Prevalence and markers of advanced liver disease in type 2 diabetes

R.M. WILLIAMSON1, J.F. PRICE2, P.C. HAYES3, S. GLANCY4, B.M. FRIER5, G.I. JOHNSTON6, R.M. REYNOLDS7 AND M.W.J. STRACHAN1 ON BEHALF OF THE EDINBURGH TYPE 2 DIABETES STUDY INVESTIGATORS

From the 1Metabolic Unit, Western General Hospital, Edinburgh EH4 2XU, 2Centre for Population Health Sciences, The University of Edinburgh, Edinburgh EH8 9AG, 3Department of Hepatology, Royal Infirmary of Edinburgh, Edinburgh EH16 4SA, 4Department of Radiology, Western General Hospital, Edinburgh EH4 2XU, 5Department of Diabetes, Royal Infirmary of Edinburgh, Edinburgh EH16 4SA, 6Pfizer Global R&D, Sandwich, Kent CT13 9NJ and 7Endocrinology Unit, University/BHF Centre for Cardiovascular Science, University of Edinburgh, Queens Medical Research Institute, Edinburgh EH16 4TJ, UK

Address correspondence to Dr Rachel Williamson, Western General Hospital, Crewe Road South, Edinburgh EH4 2XU, UK. email: rachel.williamson@luht.scot.nhs.uk

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Summary

Background: Type 2 diabetes is a risk factor for progression of non-alcoholic fatty liver disease (NAFLD) to fibrosis and cirrhosis. We examined the prevalence of advanced liver disease in people with type 2 diabetes and analysed the effectiveness of liver function tests (LFTs) as a screening tool.

Methods: Participants (n = 939, aged 61–76 years) from the Edinburgh Type 2 Diabetes Study, a randomly selected population of people with type 2 diabetes, underwent abdominal ultrasonography. Hyaluronic acid (HA) and platelet count/spleen diameter ratio (PSR) were used as non-invasive markers of hepatic fibrosis and portal hypertension. Subjects were screened for secondary causes of liver disease that excluded them from a diagnosis of NAFLD. The efficacy of LFTs [alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT)] in screening for liver disease was determined.

Results: Cirrhosis was identified by ultrasound in four participants (0.4%). Ten (1.1%) had evidence of portal hypertension (PSR < 909), and two (0.2%) had hepatocellular carcinoma. Fifty-three participants (5.7%) had evidence of hepatic fibrosis (HA > 100 ng/ml in the absence of joint disease); a further 169 had HA > 50 ng/ml. In participants with NAFLD-related fibrosis (HA > 100 ng/ml), 12.5% had an elevated ALT level and 17.5% had an elevated GGT level.

Conclusions: The prevalence of hepatic fibrosis and cirrhosis were lower than expected. The use of LFTs to screen for liver disease missed most cases of fibrosis predicted by raised HA levels.

Introduction

Non-alcoholic fatty liver disease (NAFLD) refers to hepatic steatosis in the absence of a defined secondary cause. NAFLD is associated with type 2 diabetes and estimates of prevalence of NAFLD in this group have varied, the highest being 70%. Using a validated ultrasound measure and detailed exclusion of secondary causes of liver disease, we recently reported a prevalence of NAFLD of 42.6% in over 900 older people with type 2 diabetes.2
NAFLD encompasses a spectrum of liver disease from simple steatosis to steatohepatitis, fibrosis and ultimately cirrhosis. In the general population of people with simple steatosis secondary to NAFLD, an estimated 8% progress to advanced fibrosis and cirrhosis, and this figure is higher when steatohepatitis is evident at presentation. Although type 2 diabetes is considered a risk factor for the progression of NAFLD, few studies have examined the prevalence of advanced liver disease in this population. Existing evidence is either indirect or has originated from small studies or those undertaken in highly selected populations. In one population-based study, the risk of death from liver cirrhosis was 2.5 times higher in people with type 2 diabetes compared with the general population. In another study of 132 patients with NAFLD (44 of whom had diabetes) who had undergone liver biopsy in a tertiary referral centre, 25% of those with diabetes had cirrhosis, compared to 10% of the non-diabetic cohort.

Screening for liver disease in Type 2 diabetes generally involves the measurement of standard liver function tests (LFTs) alone. Previous studies, however, suggest that LFTs may be poorly sensitive in differentiating those with NAFLD and NAFLD from those with normal livers. Furthermore, it is known that NAFLD can progress to fibrosis without significant elevation of LFTs. It has been suggested that lowering the upper limit of normal of alanine aminotransferase (ALT) to 30 U/l in men and 19 U/l in women may improve sensitivity of this measure in detecting NAFLD, but this has not been widely adopted. It is therefore likely that many cases of NAFLD in the population with diabetes are not identified and progressive liver disease is often missed. However, few data are available on the applicability of LFTs to diagnose hepatic fibrosis in people with diabetes.

Other approaches have been taken in the pursuit of a reliable non-invasive method of distinguishing those patients who have significant fibrosis. Hyaluronic acid (HA) is a component of the extracellular matrix, whose production is increased, and degradation by the liver decreased, in hepatic fibrosis. Several small studies have suggested that cut-off values of 42–50 ng/ml give optimal sensitivity and specificity in determining the presence of significant fibrosis. Higher levels may be associated with increasing severity of liver disease and increased specificity in diagnosing fibrosis and cirrhosis. One study suggested that a level >100 ng/ml had a 78% specificity and 83% sensitivity for predicting cirrhosis, with specificity being raised to 96% if a cut-off of 300 ng/ml was used. One potential confounder is that levels of HA can also be raised in patients with active joint disease.

Other routinely available markers that are predictive of fibrosis have been combined into scoring systems. The BAAT score assigned one point for each combination of increased age, BMI, ALT and triglycerides, and while a score of two gave 71% sensitivity and 80% specificity in detecting septal fibrosis, a score of three gave 14% sensitivity but 100% specificity. The BARD score allocated one point for each combination of increased BMI and the presence of diabetes, and two points for aspartate aminotransferase (AST): ALT ratio >0.8 – with a cut-off of two points, the positive predictive value (PPV) and negative predictive value (NPV) of determining severe fibrosis were 43% and 96%, respectively. The NAFLD fibrosis score, using a formula combining age, BMI, the presence of diabetes, AST:ALT ratio, albumin and platelet levels, classified 75% of participants low- or high-risk groups for severe fibrosis, with a low cut-off (below −1.455) giving a NPV of 93% and a high cut-off (above 0.676) a PPV of 90%.

Ultrasound scanning has diagnostic accuracy of 80–86% in the diagnosis of cirrhosis or extensive fibrosis in chronic liver disease and can detect consequences of portal hypertension such as increased spleen size. A low platelet count is a well-established marker of splenomegaly, and the platelet count/spleen diameter ratio (PSR) has been shown to be a reliable predictor of oesophageal varices in people with cirrhosis and can therefore be used as a surrogate marker of portal hypertension.

Hepatocellular carcinoma (HCC) is a well-recognized complication of hepatic cirrhosis. Diabetes is an established risk factor for HCC and in one population-based study, diabetes was associated with around a 2.5-fold increase in incidence of HCC, independent of alcohol intake and viral hepatitis. The prevalence of HCC in the general population of people with type 2 diabetes, however, remains unclear.

The present study aimed to estimate the prevalence of fibrosis, cirrhosis and HCC, using a range of different markers and scoring systems, in a randomly selected population of people with type 2 diabetes [the Edinburgh Type 2 Diabetes Study (ET2DS)] and to analyse the effectiveness of LFTs in screening for liver disease in this population.

**Methods**

**Participants**

The selection of subjects for the ET2DS has been described previously in detail. Briefly, subjects...
recorded as having type 2 diabetes mellitus, aged 60–74 years, were selected at random into sex and 5-year age bands from the Lothian Diabetes Register, a computerized database, which contains details of >20 000 patients with type 2 diabetes living in Lothian, Scotland, and includes both patients attending hospital and those seen only in primary care. Invitations to participate were sent to 5454 people and, of these, 1066 (20%) attended a baseline clinic. The clinical characteristics upon which the diagnosis of type 2 diabetes mellitus was confirmed has previously been described in detail.\textsuperscript{21} In brief, a diagnosis of diabetes was accepted in any individual treated with oral antidiabetic agents and/or insulin, and in any individual treated with dietary modification alone whose HbA1c was >6.5%. The clinical records of all subjects treated with dietary modification alone and with an HbA1c \( \leq \) 6.5% at the research clinic were reviewed by a consultant diabetologist (MWJS) to ensure that the diagnosis of diabetes was accurate. With regard to the classification of ‘type 2’ diabetes, the clinical records of individuals who either (i) started on insulin within one year of diagnosis of diabetes, (ii) reported evidence of pancreatic surgery or disease at the research clinic or (iii) were treated with insulin and were aged <35 years at diagnosis were also reviewed. Such individuals were considered to be at greatest risk of mis-classification. Any subject in whom it was not possible to confirm a clinical diagnosis of type 2 diabetes by review of hospital or general practitioner records was excluded. Study participants have been shown previously to be representative of all those randomly selected to participate and therefore of the target population of older men and women with type 2 diabetes living in the general population.\textsuperscript{2} A total of 939 subjects participated in the Year 1 clinic, a re-attendance rate of 88%. Baseline characteristics of those attending the Year 1 clinic have been shown to be similar to the full study population, suggesting that they remained representative of the target population.\textsuperscript{2} All participants gave written informed consent. The local ethics committee gave ethical approval for the study.

**Procedures**

Subjects attended a specially established research clinic, based in the Wellcome Trust Clinical Research Facility, Western General Hospital, Edinburgh, at baseline and after one year (Year 1). At Year 1, participants attended, after a 4-h fast, for an ultrasound examination of abdomen and venous blood sampling.

All ultrasound examinations were performed by a single ultrasonographer as previously described.\textsuperscript{2,21} Participants were given an overall liver grading based on a subjective measurement of the severity of steatosis. Validation of the ultrasound gradings for hepatic steatosis with \( ^1\)H magnetic resonance spectroscopy, the non-invasive gold standard for quantification of hepatic fat, in a subgroup of 58 participants has previously been described in detail.\textsuperscript{22} Evidence of cirrhosis was sought systemically and spleen length was measured.

Alcohol intake, use of hepatotoxic medications (amiodarone, isoniazid, methotrexate, tamoxifen and glucocorticoids) within the previous 6 months and history of joint disease were determined by questionnaire. Those participants with evidence of hepatic steatosis or abnormal blood tests of liver function had further tests performed for liver disease performed including serology for Hepatitis B and C, anti-nuclear antibody (ANA), anti-smooth muscle antibody, anti-mitochondrial antibody, ferritin and alpha fetoprotein (AFP). In addition, all participants (including those with normal liver and LFTs) seen after a certain date had these same screening blood tests performed (\( n = 644 \)). Triglycerides and HDL cholesterol were measured at Year 1. BMI, platelets and HA had been previously measured at the baseline clinic.

Participants who had significant abnormalities on hepatic USS or blood tests were referred for standard follow-up within the National Health Service. Those with focal lesions on USS had these reviewed by a consultant radiologist and received further imaging as necessary, and those with raised AFP \( > 20 \) kU/l were referred for review in a liver clinic.

Data on previous diagnoses of chronic liver disease were collected from participants by questionnaire at Year 1. In addition, data on liver diagnoses were obtained at baseline from discharge summaries via record linkage at the Information and Services Division of NHS Scotland (ISD linkage).

Upper limits of normal on the laboratory reference range of bilirubin (Bi), ALT, AST and gamma-glutamyl transferase (GGT) were 18 \( \mu \)mol/l, 50 U/l, 45 U/l and 55 U/l respectively. Analysis was also carried out using lower upper limits of normal for ALT—30 U/l for men and 19 U/l for women.\textsuperscript{10}

**Definition of NAFLD, PSR, hepatic fibrosis and HCC**

NAFLD was defined as the presence of hepatic steatosis on ultrasound scan in the absence of a secondary cause for hepatic steatosis. In addition, for this study, the definition was widened to include people with markers of fibrosis but no evidence of hepatic...
steatosis on ultrasound, in acknowledgement of the fact that steatosis can regress in patients with significant fibrosis. Secondary causes were defined as alcohol consumption ≥14 U/week or participant report of a current or previous problem with alcohol excess, use of hepatotoxic medication (glucocorticoids, isoniazid, methotrexate, amiodarone and tamoxifen) within the 6 months prior to the Year 1 clinic, positive hepatitis B or C serology, ferritin > 1000 μg/l, clinically significant positive immunology titres (anti-smooth muscle antibody titre ≥ 1:160 or anti-mitochondrial antibody titre ≥ 1:40) or a previous diagnosis of a secondary cause for chronic liver disease (alcoholic liver disease, autoimmune hepatitis, primary biliary cirrhosis, cholangitis or liver metastases). Subjects were considered to have a previous diagnosis of a secondary cause for chronic liver disease if ISD linkage revealed such a diagnosis, or if a participant report of a diagnosis was confirmed by their medical records.

PCR was defined as the ratio of platelet count (per cubic millimetre) to spleen diameter (millimetre). Hepatic fibrosis was defined on the basis of HA levels—values of >100 ng/ml, in the absence of arthritis, were taken as evidence of definite fibrosis and possible cirrhosis. A cut-off of 50 ng/ml was taken to indicate possible fibrosis, values >75 ng/ml are also reported as this is the upper limit of normal on our laboratory reference range. HCC was defined, in accordance with accepted guidelines, by one of the following: two imaging techniques showing a focal lesion over 2 cm in diameter with arterial hypervascularisation; one imaging technique showing a focal lesion >2 cm in diameter in association with AFP levels > 400 ng/ml (484 kU/l); suggestive histology following biopsy of a lesion.

Fibrosis clinical scoring systems

Participant scores on established scoring systems (BAAT, BARD and NAFLD fibrosis scores) were calculated. The BAAT scoring system is outlined above. NAFLD fibrosis score was calculated as previously published. Scores of 2–4 on both the BAAT and BARD scores were considered to be predictive of hepatic fibrosis. On the NAFLD fibrosis score, a score of >0.676 was considered to be predictive of fibrosis, and a score of −1.455–0.676 was indeterminate for fibrosis. In view of the fact that these systems have been developed to assess the severity of NAFLD alone, they were used only in those participants in whom another secondary cause for liver disease had been excluded.

Statistical analyses

Statistical analysis was performed using SPSS software version 14.0 (SPSS Inc., Illinois, USA). Data not conforming to a normal distribution (in this study GGT measurements) were log-transformed prior to parametric analysis. Statistical analysis included the one-way analysis of variance and chi-squared test to compare biochemical characteristics between groups. PPV and NPV were used to analyse the utility of LFTs in predicting hepatic fibrosis.

Results

Prevalence of markers of fibrosis, cirrhosis and HCC

Baseline characteristics of the 939 participants, aged 61–75 years, who attended the Year 1 clinic are shown in Table 1. Hepatic cirrhosis on ultrasound scan was found in four members of the study population, a prevalence of 0.4%. Portal hypertension,

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Year 1 (n = 939)</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>68.9 ± 4.2</td>
</tr>
<tr>
<td>Sex [% (n) male]</td>
<td>52.0 (488)</td>
</tr>
<tr>
<td>Race [% (n) Caucasian]</td>
<td>98.3 (923)</td>
</tr>
<tr>
<td>BMI- measured at baseline clinic (kg/m²)</td>
<td>31.3 ± 5.7</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>9.0 ± 6.4</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.2 ± 1.1</td>
</tr>
<tr>
<td>Diet-controlled [% (n)]</td>
<td>19.4 (182)</td>
</tr>
<tr>
<td>Oral anti-diabetic agent users [% (n)]</td>
<td>74.4 (699)</td>
</tr>
<tr>
<td>Metformin users [% (n)]</td>
<td>63.7 (598)</td>
</tr>
<tr>
<td>Thiazolidinedione users [% (n)]</td>
<td>17.5 (164)</td>
</tr>
<tr>
<td>Insulin users [% (n)]</td>
<td>15.8 (148)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>138.1 ± 18.5</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>74.1 ± 9.6</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.2 ± 0.8</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol (mmol/l)</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol (mmol/l)</td>
<td>2.2 ± 0.7</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td>1.7 ± 0.9</td>
</tr>
<tr>
<td>Statin users [% (n)]</td>
<td>81.6 (767)</td>
</tr>
<tr>
<td>Aspirin users [% (n)]</td>
<td>67.7 (636)</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitor users [% (n)]</td>
<td>52.0 (488)</td>
</tr>
<tr>
<td>Current or ex-smokers [% (n)]</td>
<td>60.0 (563)</td>
</tr>
</tbody>
</table>

Data are mean±standard deviation or proportions, in whole cohort of participants unless stated (number of participants in brackets)
defined as a platelet count/spleen diameter ratio <909, was present in 10 participants (1.1%), including one participant who had cirrhosis on ultrasound scan. A total of 876 participants were fully assessed for secondary causes of liver disease. Of these, 663 participants had no secondary cause identified, and in this subgroup findings suggestive of fibrosis or cirrhosis would be presumed secondary to NAFLD. Hepatic cirrhosis on ultrasound scan was found in one person (0.2%) in this subgroup and low platelet count/spleen diameter in four other people (0.6%).

The prevalence of definite hepatic fibrosis, defined as HA level > 100 ng/ml in the absence of joint disease, was 5.7% in the entire study population of 939 participants. The corresponding figures for HA level > 50 ng/ml and > 75 ng/ml were 23.6% and 12.2%, respectively. Of the population, 0.5% had HA level > 300 ng/ml. An additional 20.6% of participants had HA levels > 50 ng/ml but also had evidence of arthritis. Of the 13 participants with evidence of cirrhosis on ultrasound scan or a low platelet count/spleen diameter ratio, four (30.8%) had HA levels 50–100 ng/ml and a further six (46.2%) had HA levels > 100 ng/ml.

In the subgroup of participants with no secondary cause for liver disease, 40 participants (6.1%) had HA > 100 ng/ml in the absence of joint disease, 166 participants (25.2%) had HA > 50 ng/ml, 86 participants (13.0%) had HA > 75 ng/ml and 4 participants (0.6%) had HA > 300 ng/ml.

Two participants had definite HCC, a prevalence in the study population of 0.2%. In one case, this was confirmed on histology following biopsy of a 3.7 cm liver mass on a background of cirrhosis seen on USS, in association with raised AFP levels of 40 kU/l. A second participant had a very high AFP (2712 kU/l); no mass was seen on USS, but appearances on magnetic resonance imaging were supportive of a diagnosis of HCC. Neither participant had a secondary cause for liver disease, giving a prevalence of 0.3% in the group with possible NAFLD.

### Comparison of clinical fibrosis scoring systems with radiological and biochemical markers

The three clinical scoring systems for prediction of fibrosis secondary to NAFLD were used as alternative means of calculating prevalence of fibrosis in the subgroup with no secondary cause for liver disease. The BARD score was positive in 92.6% compared to 79.3% for the BAAT score, while 16.4% of the subgroup had a positive NAFLD Fibrosis Score, and in a further 66.8% this score was indeterminate.

The only participant in this subgroup to have cirrhosis on ultrasound scan had positive BARD, BAAT and NAFLD Fibrosis scores. When the prevalence of positive fibrosis scores were compared across three groups based on HA measurements [HA < 50 ng/ml (or arthritis present); HA 50–100 ng/ml in the absence of arthritis; and HA > 100 ng/ml in the absence of arthritis], the only positive correlation was with the NAFLD fibrosis score with the prevalence of a positive score rising from 13.7% to 21.3% to 42.5% in the three HA groups respectively \((P<0.001)\). Conversely, 72.5% of those with a positive NAFLD fibrosis score had a HA measurement >50 ng/ml.

### Comparison of tests of liver function with markers of fibrosis

Standard tests of liver function were compared between three groups according to the HA level in

<table>
<thead>
<tr>
<th>Test</th>
<th>HA &lt; 50 ng/ml (n = 494)</th>
<th>HA 50–100 ng/ml (n = 126)</th>
<th>HA &gt; 100 ng/ml (n = 40)</th>
<th>Cirrhosis on USS (n = 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT (U/l)</td>
<td>33.3 (12.5)</td>
<td>34.0 (13.5)</td>
<td>34.9 (14.5)</td>
<td>38.0</td>
</tr>
<tr>
<td>ALT &gt; 50 U/l, n (%)</td>
<td>34 (6.9)</td>
<td>9 (7.1)</td>
<td>5 (12.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>AST (U/l)</td>
<td>30.1 (9.9)</td>
<td>31.5 (9.4)</td>
<td>35.3 (12.6)*</td>
<td>62.0</td>
</tr>
<tr>
<td>AST &gt; 45 U/l, n (%)</td>
<td>29 (5.9)</td>
<td>8 (6.3)</td>
<td>4 (10.0)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>GGT (U/l, mean logGGT)</td>
<td>1.2 (0.3)</td>
<td>1.2 (0.3)</td>
<td>1.4 (0.5)*</td>
<td>1.6</td>
</tr>
<tr>
<td>GGT &gt; 55 U/l, n (%)</td>
<td>36 (7.3)</td>
<td>7 (5.6)</td>
<td>7 (17.5)*</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

HA, hyaluronic acid.

*Significant differences between the groups stratified according to HA level by one-way ANOVA or chi-squared test \((P<0.05)\).

Data are mean ± standard deviation unless stated otherwise.
participants with no secondary cause for liver disease (Table 2). Mean levels of ALT, AST and GGT remained within the laboratory normal reference range in all three groups. Similarly, mean levels of ALT, AST and GGT remained within the normal range in all three groups when participants were divided according to NAFLD fibrosis score (less than 1.455; 1.455 to 0.676; and >0.676: data not shown). The PPV and NPV of ALT and GGT in predicting fibrosis as diagnosed using HA levels and the NAFLD fibrosis score are presented in Table 3.

The PPV and NPV of proposed new upper limits of normal of ALT (>30 U/l for men; >19 U/l for women) are also shown in Table 3.

Conclusions
Detection of advanced liver disease using non-invasive methods is challenging. This study examines the prevalence of markers of hepatic fibrosis and cirrhosis, and their relationship to standard tests of liver function, in a large randomly selected cohort of older people with Type 2 diabetes. The prevalence of hepatic fibrosis was 5.7% and that of ultrasound-diagnosed cirrhosis under 1%. The use of LFTs as a screening tool missed the majority of cases of fibrosis predicted by raised HA levels and the NAFLD fibrosis score are presented in Table 3.

The PPV and NPV of proposed new upper limits of normal of ALT (>30 U/l for men; >19 U/l for women) are also shown in Table 3.

Subjects in this study were all aged 61–76 years at the time of examination and were predominantly Caucasian. Previous studies have shown that the prevalence of NAFLD and its progression to fibrosis and cirrhosis increases with age. It is therefore possible that the results from our study population may not be representative of those from other age ranges. At baseline, approximately one-fifth of people invited to attend from the Lothian Diabetes Register did so—analysis suggested that this population was representative of that invited, most importantly in terms of duration of diabetes, HbA1c and treatment with insulin.

HA was the main marker of fibrosis used in this study, with cut-offs for fibrosis and cirrhosis defined as in previous reports.11–15 Liver biopsy, the gold standard, would have been neither feasible nor ethical, and in contrast HA measurement is relatively non-invasive. We attempted to improve specificity by excluding participants with arthritis (another cause of raised HA) from the fibrosis categories, and also by using a high cut-off (100 ng/ml) for our definition of definite evidence of fibrosis. While we can be reasonably confident that the proportion of the study population with fibrosis is >5.7% (those with HA levels >100 ng/ml, without joint disease), it is possible that the prevalence of fibrosis was lower than the 26% predicted by HA levels >50 ng/ml.

A low platelet count is a well-established consequence of hypersplenism, and the platelet count/spleen diameter has previously been validated as a marker of portal hypertension.20 This validation was,
however, carried out in patients with known cirrhosis, and it is possible that its use is less applicable in our study population. In particular, it is possible an alternative diagnosis may have underpinned the finding of hypersplenism in some of our participants, and this may have contributed to the lack of overlap seen in our measures of cirrhosis and platelet count/spleen diameter ratio.

The prevalence of HCC in our cohort was 0.2%, a figure which is comparable to that previously found on screening both a general population in Italy (prevalence of 0.7%).\textsuperscript{24} It is also in keeping with the only previous large-scale study, carried out in Taiwan,\textsuperscript{25} that has looked at prevalence of HCC in a subgroup of people with type 2 diabetes, in which the prevalence was 0.1%. This population, unlike ours, had a high prevalence of viral hepatitis. In contrast, prevalence of HCC is higher in populations with known cirrhosis, and in one small-scale study the prevalence in an obese group with cryptogenic cirrhosis was 30%.\textsuperscript{26}

Although significant increases were noted in the values of some conventional LFTs through the groups with increasing evidence of liver damage, mean values remained within normal limits. This is consistent with previous studies which have shown that progression to cirrhosis can occur without major perturbation in the LFT values.\textsuperscript{5} Although the NPVs for ALT and GGT were high in predicting lower HA levels, these values are affected by the very low population prevalence of fibrosis. The use of lower values for the upper limit of normal of ALT did not materially change the results. Currently, liver screening in type 2 diabetes is carried out using conventional LFTs alone, and our data suggest that such an approach misses the majority of cases of hepatic fibrosis.

The only clinical scoring system to positively correlate with HA measurements was the NAFLD fibrosis score, which predicted definite fibrosis in 16.4% of participants with no secondary cause for liver disease. A further 66.8% of subjects had an indeterminate score. This is a much higher proportion than in the original article, which suggested that such patients should be considered for liver biopsy.\textsuperscript{18} The BARD and BAAT scores both estimated that a very high percentage of participants in this study had fibrosis but in view of the emphasis on age, BMI and diabetes in these scoring systems, this could have been anticipated. Interestingly, when the BARD score was validated in a subgroup with type 2 diabetes in the initial study, the AUC was lower than in the group as a whole (0.53 vs. 0.80). This supports the concept that these more simple scoring systems, while useful in the general population of patients with NAFLD, may be less applicable to populations of people with type 2 diabetes. The risk of their indiscriminate use is that they may identify large numbers of patients for biopsy without any definitive evidence of a high prevalence of advanced liver disease.

In conclusion, this study provides an estimate of prevalence of hepatic fibrosis in a large population of older people with type 2 diabetes. There are challenges in detecting advancing liver disease, and current screening methods using conventional LFTs are almost certainly inadequate. Further work is required to refine identification of these patients, particularly in those in whom liver biopsy would be difficult to justify. This may require a panel of biochemical markers, for example, the Enhanced Liver Fibrosis panel or cytokeratin-18, or a radiological method such as transient elastography.

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