stratified by both alanine aminotransferase (ALT) and Fib-4 index using local reference ALT criteria (a) and the modified Prati *et al.* criteria [16]. (b). Patients with Type 1 diabetes stratified by both ALT and Fib-4 index using local reference thresholds (c) and the modified Prati *et al.* criteria [16] (d).

Table 1 Clinical characteristics of individuals, stratified by type of diabetes

Characteristic	Type 2 diabetes <i>n</i> =141	Type 1 diabetes <i>n</i> =251
Age, years	53.5 (15.4)	40.6 (16.7)
Men/Women, <i>n</i>	86/55	140/111
Duration of diabetes, years	12 (7.7)	21 (15.1)
ALT, U/L	32.2 (23.4)	22.5 (25.8)
AST, U/L	24.9 (13.7)	23.3 (22.3)
Platelets, $\times 10^9$ /L	275 (750)	275 (76)
Fib-4	1 (1.1)	0.8 (0.7)
Bilirubin, μ m/L	10 (5.4)	10.7 (7.1)
ALP, U/L	82.8 (40)	91.3 (73.3)
Albumin, g/L	37.8 (3.2)	37.9 (3.5)
Total cholesterol, mmol/L	4.7 (1.9)	4.5 (1.0)
Creatinine, μ mol/L	81.4 (34.8)	75.6 (35.4)
HbA _{1c} , mmol/mol	67 (21)	68 (18)
HbA _{1c} , %	8.4 (1.6)	8.4 (1.9)
Weight, kg	99.1 (27.5)	77.9 (16)
Systolic blood pressure, mmHg	148 (24)	138 (21)
Diastolic blood pressure, mmHg	84 (12.2)	83 (16)
Indeterminate/high Fib-4 (>1.29), <i>n</i> (%)	29 (20.6)	41 (29.0)
High Fib-4 (>2.67), <i>n</i> (%)	4 (2.8)	4 (1.6)
High ALT* (>40U/L), <i>n</i> (%)	32 (22.7)	14 (5.6)
High ALT [†] (>30U/L men, >19 U/L women), <i>n</i> (%)	66 (46.8)	57 (22.7)

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase.

Data are mean (SD), unless otherwise stated.

*Local reference criteria. [†]Prati *et al.* criteria [16].

Fig 1a

Please rate how you feel about the statements below.					
Statement	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
"NAFLD is a condition that does not impact significantly on the majority of patients with diabetes that I treat"	12.1%	49.2%	16.7%	20.5%	1.5%
"Whilst a lot is talked about NAFLD, I do not perceive this as a significant problem in my clinics"	13.6%	43.2%	25.8%	16.7%	0.8%
"I am concerned about missing a diagnosis of severe NAFLD"	0.8%	17.6%	16%	50.4%	15.3%
"I do not think my patients with diabetes are aware of NAFLD"	3%	2.3%	0.8%	47.4%	46.6%

Fig 1b

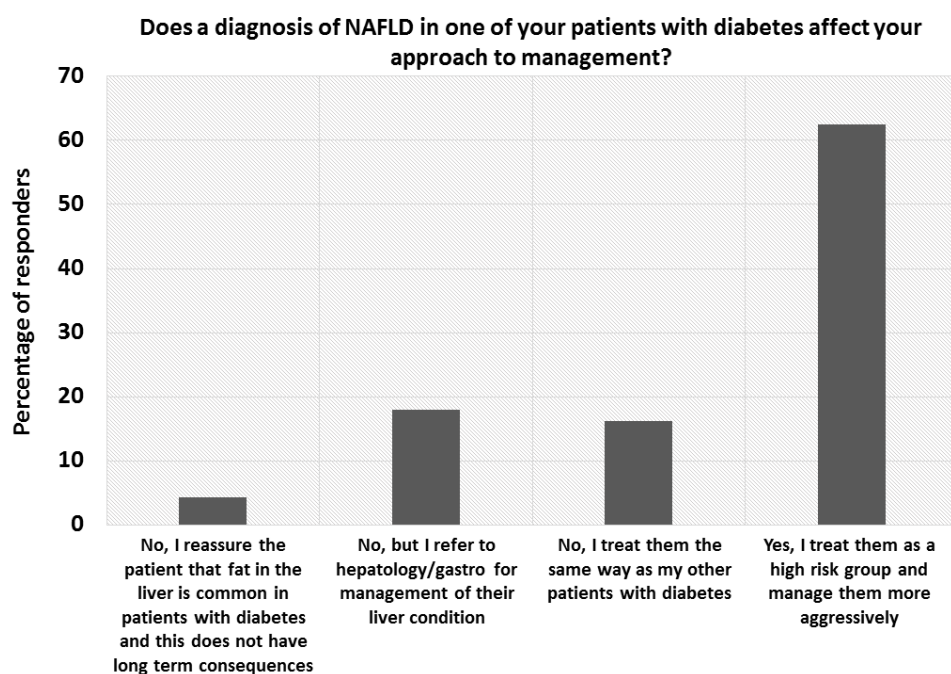


Fig
1c

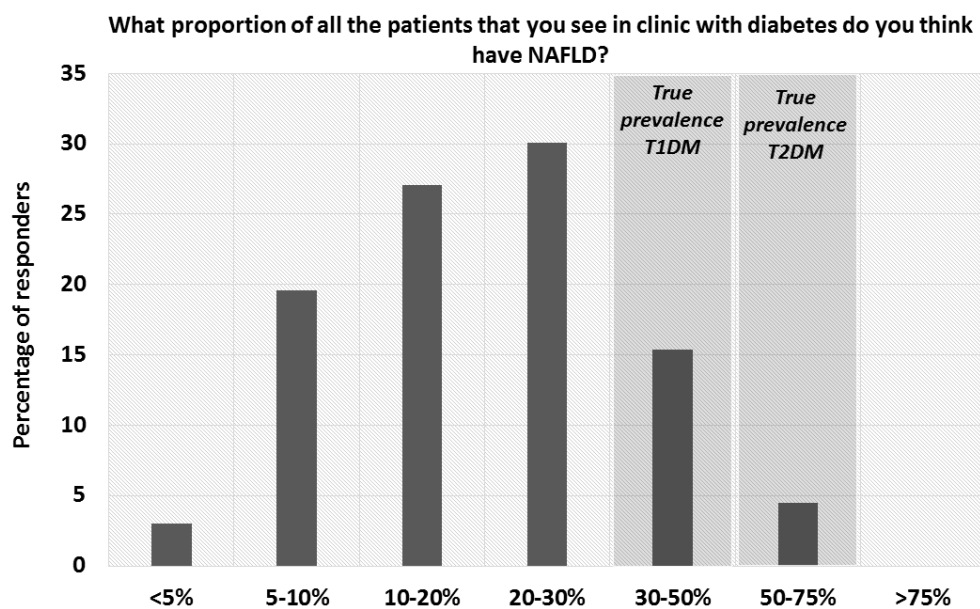


Fig
1d

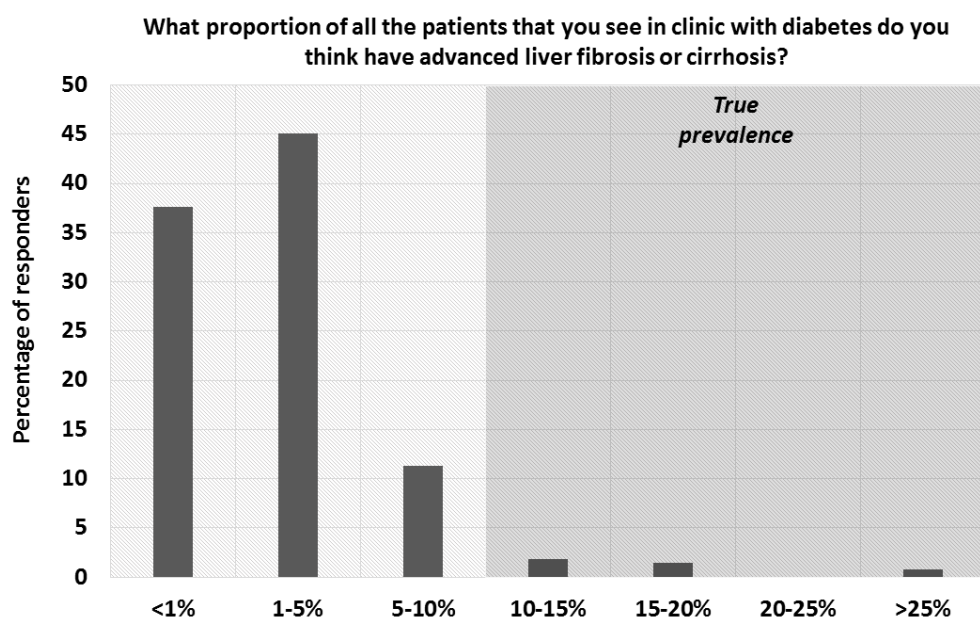
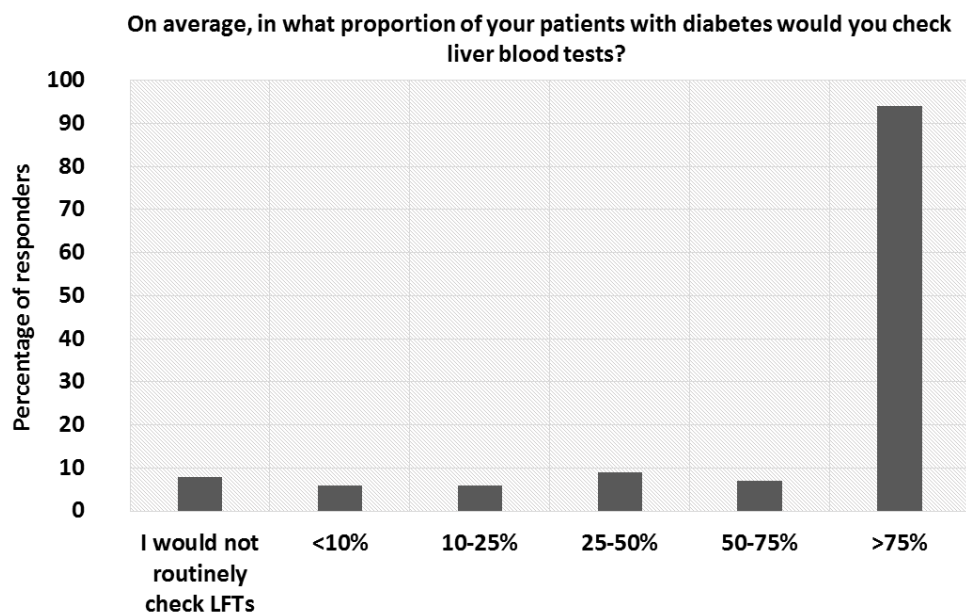


Fig
2a



b

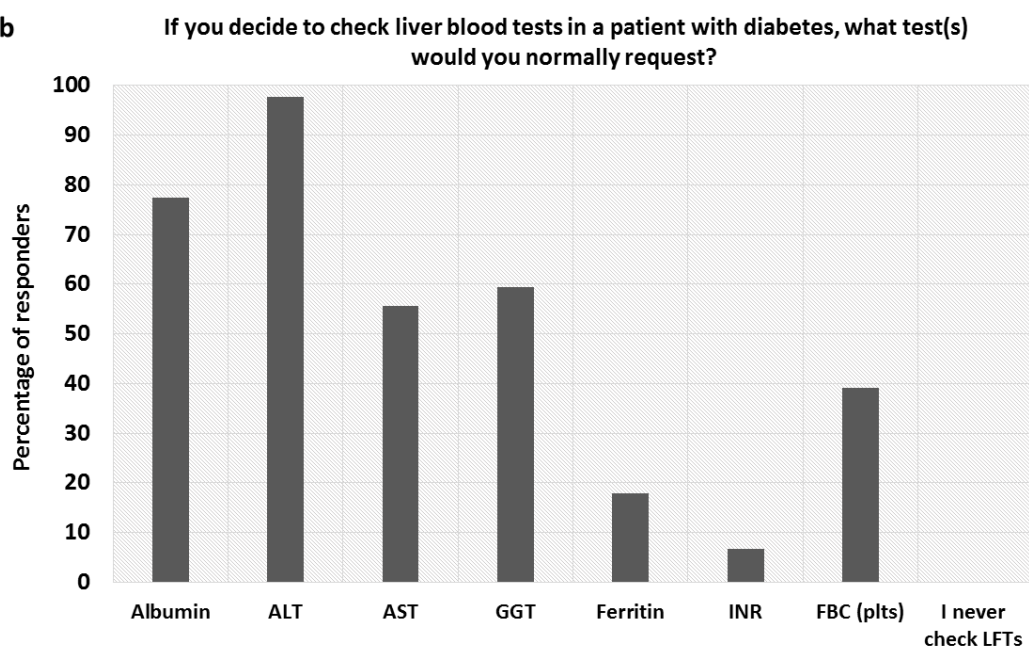


Fig 2c

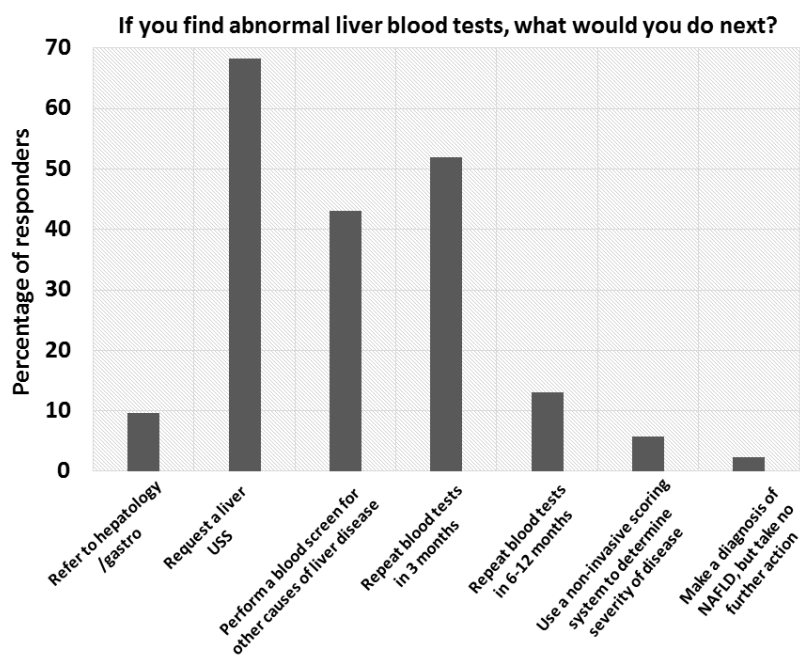


Fig 2d

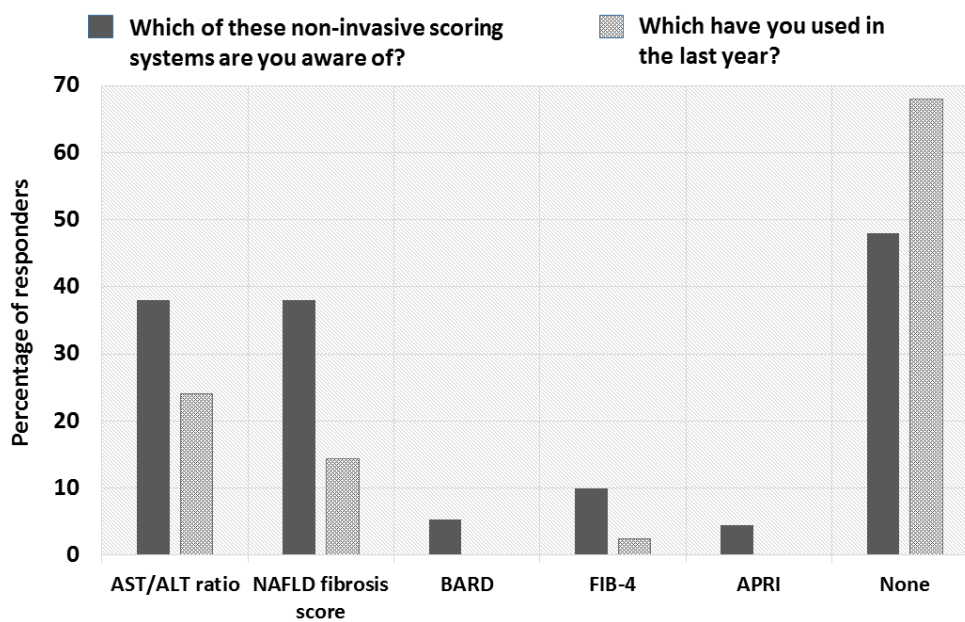


Figure 3

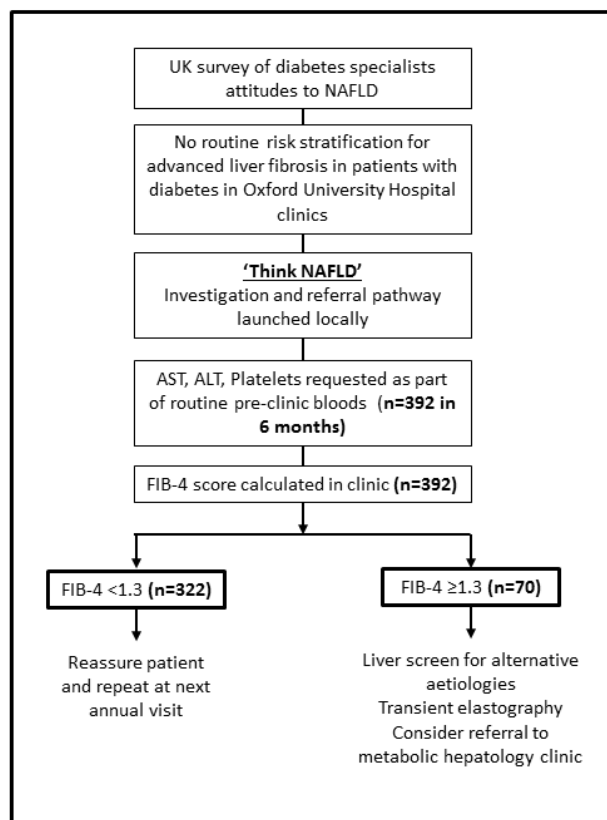


Figure 4

