by Andrew Yeoman and Jane Diggle

Identifying liver disease in people with diabetes

This is a challenge, as most of those with early disease, and even a proportion with more advanced disease, are entirely asymptomatic.

A number of liver blood tests are available, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), bilirubin, albumin and international normalised ratio (INR). Incidental abnormal results often raise the suspicion of liver disease.

NAFLD is the commonest cause of abnormal liver tests in people with diabetes.

However, it is important to rule out other pathologies and remember that liver blood tests may be normal in NAFLD.

Routine screening for NAFLD in those with diabetes is not currently recommended.

Interpreting liver blood tests

(adapted from Wainwright[3])

- NAFLD typically manifests as increased ALT and AST (with a greater increase in ALT) compared to alcohol-related liver disease, which normally results in higher AST than ALT.
- As NAFLD progresses with ongoing fibrosis, the AST level tends to increase relative to the ALT.
- GGT can also be mildly elevated in NAFLD and often more so in alcohol-related disease.
- Serum albumin and bilirubin give the true measure of liver function, but can be abnormal for a number of non-hepatic causes (e.g. right-sided heart failure and, to a lesser extent, thyroid dysfunction and diabetes).
- An increased ALP and bilirubin may suggest a degree of intrahepatic cholestasis and more serious structural liver pathology.
- Albumin and INR are markers of synthetic liver function. Abnormalities indicate more advanced liver disease, such as cirrhosis.

Reference ranges for liver tests used at University Hospital Southampton.*

Analyte	Reference range (adult)
Alanine aminotranferase	7–35 U/L (female); 10–40 U/L (male)
Aspartate aminotransferase	15–41 U/L
Gamma-glutamyl transferase	<38 U/L (female); <55 U/L (male)
Alkaline phosphatase	30–130 U/L
Total bilirubin	<21 µmol/L

*Laboratories may have their own reference ranges that differ slightly from those presented here.

Liver blood tests are not sensitive tests for diagnosing NAFLD and will not inform regarding the presence of liver fibrosis (refer to **Step 2**).

Individuals with abnormal liver blood tests should be considered for investigation with a liver aetiology screen, irrespective of level and duration of abnormality.

STEP 1: Making the diagnosis

Elevated transaminases (ALT/AST) with a negative serological screen are highly suggestive of NAFLD, but a diagnosis requires evidence of hepatic steatosis on imaging or histology AND the exclusion of other causes of liver diseases.

Always take an alcohol history to rule out alcohol-related liver disease. NAFLD should be diagnosed only when consumption of alcohol is ≤21 units/week for men and ≤14 units/week for women). Liver damage may be caused both by alcohol and NAFLD.

Obtain a history to identify anything that may predispose to liver disease, including:

- Alcohol consumption
- Blood-borne virus risk (prior surgery or blood transfusion, IV drug use, tattooing, sexual history, country of origin)
- Detailed drug history (including over the counter remedies)
- Record BMI and waist circumference.

STEP 2: Assess for signs of liver damage (fibrosis)

The key step once a diagnosis of NAFLD has been made is to assess whether there is significant liver damage (fibrosis), as those with more advanced fibrosis will be at greatest risk of liver-related complications and ultimately liver cirrhosis.

Use a validated risk assessment tool (Fibrosis-4 or the NAFLD fibrosis score) that can be incorporated into primary care electronic systems.

These can be accessed free online:

- Fib-4 Score: http://bit.ly/2MMWYxf
- NAFLD Fibrosis Score: http://www.nafldscore.com

About this series

The aim of the "How to" series is to provide readers with a guide to clinical procedures and aspects of diabetes care that are covered in the clinic setting.

What and why

- Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum from simple fatty liver (steatosis), to non-alcoholic steato-hepatitis (NASH) where the liver is inflamed through to fibrosis (with formation of scar tissue) and ultimately cirrhosis. Complications include ascites, variceal bleeding, hepatic encephalopathy and hepatocellular carcinoma.
- The most important risk factors are obesity and type 2 diabetes. It has been estimated that around 70-75% of these individuals have some form of NAFLD[1].
- The presence of features of the metabolic syndrome, including central obesity (waist circumference ≥94 cm in men, ≥80 cm in women), insulin resistance, hypertension (BP >135/85), raised triglycerides (>1.7 mmol/L) and low HDL-cholesterol (<1 mmol/L for men, <1.3 mmmol/L for women), further increase the risk[2].

Citation: Yeoman A, Diggle J (2019) How to diagnose and manage NAFLD in diabetes. *Diabetes & Primary Care* **21**: 5–6

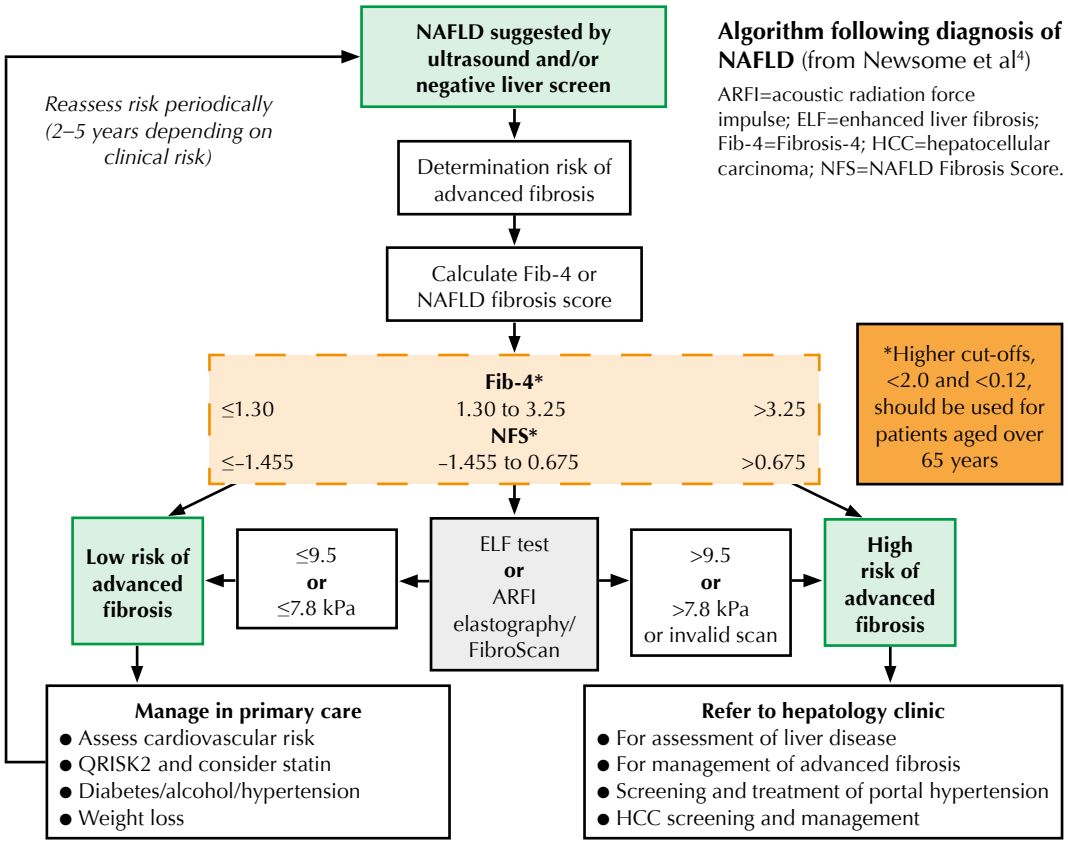
STEP 2 (contd)
Interpreting the score

Individuals with an initial risk score above the given threshold should be considered for further testing which, dependent on the local pathway and availability, may be undertaken in primary care (ELF test) or may require secondary care referral (Fibroscan).

The ELF test

This combines three serum biomarkers. The extent of liver damage is determined by a score based on measurement of: hyaluronic acid (HA); procollagen III amino terminal peptide (PIIINP); tissue inhibitor of metalloproteinase 1 (TIMP-1).

- ELF score ≥10.51 confirms advanced liver fibrosis.
- With an ELF score <10.51, advanced liver fibrosis is unlikely, but re-testing is recommended every 3 years.



Algorithm following diagnosis of NAFLD (from Newsome et al[4])

ARFI=acoustic radiation force impulse; ELF=enhanced liver fibrosis; Fib-4=Fibrosis-4; HCC=hepatocellular carcinoma; NFS=NAFLD Fibrosis Score.

STEP 3: Management of NAFLD in primary care

Lifestyle modifications

The mainstay of treatment is weight reduction. Aim for a 7–10% weight loss to bring about meaningful reductions in liver fat, liver enzymes and possibly fibrosis[5].

Increased physical activity combined with a reduced calorie diet reduces liver fat content[6].

- Recommend 150 minutes of moderate-to-vigorous physical activity a week (around 20–30 minutes/day).

There is insufficient evidence to prove any dietary approach is superior to another. It is more likely that the degree of adherence and weight loss achieved that predicts outcomes, rather than the dietary strategy itself.

Options to consider include:

- Daily calorie restriction (500–1000 fewer calories).
- Very low energy (600–800 kcal/day) total or partial meal replacement for 8–12 weeks under supervision (e.g. LighterLife, Cambridge Weight Plan).
- Macronutrient specific (e.g. Mediterranean diet, high protein, low carbohydrate, high fat, low fat/high fibre).
- Fasting approaches (5:2, alternate day, time-restricted eating).

Encourage those who drink alcohol not to exceed the recommended limits (<14 units/week spread over 3 days or more, with at least two consecutive alcohol-free days).

- Provide smoking cessation support and advice to smokers.

There is a significant increased risk of cardiovascular disease (CVD) in people with diabetes; this risk is even greater in those with NAFLD. Aggressive CV risk factor reduction, that addresses hypertension, dyslipidaemia and poor glycaemic control through lifestyle modification, is a priority.

Pharmacological interventions

Most people will also need medications to lower CV risk, including antihypertensives, statins and blood glucose-lowering drugs.

Statins should NOT be avoided in patients with NAFLD and abnormal liver bloods. However, if a 2-fold rise in ALT is seen following statin initiation, they should be discontinued.

There are no licensed pharmacological therapies for NAFLD, though several clinical trials are ongoing.

The following agents, used in the treatment of diabetes, have been studied in NAFLD:

- Pioglitazone may help to reverse excess fat in the liver[7], but there are no data to suggest that this is associated with improved liver outcomes longer term. Careful monitoring of liver function tests is needed. Pioglitazone should be avoided in severe hepatic impairment.
- Glucagon-like peptide 1 (GLP-1) receptor agonists are a possible treatment option. In one study, patients treated with liraglutide were 4.3 times more likely to see resolution of NAFLD than patients treated with placebo[8].
- SGLT2 inhibitors are being explored as possible treatments for NAFLD and NASH.

STEP 4: Referral

Refer adults and young people diagnosed with advanced liver fibrosis to a relevant specialist in hepatology.

Areas of uncertainty

If NAFLD evident but:

- Patient is lean (may have lipodystrophy/LAL-D)
- High transferrin saturation
- Heterozygous alpha-1 antitrypsin genotype
- Low-titre autoantibodies.

Referral to hepatology should be considered, irrespective of fibrosis risk, as liver biopsy may be required to exclude a second liver disease.

References

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Further resource

NICE (2016) *Non-alcoholic fatty liver disease (NAFLD): assessment and management* (NG49). www.nice.org.uk/guidance/ng49

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