Research Article

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Presence and severity of non-alcoholic fatty liver disease in a large prospective primary care cohort

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Background & Aims: Non-alcoholic fatty liver disease (NAFLD) is a common cause of abnormal LFTs in primary care, but there are no data defining its contribution nor reporting the range of NAFLD severity in this setting. This study seeks to calculate the range of disease severity of NAFLD in a primary care setting.

Methods: Adult patients with incidental abnormal LFTs, in the absence of a previous history, or current symptoms/signs of liver disease were prospectively recruited from eight primary care practices in Birmingham. NAFLD was diagnosed as fatty liver on ultrasound, negative serological liver aetiology screen, and alcohol consumption $\leqslant$30 and $\leqslant$20 g/day in males and females, respectively. The NAFLD Fibrosis Score (NFS) was calculated to determine the presence or absence of advanced liver fibrosis in subjects identified with NAFLD.

Results: Data from 1118 adult patients were analysed. The cause of abnormal LFTs was identified in 55% (614/1118) of subjects, with NAFLD (26.4%; 295/1118) and alcohol excess (25.3%; 282/1118) accounting for the majority. A high NFS (>0.676) suggesting the presence of advanced liver fibrosis was found in 7.6% of NAFLD subjects, whereas 57.2% of NAFLD patients had a low NFS (<−1.455) allowing advanced fibrosis to be confidently excluded.

Conclusions: NAFLD is the commonest cause of incidental LFT abnormalities in primary care (26.4%), of whom 7.6% have advanced fibrosis as calculated by the NFS. This study is the first of its kind to highlight the burden of NAFLD in primary care and provide data on disease severity in this setting.

Keywords: Primary care; Non-alcoholic fatty liver; Fibrosis; Liver function test.
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Abbreviations: (A)LFT, (abnormal) liver function tests; UHB, University Hospital Birmingham; PCP, primary care practitioner; UK, United Kingdom; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; HCC, hepatocellular carcinoma; BALLETS, Birmingham and Lambeth Liver Evaluation Testing Strategies; USS, ultrasound; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; A-1AD, alpha 1 antitrypsin deficiency; HBV, viral hepatitis B; HCV, viral hepatitis C; AIH, autoimmune hepatitis; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; BMI, body mass index; NFS, NAFLD Fibrosis Score; IFG, impaired fasting glucose; NPV, negative predictive value; PPV, positive predictive value; MW, Mann, Whitney *U* test; IQR, interquartile range.

Introduction

The incidence of liver disease is rising throughout the world and now accounts for 1.5% of deaths in the UK (www.statistics.gov.uk). In parallel with this, there has been a year on year rise in the number of liver function test (LFT) profiles carried out in UK primary care practices (from 62,300 to 109,619/year between 2002 and 2010; University Hospital Birmingham (UHB) laboratories audit, UK). Primary care practitioners (PCPs) are thus commonly faced with the scenario of abnormal liver function tests (ALFT) in patients in whom there are no clinical risks, signs or symptoms of liver disease. Non-alcoholic fatty liver disease (NAFLD) is now recognized as the most common cause of hepatic dysfunction in general population [1,2], however, this is yet to be confirmed in primary care practice. Furthermore, because of the indolent asymptomatic nature of NAFLD, identifying those with advanced disease in whom specific interventions may be required remains a clinical challenge in primary care.

The prevalence of NAFLD has risen markedly to 14–34% of the general-population in Europe [2,3], Asia [4], and America [5] in recent years. Whilst patients with simple NAFLD are believed to have benign disease, there is now clear evidence that those who have progressed to non-alcoholic steatohepatitis (NASH) and fibrosis are at a much higher risk of developing hepatocellular carcinoma (HCC), liver failure, and death [6,7]. The majority of data describing the severity of liver fibrosis in NAFLD arises from selected populations in secondary referral centres [7–13]. In a large UK prospective study, Skelly *et al.*

demonstrated that 18% (23/120) of biopsy confirmed NASH patients had significant fibrosis after presenting to their secondary care centre with unexplained ALFTs [12]. This and other such studies [9,10] included patients in whom the decision to refer had been made on clinical grounds by PCPs/consultant colleagues and were then rigorously screened in liver clinics for other disease aetiologies prior to proceeding to liver biopsy. These studies are, therefore, influenced by ascertainment bias and may overestimate the severity of NAFLD emerging from primary care.

It is currently expected with the alarming growth of obesity and type 2 diabetes that the burden of NAFLD on primary care and liver services will continue to rise in the UK [14]. To date, no studies have determined the underlying disease severity of NAFLD in primary care. PCPs remain at the forefront of identifying the patients with advanced NAFLD who require further evaluation, closer surveillance for complications (and interventions where appropriate) and stricter lifestyle modifications. By investigating a large UK primary care sample of patients with incidental ALFTs and absent clinical features of liver disease, this study is the first of its kind to determine the presence and disease severity of silent NAFLD in a primary care setting.

Materials and methods

Study population

Birmingham and Lambeth Liver Evaluation Testing Strategies (BALLETS) is a prospective study of patients with an incidental finding of ALFTs in primary care funded by NIHR Health Technology Assessment program (http://www.hta.ac.uk/1459). Patients were prospectively recruited from primary care practices from Birmingham and Lambeth areas, between 2006 and 2008. The primary aim of the BALLETS study was to assess the clinical utility of ALFTs in patients in whom liver disease was not suspected clinically by the PCP. St. Thomas' Hospital Research Ethics Committee approved the study and all study participants gave signed informed consent to be included.

This current cross-sectional sub-study utilizes baseline data from patients enrolled in the BALLETS study from the eight primary care practices within the Birmingham region only. PCPs from participating practices reviewed all new incidental ALFT results arising from their practices in patients in whom the clinical suspicion of underlying liver disease was absent or low. Patients over eighteen years old were eligible for the sub-study if one or more LFT analyte was abnormal and there was no previous documented history of liver disease, intravenous drug use and/or alcohol-related health problems. Current signs or symptoms suggestive of liver disease, pregnancy, and a diagnosis of disseminated malignancy were also considered exclusion criteria. Eligible patients who consented for the study completed an interview during which current illnesses, past medical history, alcohol consumption, socio-demographic details, and drug history were recorded. Reasons for the original LFTs being ordered by the PCP were also recorded. Patient's height, weight, and waist circumference were measured. All patients had a repeat set of LFTs and a full serological liver aetiology screen (viral, genetic and autoimmune) at the study visit. An abdominal ultrasound scan (USS) was obtained in the fasted state using an ultrasound machine (TITAN® Sonosite) operated by one of five (10–30 years experience) abdominal sonographers. All scans were recorded on tape and 50 of these were selected at random and validated by a consultant radiologist (Olliff S).

PCPs were sent a consolidated report of all study investigations. The study team recommended to the PCP the need for a hepatology referral to the tertiary liver clinic (UHB) in the event of one of the following: (1) positive serological liver aetiology screen; (2) sonographic features of cirrhosis (coarse echotexture, irregular contour), space occupying liver lesion(s) or biliary duct dilatation. All liver clinic letters were retrospectively reviewed (until 1st May 2010) to identify which of these diagnoses were followed up and confirmed by a liver specialist (Supplementary Table 1).

Data definitions

The sub-study LFT profile consisted of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), total bilirubin, and albumin measurements. Seven of the eight Birmingham practices sent samples to a central laboratory at UHB, whilst the remaining practice sent samples to the laboratory of Russells Hall Hospital. Initial LFTs requested by the PCP were used as a criterion for study entry, whereas the repeat LFTs undertaken at the study visit were performed to increase the likelihood of a complete panel of the six analytes listed and to avoid analyte selection bias that may have occurred in the primary care practice. The analytes were classified as normal or abnormal based on reference ranges specific to each of the two individual laboratories, which are compliant with International Quality Control Standards (Supplementary Table 2). The full blood liver aetiology screen consisted of viral hepatitis B (HBV) surface antigen, viral hepatitis C (HCV) antibody, caeruloplasmin, iron and transferrin saturation, alpha-1 anti-tryspin, anti-smooth muscle, and anti-mitochondrial antibodies.

Body mass index (BMI) was defined as weight in kilograms divided by the square of the height in metres (kg/m^2). Obesity was defined as BMI $\geqslant$30 kg/m^2. Alcohol intake was reported as standard units (1 U = 10 g alcohol) of alcohol consumed on average per week in the 6 months prior to recruitment. Mild (female 1–7 U, male 1–11 U/week) and moderate (female 8–14 U, male 12–21 U/week) alcohol consumption were defined as drinking within the current UK health guidelines (female $\leqslant$14, male $\leqslant$21 U/week; British Medical Association 1995). At-risk alcohol consumption was defined as exceeding these guidelines.

For the purposes of this sub-study, type 2 diabetes was defined in patients with a documented history of the disease or a recorded drug history of anti-diabetic medication. Hypertension was defined as a past medical history of the disease or a current recorded drug history of two or more anti-hypertensive medications.

The diagnosis of NAFLD was based on the following criteria: (1) sonographic diagnosis of fatty liver, defined as diffusely increased liver echogenicity (>right renal parenchyma) with vascular blurring; (2) a negative history of alcohol consumption exceeding current UK health guidelines; and (3) exclusion of liver disease of other aetiology including drug-induced, autoimmune, viral hepatitis, cholestatic, metabolic and genetic liver disease.

NAFLD Fibrosis Score

The NAFLD Fibrosis Score (NFS) [8] is a simple non-invasive scoring system designed to identify or exclude advanced fibrosis (classified as Kleiner stages F3 and F4 [15]) in patients with an established diagnosis of NAFLD on imaging. The NFS was developed and validated by Angulo *et al.* [8] in over 700 liver biopsy-proven patients with NAFLD and is routinely used in liver clinics to select those at risk of disease progression and HCC. The NFS utilizes a number of simple clinical and laboratory independent predictors of advanced liver fibrosis: NFS = $-1.675 + 0.037 \times$ age (years) $+ 0.094 \times$ BMI (kg/m^2) $+ 1.13 \times$ IFG/diabetes (yes = 1, no = 0) $+ 0.99 \times$ AST/ALT ratio $- 0.013 \times$ platelet count ($\times 10^9$/L) $- 0.66 \times$ albumin (g/dl) [8]. The low cut-off score (<$-$1.455) has a negative predictive value (NPV) of 88–93% and the high cut-off score (>+0.676) has a positive predictive value (PPV) of 79–90% for the presence of advanced fibrosis in NAFLD in secondary care populations [8,16]. The NFS was calculated retrospectively using the web-based calculator (http://NAFLDscore.com).

As the original BALLETS study protocol did not incorporate a platelet count, retrospective data collection of the electronic haematology laboratory archive at the UHB enabled platelet counts within 6 months of patient enrolment to be recorded. To avoid false positive or false negative NFS, the scoring system was not applied to participants with a past medical history of platelet disorders, on myelosuppressive medications or an active systemic-inflammatory disease.

Statistical analysis

Descriptive statistics were applied to characterize the whole study cohort and the identified NAFLD group. Continuous clinical and laboratory variables are reported as medians and interquartile ranges (IQR) as all variables had a non-parametric distribution on D'Agostino and Pearson Omnibus Normality testing (GraphPad Prism 5). Categorical variables are reported as numbers and percentages. Due to a variation in normal reference ranges between the two laboratories utilized for the initial PCP LFT samples, blood results from Russell Hall Hospital (n = 89 patients) were standardised to the central laboratory reference ranges at UHB using the proportion of the upper (or lower with albumin) limit of normal.