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COMMENTARY

EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease: is universal screening appropriate?

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Abstract Non-alcoholic fatty liver disease (NAFLD) is very common in people with type 2 diabetes and although estimates for the prevalence NAFLD vary according to age, obesity and ethnicity, some studies have indicated that up to 75% of patients with type 2 diabetes may be affected. During the last 15 years there has been a vast amount of research into understanding the natural history, aetiology and pathogenesis of NAFLD; and now there is a better understanding of the strengths and limitations of diagnostic tests for NAFLD, the influence of lifestyle changes and the effects of potential treatments. With this advance in knowledge, it is apposite that a number of organisations have started to develop guidelines for the diagnosis and management of NAFLD. Given the high proportion of patients with type 2 diabetes who are affected by this liver condition, it is now important to consider how any guideline will affect the care, diagnosis and treatment of patients with type 2 diabetes. It is to the credit of the European Association for the Study of the Liver (EASL), the European Association for the Study of Diabetes (EASD) and the European Association for the Study of Obesity (EASO) that guidelines for NAFLD have been produced (*Diabetologia* DOI: 10.1007/s00125-016-3902-y) and a consensus achieved between these three organisations. The purpose of this commentary is to discuss briefly the EASL–EASD–EASO clinical practice guidelines with a focus on their relevance for clinicians caring for patients with type 2 diabetes.

Keywords ELF · Enhanced liver fibrosis · Guideline · NAFL · NASH · Non-alcoholic fatty liver disease · Non-alcoholic steatohepatitis · Non-alcoholic fatty liver · NAFLD diagnosis · Pioglitazone · Steatosis · Treatment · Type 2 diabetes

Christopher Byrne was asked by *Diabetologia* and the European Association for the Study of Diabetes to discuss the practical, ethical and economic implications of the EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. The views expressed are those of the authors and not those of the society.

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Abbreviations

ELF	Enhanced liver fibrosis
FDA	Food and Drug Administration
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis

Recent data from the USA shows that non-alcoholic fatty liver disease (NAFLD) is now the second most frequent indication for liver transplantation [1], with the prediction that it will become the most frequent indication in the next 10 years. Importantly, for clinicians caring for patients with diabetes, incident type 2 diabetes mellitus is a strong risk factor for developing clinically significant liver fibrosis [2]. Recently, it has become increasingly clear that NAFLD is also an emerging risk factor for cardiovascular disease, chronic kidney disease and, maybe, certain cancers [3].

It is now evident that NAFLD is a strong, independent risk factor for new-onset type 2 diabetes [4], and when type 2 diabetes occurs, this disease is a strong risk factor for liver-related hospital admissions and death [5]. Current evidence shows there is the potential for decreasing risk of incident type 2 diabetes with resolution of fatty liver [6], and certain therapies (such as pioglitazone) are effective for treating both hyperglycaemia and liver disease in NAFLD [7]. Thus, the time is now right to consider whether targeted case finding for NAFLD should be advocated for patients at high risk of, or with established, type 2 diabetes [8]. Consequently, given the growing evidence of a strong bi-directional link between type 2 diabetes and NAFLD, it is apposite that many scientific organisations, such as the National Institute for Health and Care Excellence (NICE) in the UK and the EASL, EASD and EASO, are now producing clinical practice guidelines for the diagnosis and management of NAFLD.

The EASL–EASD–EASO guidelines published in this edition of *Diabetologia* [9] recommend that individuals with metabolic risk factors should undergo liver ultrasonography (to identify liver fat) with additional assessment of serum liver enzyme concentrations. Depending on the presence (or not) of liver fat and whether serum liver enzyme concentrations are abnormal or not, the proposed guideline algorithm [9] then recommends further stratification according to the results of non-invasive fibrosis markers (that include the NAFLD fibrosis score, Enhanced Liver Fibrosis [ELF] or fibrosis 4 calculator [FIB-4] scores). Depending on the results of these tests, the algorithm recommends either follow-up at 3–5 years or specialist referral for a decision as to whether to undertake a liver biopsy, and/or initiation of therapy. Alternatively, for NAFLD patients with mild abnormalities of non-invasive fibrosis markers, further follow-up at 2 years with repeat testing is advocated. Obviously, advocating such a diagnostic strategy is predicated on the notion that

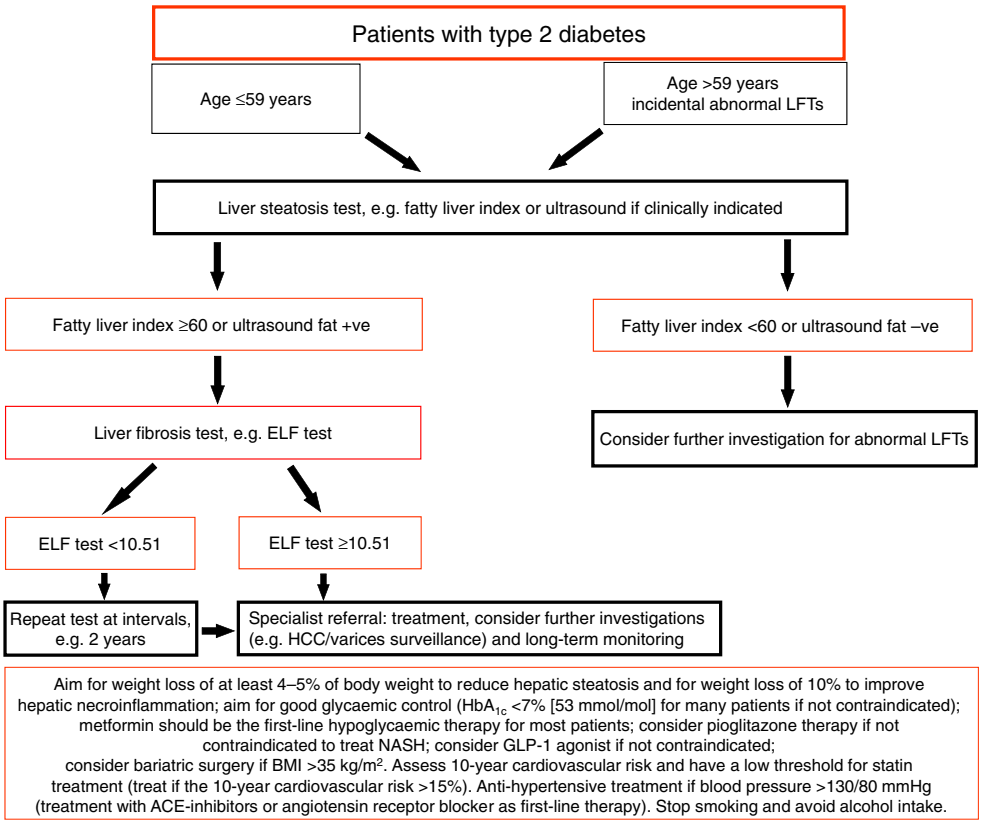

Fig. 1 Proposed pragmatic algorithm for the diagnosis and management of NAFLD in patients with type 2 diabetes. The algorithm has been developed by the authors using both available evidence and guidelines and also contains personal opinions of the authors where uncertainty exists and evidence is not available. For example, to date it is uncertain what age threshold should be applied and whether all patients with type 2 diabetes and NAFLD should be treated to a specific HbA_{1c}, LDL-cholesterol and blood pressure and whether all patients with a diagnosis of NAFLD should be advised to be abstain from alcohol. The algorithm can be used to identify patients for treatment. Although histological examination of the liver is the 'gold standard' to stage NAFLD severity, in our opinion, liver biopsy is not a feasible diagnostic test for the large numbers of patients who would potentially be eligible. In addition, we consider that liver biopsy is not a suitable test for monitoring responses to therapy or for following disease progression. Although presently not validated specifically in people with type 2 diabetes, we recommend that clinicians use the ELF test as a simple, inexpensive first-line test to identify people with clinically significant liver fibrosis. Whilst the NAFLD fibrosis score (see text) also has an acceptable sensitivity and specificity for identifying patients with significant fibrosis, this score is influenced by having diabetes as a component factor in the algorithm. Furthermore, below the threshold (>0.676 see text), the test has limited value for diagnosing or excluding significant fibrosis

the right patient groups are being targeted, the diagnostic tests are cost-effective, and a potential treatment/management plan exists that is both clinically effective and cost-effective.

Consequently, what are we to make of the EASL–EASD–EASO clinical practice guidelines that are advocating a paradigm shift in current clinical practice? Before considering this recommendation, it is important for us to bear in mind certain evidence that is pertinent to the debate that will no doubt result from publication of these guidelines. First, serum liver enzyme concentrations are sometimes normal in patients with NAFLD and these tests therefore cannot be used to diagnose or monitor disease status in NAFLD. Also, liver ultrasonography is a relatively expensive diagnostic test requiring equipment, technical expertise and usually a hospital visit. Ultrasonography is also a relatively insensitive technique for detecting liver fat (and cannot diagnose either liver inflammation or fibrosis in patients with non-alcoholic steatohepatitis [NASH]). In addition, liver fat infiltration must be at least 20–30%, before ultrasonography will enable diagnosis of hepatic steatosis (N.B. a diagnosis of hepatic steatosis can be made by more sensitive magnetic resonance-based techniques if the liver fat infiltration is >5% [10].) Serum fibrosis markers, such as the ELF score, have reasonable sensitivity and specificity for diagnosing advanced liver fibrosis (F3/F4 fibrosis on histology) and it is the severity of liver fibrosis that is the best prognostic marker of liver disease outcomes in NAFLD [11]. Finally, liver biopsy is an invasive and expensive diagnostic test (approximately £700 per person in the UK) that is also an unpleasant investigation for patients, associated with significant morbidity. Thus, liver biopsy is not a suitable investigation for monitoring disease progression or responses to therapy. With these caveats of liver biopsy, one also needs to be cautious how the results of treatment-induced improvements in liver histology should be interpreted. Currently, the US Food and Drug Administration (FDA) only recognises NASH as a clinical indication for treatment (and not fatty liver alone). The FDA decrees that for a 'treatment' to be considered effective in NASH, there must be at least a two-point improvement in the NAFLD Activity Score (NAS). The NAS is a composite score from a maximum of three points for the severity of liver fat, two points for ballooning of hepatocytes and three points for inflammation. In addition, the FDA requires that the treatment should also produce no progression of liver fibrosis. Thus, the conundrum we face at present is that improvements in NAS score are being used to judge the clinical efficacy of a new treatment, yet improvements in NAS score do not strongly predict changes in clinically relevant liver outcomes.

So, how should clinicians caring for type 2 diabetic patients proceed in 2016? The high prevalence of type 2 diabetes means that any case finding strategy to diagnose NAFLD that focusses on the whole population of type 2 diabetic patients will be very expensive. Since the cost-effectiveness of any case finding strategy will improve with its implementation at a younger vs older age, we consider that a targeted approach focussing on age stratification is sensible. However, we acknowledge that more cost-effectiveness modelling is required to identify a precise age cut-off for case finding of NAFLD. At present, since the mean age of incident type 2 diabetes in the UK is approximately 59 years, we suggest using that age to select patients with type 2 diabetes for NAFLD diagnostic tests. In our opinion, advocating the widespread use of ultrasonography as the preferred first-line diagnostic procedure for diagnosing hepatic steatosis is probably too expensive a procedure for public healthcare systems such as the UK National Health Service. Rather, the use of simpler surrogate markers for diagnosing liver fat, such as the fatty liver index (a composite score derived from BMI, waist circumference, fasting triacylglycerol and γ-glutamyltransferase [GGT] concentrations) would be a less expensive first-line approach that also has an acceptable sensitivity and specificity for identifying liver fat. Similarly, in type 2 diabetes, patients who have a 'positive' fatty liver index (≥60), the use of non-invasive fibrosis marker tests, e.g. the ELF score, with a threshold of ≥10.51 (or perhaps a NAFLD fibrosis score >0.676) could be a relatively inexpensive strategy for identifying those patients, who would then be targeted for intensive lifestyle advice and consideration of pioglitazone treatment (if not contraindicated). Such a pragmatic approach (illustrated in Fig. 1) would also avoid liver biopsy in the majority of type 2 diabetic patients and such patients could then be followed up with repeat serum fibrosis marker monitoring.

Whilst no guideline is perfect, nor will any guideline be the definitive last word on the subject, the authors of the EASL–EASD–EASO clinical practice guidelines should be congratulated for tackling this important and difficult issue. There is considerable research activity in this field and it is highly likely these published guidelines will need updating in the near future.

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Duality of interest CDB is Principal Investigator for the Wessex Evaluation of fatty Liver and Cardiovascular markers in NAFLD (non-alcoholic fatty liver disease) with OMacor thErapy (WELCOME) trial, and the INvestigation of SYnbiotic TreatmEnt in NAFLD (INSYTE) trial. The WELCOME randomised placebo-controlled double-blind trial tested the effects of high dose purified *n*-3 long-chain fatty acids on a range of liver and cardiometabolic outcomes in NAFLD (www.clinicaltrials.gov NCT00760513). The INSYTE randomised placebo-controlled double-blind trial is testing the effects of a synbiotic on liver fat, disease biomarkers and intestinal microbiota in NAFLD and is currently in recruitment phase (www.clinicaltrials.gov NCT01680640). Both the WELCOME and INSYTE studies assess quantitative changes in liver fat with the interventions by magnetic resonance spectroscopy, as one primary outcome in each trial. CDB is the Expert Diabetologist Advisor and Panel member for the National Institute for Care Excellence (NICE) NAFLD Guideline Development Group. The opinion contained within the commentary is that of the authors. GT has no duality of interest.

Contribution Both authors were responsible for drafting the article and revising it critically for important intellectual content. Both authors approved the published version.

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