Q&A
Diabetes and the liver

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Q Are there any signs or symptoms that would raise a suspicion of liver impairment?

The majority of people with early disease, and a sizeable proportion of those with more advanced disease, will be entirely asymptomatic, making identification of cases challenging (Targher and Byrne, 2013). Some individuals will develop non-specific symptoms such as fatigue, and a minority complain of right upper quadrant pain. Characteristic clinical signs can appear once a person develops cirrhosis: palmar erythema, spider naevi, gynaecomastia and prominent abdominal veins (Rinella, 2015). Features can become more pronounced in those with decompensated cirrhosis, with the possible addition of ascites, jaundice, splenomegaly, nail changes or asterixis. It is not uncommon for development of advanced liver disease to go unnoticed until a crisis point occurs and the individual presents with features of cirrhosis. Identifying those at high risk of progressive disease is vital.

Q There are a number of liver function tests including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), alkaline phosphatase (AP), gamma glutamyl transferase (GGT), bilirubin, albumin and international normalised ratio (INR). Should people with diabetes have all of these tested – and, if so, how often? What does each tell us?

And when and how should abnormalities be acted upon?

The commonest cause of abnormal liver function tests in people with diabetes is non-alcoholic fatty liver disease (NAFLD), which is estimated to be present in up to 70% of such individuals (Chalasani et al, 2012). However, it should be considered that many people with NAFLD exhibit entirely normal liver function tests. NAFLD classically manifests biochemically as increased ALT and AST, with a greater increase noticed in ALT. This pattern can be useful in distinguishing NAFLD from alcohol-related liver disease, which normally results in higher AST than ALT (Sattar et al, 2014).

As NAFLD progresses with ongoing fibrosis, the AST level tends to increase relative to the ALT. GGT can also be mildly elevated along with the transaminases. An increased AP and bilirubin could be suggestive of a degree of intrahepatic cholestasis, which may indicate more serious structural liver pathology. Albumin and INR are markers of synthetic liver function and will only be abnormal in advanced liver disease such as cirrhosis (Perlemuter et al, 2007).

There are now data available to support the use of liver fibrosis markers in a primary care setting as a way to triage those with known liver disease into prognostic groups and to aid decision making when considering which individuals warrant referral into secondary care services (Sheron et al, 2012).

Liver function tests are not sensitive tests for diagnosing NAFLD and are associated with a high proportion of false-negative results. Screening for NAFLD, even in high-risk groups such as those with diabetes or obesity, is not currently recommended owing to uncertainties

related to diagnostic tests and the lack of a definitive treatment (Chalasani et al, 2012).

What factors are known to increase the risk of NAFLD?

The most important risk factors for NAFLD are obesity and type 2 diabetes. In addition to this, the presence of features of the metabolic syndrome (characterised by central obesity, insulin resistance, hypertension, elevated triglycerides and low HDL-cholesterol) increase the risk of developing NAFLD. The more adverse metabolic features that individuals have, the higher their risk of developing more progressive liver disease such as non-alcoholic steatohepatitis (NASH) and cirrhosis (Rinella, 2015).

How is NAFLD diagnosed?

To diagnose NAFLD, it is necessary to demonstrate hepatic steatosis on imaging or histology in the absence of significant alcohol consumption and other causes of steatosis or chronic liver disease (Chalasani, 2012).

A diagnosis of NAFLD should be suspected in people who have diabetes or are obese, and especially in those who exhibit multiple features of the metabolic syndrome. The majority of individuals are asymptomatic and are identified on routine blood tests demonstrating elevated transaminase levels. Transaminase levels do not have to be elevated for the diagnosis; however, raised levels are found in 50% of people with NAFLD and 80% of those with NASH (Yan et al, 2007).

Liver ultrasound scanning can identify steatosis and assist with the diagnosis; however, it is important to note that it is not 100% sensitive for the diagnosis and, thus, NAFLD is not excluded by a negative scan. Computed tomography or magnetic resonance imaging can also be used, although no imaging modality is able to differentiate simple steatosis from more advanced forms of liver disease such as NASH. Currently, the only way to reliably diagnose NASH is by liver biopsy (Adams and Feldstein, 2011). Biopsy is rarely performed for this indication, although it can have some utility in cases of diagnostic uncertainty, as guided by specialist services.

How likely is it for NAFLD to progress to more serious forms of liver disease (e.g. cirrhosis and, eventually, liver failure)?

Approximately 20% of the general population, and 70% of those with type 2 diabetes, have NAFLD (Chalasani et al, 2012). This condition is characterised by simple fatty infiltration of the liver which exceeds 5% of the total liver weight. A subset of these individuals will progress to more serious forms of liver disease such as NASH, which is characterised by increasing hepatic fibrosis and inflammation. It is estimated that 5–6% of the general population has NASH (Bellentani and Marino, 2009). Up to 20% of these individuals will go on to develop liver cirrhosis, which brings with it the risk of further complications such as hepatocellular carcinoma (Caldwell and Argo, 2010).

People with diabetes have a two- to three-fold increased risk of dying from chronic liver disease as compared with the general population, and this is largely attributed to NAFLD (Zoppini et al, 2014).

To what extent does damage to the liver impact on the body's ability to control blood glucose levels? And is hypoglycaemia more common?

The liver plays a key role in carbohydrate metabolism and acts to regulate blood glucose levels through glycogenesis and glycogenolysis. In addition to this, the liver is critically involved in metabolism of insulin, with approximately 50% of insulin secreted by the pancreas being removed by first-pass extraction in the liver. In the early stages of liver disease this does not generally result in significant problems with regard to management

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

Analyte	Reference range (adult)
Alanine aminotranferas	7–35 U/L (female); 10–40 U/L (male)
Aspartate aminotransferas	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 thosed presented here.

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of diabetes. However, if the person progresses to cirrhosis then the capacity of the liver to effectively store glycogen can become compromised, which can have a significant impact on the risk of hypoglycaemia. All people with diabetes who are being treated with oral hypoglycaemic agents or insulin, who also have cirrhosis resulting from NAFLD or any other cause, must be very carefully counselled regarding the recognition and management of hypoglycaemia (Khan et al, 2012). All dose increases, particularly for insulin, must be carefully considered and monitored, ideally with the close support of a diabetes nurse specialist.

Q Which blood glucose-lowering agents are safe to use in those with hepatic impairment?

This is a key consideration for all clinicians involved in managing people with diabetes, as many hypoglycaemic agents are contraindicated or have to be used with caution in the setting of chronic liver disease. As with the risk of hypoglycaemia, most concerns arise only with cirrhosis and not earlier stages of liver disease.

- **Metformin:** In the setting of cirrhosis, this may be associated with an increased risk of developing lactic acidosis (Brackett, 2010). Current recommendations are to withdraw the agent if tissue hypoxia is likely to occur (Joint Formulary Committee, 2015). In practical terms, metformin is likely to be relatively safe if chronic liver disease is stable but should definitely be withdrawn if liver function is acutely deteriorating or is decompensated. It has also been suggested that the maximum daily dose should be 1500 mg in people with chronic liver disease (Khan et al, 2012).
- **Insulin secretagogues:** These agents are metabolised by the liver, and thus they are likely to have a prolonged duration of action in people with cirrhosis. The risk of hypoglycaemia is markedly increased in this setting, and agents should be either used at a reduced dose or avoided entirely (Joint Formulary Committee, 2015).
- **Thiazolidinediones:** Pioglitazone remains available for use, and there are some data to suggest that it actually improves liver biochemical and histological parameters in people with NASH (Aithal, 2008). However, there are currently no data to suggest that this is associated with improved liver outcomes in the longer term. There are concerns that, in some instances, use of glitazones have been associated with a deterioration in liver function, and therefore careful monitoring of liver function tests is advised (Yokoi, 2010). The *British National Formulary* advises avoiding pioglitazone entirely in cases of severe hepatic impairment such as people with cirrhosis (Joint Formulary Committee, 2015).
- **Insulin:** Insulin therapy is likely to be the safest option in people with co-existing diabetes and chronic liver disease (Khan et al, 2012). There is no increased risk of hepatotoxicity associated with insulin use. However, as described above, this group of patients are at increased risk of hypoglycaemia and should be counselled and managed accordingly.
- **Dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 agonists and sodium–glucose cotransporter 2 inhibitors:** There are some differences in indication, with regard to hepatic impairment, between the agents in these newer classes of therapy (see https://www.medicines.org.uk for more details); however, in general, the data available are limited, and most resources advise avoiding these agents in people with cirrhosis.

Q What is the link between NAFLD and cardiovascular disease?

People with NAFLD are undoubtedly at increased cardiovascular risk (Bhatia et al, 2012). NAFLD is often accompanied by established cardiovascular risk factors such as type 2 diabetes, central obesity, elevated triglycerides and low levels of HDL-cholesterol, but it is also recognised as being an independent cardiovascular risk factor in its own right. One study in particular has shown that, in a cohort of people with type 2 diabetes, ultrasound findings suggestive of NAFLD were associated with an approximately 90% increased risk of incident cardiovascular events after adjusting for other risk factors such as components of the metabolic syndrome (Targher et al, 2007). It is likely that conventional methods for assessing and quantifying cardiovascular risk will under-estimate

risk in people with NAFLD because such methods generally do not take into account some specific aspects known to increase risk in this setting such as insulin resistance, central adiposity and hypertriglyceridaemia (Dekker et al, 2005).

Q Is it safe to prescribe statins in people with T2D with elevated transaminases or liver disease?

Statins form the mainstay of pharmacological treatment for cardiovascular risk reduction and are a crucial part of the management of people with diabetes and NAFLD. Some practitioners are understandably concerned about prescribing statins for people with liver disease, especially those with abnormal liver function tests. Fortunately, there is evidence from numerous clinical trials that the risk of significant liver damage arising from statin use is extremely rare (Kashani et al, 2006). Importantly, there is also no evidence that the use of statins in those with established liver disease is associated with increased risk of liver deterioration (Russo and Jacobson, 2004). Statin medications should not be withheld from people with NAFLD unless transaminase levels are greater than 3 times the upper limit of normal, as per standard guidance. In cases where individuals have transaminase levels of this magnitude but statins are considered to otherwise be of benefit, discussion with specialist hepatology services is recommended as treatment may still be indicated.

Q What are the key lifestyle measures for people with diabetes who are diagnosed with NAFLD?

No drug treatment has been conclusively shown to have a beneficial, clinically significant effect on long-term outcomes in people with NAFLD. Therefore, the cornerstone of treatment remains lifestyle measures.

Lifestyle modification in NAFLD has been assessed in two recent systematic reviews (Peng et al, 2011; Thoma et al, 2012). Weight loss has been shown to result in a reduction in liver enzymes and histological improvement in some cases. Individuals should be advised about the benefits of dietary modification and should be encouraged to restrict caloric intake to 25–35 kcal/kg/day. Low-fat, low-carbohydrate diets are likely to be beneficial, although, clearly, personalised weight management strategies will be required as weight loss will not be appropriate in all cases.

Individuals should also be encouraged to increase their level of physical activity, ideally achieving 30 minutes of moderate-to-intense activity 3–5 times weekly. ■

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