Non-alcoholic fatty liver disease and type 2 diabetes: An overview of the problem

Patrick Wainwright

Non-alcoholic fatty liver disease (NAFLD) encompasses a range of liver disorders from simple fat infiltration (steatosis) to end-stage cirrhosis. It is closely associated with type 2 diabetes, obesity and the metabolic syndrome. Up to 70% of people with type 2 diabetes also have NAFLD, and this markedly increases their risk of cardiovascular disease and all-cause mortality compared with people who have diabetes alone. As well as making diabetes more difficult to control, NAFLD is also associated with an increased risk of developing chronic kidney disease and dying from chronic liver disease. Diagnosis of NAFLD can be problematic as people are often asymptomatic and routine tests, such as liver enzymes, are often normal. Weight loss and lifestyle modification form the cornerstone of management. Research is currently ongoing in this area to find effective treatments, although at present there are no definitive treatments available that have been shown to affect long-term prognosis.

Non-alcoholic fatty liver disease (NAFLD) is a growing global public health problem and is now the most common cause of chronic liver disease in much of the developed world (Anstee et al, 2011; Targher and Byrne, 2013). It comprises a wide spectrum of disorders ranging from simple fat accumulation (steatosis) in the liver, through to non-alcoholic steatohepatitis (NASH), which involves a degree of inflammation within the liver along with an element of fibrosis, to cirrhosis and, ultimately, end-stage liver disease. It is defined as fatty infiltration of the liver that accounts for >5% of the liver weight, in the absence of excessive alcohol consumption or other clear identifiable causes, such as viral hepatitis. NAFLD is now one of the most common indications for liver transplantation in the UK (Targher and Byrne, 2013).

To put this disease into perspective, the worldwide prevalence of NAFLD is estimated at 20% in the general population and at 70% amongst people with type 2 diabetes (Chalasani et al, 2012). A proportion of these individuals will progress to NASH, the prevalence of which is estimated to be 5–6% in the general population (Bellentani and Marino, 2009). As many as 20% of people with NASH will develop liver cirrhosis, with the risk of serious complications such as hepatocellular carcinoma, over a 10-year period (Caldwell and Argo, 2010). The progression of liver disease seen in NAFLD is summarised in *Figure 1* (overleaf). Obesity, insulin resistance and type 2 diabetes are all strongly associated with NAFLD, and the obesity epidemic is considered to be a major driving force behind the increasing prevalence of the disease. NAFLD is considered to be a hepatic manifestation of the metabolic syndrome, and thus it is commonly encountered in the context of people with hypertension, hyperglycaemia, raised total cholesterol and triglyceride levels and low HDL-cholesterol levels. A case report from University Hospital Southampton is detailed below to illustrate

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Article points

1. Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in much of the developed world, occurring in 20% of the general population and 70% of people with type 2 diabetes.
2. NAFLD makes it more difficult to achieve good glycaemic control and is also associated with an increased risk of serious comorbidities and overall mortality.
3. Lifestyle and weight loss have been found to improve both the signs and the risk of NAFLD. Bariatric surgery, orlistat, antihypoglycaemic agents, and vitamin E and omega-3 supplements have also been shown to improve the disease in the short term, but evidence for their long-term effects is lacking.

Key words

- Non-alcoholic fatty liver disease
- Type 2 diabetes

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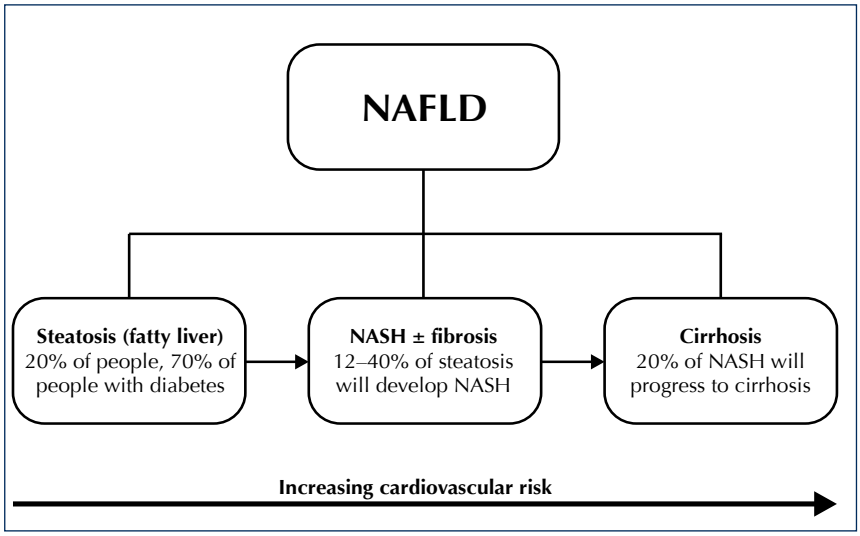

Figure 1. Progression of liver disease seen within the NAFLD spectrum.
NAFLD: Non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis.

the signs and effects of NAFLD in a woman with type 2 diabetes.

Case report

A 48-year-old woman had been diagnosed with type 2 diabetes 5 years previously. At the time of diagnosis, she was noted to have an alanine transaminase (ALT) level of 52 unit/L (reference range, 7–35 unit/L) with no clear cause and she denied any alcohol intake. Ultrasound of the liver revealed evidence of fatty infiltration consistent with NAFLD. The total cholesterol level was 5.7 mmol/L, triglyceride levels were 4.1 mmol/L (reference, <1.5 mmol/L) and the HDL-cholesterol level was 0.95 mmol/L (reference range, 0.9–2.21 mmol/L). BMI was 31 kg/m^2. The woman was referred to the secondary care diabetes service as she had become extremely insulin-resistant, requiring >300 units of insulin daily, and was switched to highly-concentrated U-500 insulin. Follow-up ultrasound scanning revealed an enlarged spleen and she was referred to hepatology services to investigate the possibility of early liver cirrhosis.

How can NAFLD be recognised and diagnosed?

A diagnosis of NAFLD should be suspected in people who have either diabetes or obesity, especially if they exhibit multiple features of metabolic syndrome and are known to be insulin-resistant. Diagnosis of NAFLD is challenging as most individuals are asymptomatic and routine screening is currently not recommended because of the lack of a diagnostic test with the requisite sensitivity and specificity. The most common abnormality seen on routine investigation is a mild or moderate increase in serum liver enzymes, such as ALT or aspartate transaminase, although normal levels do not exclude the diagnosis (Adams and Feldstein, 2011). Other components of the liver function test profile, such as alkaline phosphatase and gamma-glutamyl transferase levels, may also be abnormal. Evidence of impaired hepatic synthetic function, such as decreased albumin levels and increased prothrombin time, are less common and are suggestive of advanced liver disease (Perlemuter et al, 2007).

Simple imaging modalities such as ultrasound, as well as more sophisticated methods such as computed tomography and magnetic resonance imaging, are able to identify ectopic fat within the liver and can be used to assist with diagnosis. However, none of these methods are 100% sensitive for the detection of fat; therefore, a negative scan does not exclude the diagnosis. Importantly, these methods are not able to differentiate between simple steatosis and the more advanced stages of NAFLD. They cannot reliably identify the inflammation that is the hallmark of NASH or determine the level of fibrosis. As such, liver biopsy and histological examination remain the gold standard for confirming a diagnosis of NAFLD and determining the stage of disease (Perlemuter et al, 2007). However, due to limitations of cost and risk associated with the procedure, biopsy is rarely performed in clinical practice, although it does have utility in cases of diagnostic uncertainty.

People with NAFLD are at increased risk of developing type 2 diabetes

There are several prospective epidemiological studies that have demonstrated an association between NAFLD and incident diabetes (Fan et al, 2007; Sung and Kim, 2011; Bae et al, 2011). Interpretation of these data is difficult, however, given the inherent problems associated with NAFLD diagnosis.

A recent Australian study has demonstrated that people with NAFLD are three times more likely to develop diabetes than the general population and 50% more likely to develop metabolic syndrome (Adams et al, 2009). Further analysis revealed that the increased risk of developing metabolic

complications could be explained by increases in abdominal obesity and insulin resistance. Therefore, people who develop NAFLD should have regular surveillance to investigate the possibility of their developing type 2 diabetes.

People with type 2 diabetes and NAFLD have worse glycaemic control than those with diabetes alone, and their mortality and morbidity is markedly increased

People with NAFLD tend to have far higher degrees of insulin resistance and often have worse glycaemic control than those with diabetes alone (Williamson et al, 2011). The degree of hepatic fat content is closely correlated with the dose of insulin that an individual requires for good glycaemic control. A decrease in hepatic fat content achieved by dieting has been shown to reduce insulin resistance, resulting in lower levels of insulin required (Ryysy et al, 2000).

In addition to this, it has been reported that, in a population of people with type 2 diabetes, those with NAFLD had a 2.2-fold increase in all-cause mortality risk compared to those without NAFLD (Adams et al, 2010). There is mounting evidence that NAFLD represents a significant additional cardiovascular risk factor amongst people with diabetes. A significantly higher prevalence of cardiovascular disease (CVD), stroke and peripheral vascular disease has been reported in people with NAFLD and concurrent diabetes than those with NAFLD alone (Targher et al, 2007). CVD is the leading cause of mortality among people with diabetes and the increased risk associated with NAFLD underlines the importance of being aware of the disease in this population, as diagnosis may then enable more aggressive risk reduction in the form of intensive LDL-cholesterol lowering with high-potency statins. It should be noted that statin treatment is safe in people with NAFLD and should not be withheld as a result of mild or moderate increases (up to three times the upper limit of normal) in serum liver enzyme levels.

People with diabetes are also at greatly increased risk of developing liver cirrhosis. A recent study of over 1 million people in the US suggested that the relative risk of cirrhosis was 2.33 compared to people without diabetes (Campbell et al, 2012). In addition to this, it is known that obesity increases the risk of developing hepatocellular carcinoma by two to five times, and type 2 diabetes doubles this risk independently of other risk factors for liver disease (Starley et al, 2010). It has also been repeatedly shown that people with diabetes have a significantly increased risk of mortality from chronic liver disease, and recent data suggest that this is from non-alcoholic and non-viral causes that are predominantly related to NAFLD (Zoppini et al, 2014). The presence of NAFLD can also predict the development and subsequent progression of chronic kidney disease (CKD) in people with diabetes, which will lead to higher morbidity and mortality rates (Targher et al, 2008).

What treatments are available for NAFLD?

Lifestyle changes and general management

There are very few high-quality clinical trials available to inform evidence-based treatments for NAFLD. However, all individuals should be counselled about the importance of effective lifestyle modification to facilitate sustained weight loss as well as, ideally, abstaining from alcohol as far as possible. Data from long-term outcome studies are lacking; however, two recently published systematic reviews assessed six randomised controlled trials and 17 observational studies related to dieting, weight loss and general lifestyle changes (Peng et al, 2011; Thoma et al, 2012). Beneficial effects of weight loss were generally reported, including a reduction in serum liver enzyme levels in most studies and histological improvements of reduced hepatic steatosis and inflammation (but no changes in hepatic fibrosis) in five studies. These results indicate that people with NAFLD should restrict their caloric intake to 25–35 kcal/kg/day, with a low-fat and low-carbohydrate diet to achieve a gradual weight loss of 5–10% of baseline weight. People should be advised against more rapid weight loss (>1.6 kg/week), as this may be associated with a worsening of hepatic fibrosis (Anderson et al, 1991). Clearly, weight management strategies must be personalised, as weight loss may be inappropriate or even unsafe in older people.

All people with NAFLD should be assessed for their level of physical activity and be encouraged to achieve 30 minutes of moderate-to-intense physical activity three to five times per week. A recent study of over 70 000 Korean people without diabetes

Page points

1. NAFLD increases insulin resistance, with a close correlation between the degree of hepatic fat and insulin dose requirements, such that people with the disease find it more difficult to achieve good glycaemic control.
2. NAFLD has also been linked to a doubled risk of all-cause mortality in people with type 2 diabetes, as well as increased risk of cardiovascular disease, liver cirrhosis, hepatocellular carcinoma and chronic kidney disease.
3. While there is little high-quality evidence to inform treatment decisions, systematic reviews have shown that diet and weight loss are effective at reducing the signs of NAFLD, although rapid weight loss of >1.6 kg/week should be avoided as this can worsen liver fibrosis.

Page points

1. Orlistat can improve NAFLD, although its effects do not seem to extend beyond the benefits of weight loss.
2. Bariatric surgery also has positive effects and has even been shown to induce complete remission in the majority of patients in one study with a follow-up of 18 months; however, it can sometimes result in worse fibrosis.
3. Antihypoglycaemic agents such as metformin and pioglitazone have been found to improve NAFLD in the short term, but their effects do not seem to persist over the long-term or after treatment cessation.

showed that regular exercise was associated with a significant reduction in liver enzyme concentrations in those with a diagnosis of NAFLD, as well as a significantly reduced risk of developing NAFLD if they did not have a diagnosis to begin with (Bae et al, 2012). Increased physical activity is thought to bring about these beneficial changes by increasing insulin sensitivity, and this can occur even in the absence of weight loss.

It is important that all people with NAFLD be educated about the nature of their liver disease and the steps that they themselves can take to improve their liver health in the years to come.

Are other weight loss interventions effective in NAFLD?

Orlistat is commonly prescribed to aid with weight loss and can have a modest clinical effect in some people. Although there is a lack of high-quality evidence available, orlistat does not seem to confer any particular benefit to liver health independently of its effects on weight loss (Peng et al, 2011). Sibutramine and rimonabant have both been withdrawn from the market in the UK as weight loss medications and will not be considered as potential treatments for NAFLD in this article.

Bariatric surgery is an increasingly popular therapeutic option for significant and sustained weight loss in people who are morbidly obese and those with less severe obesity but a significant burden of metabolic disease, such as type 2 diabetes, dyslipidaemia or hypertension. Bariatric surgery is a safe and cost-effective intervention, and has proven efficacy in reducing both weight and obesity-related comorbidities. The most common bariatric surgery procedure in the UK is the Roux-en-Y gastric bypass (RYGB), and there is considerable evidence to suggest that this procedure is associated with an improvement in NAFLD. A recent review examined 12 studies with follow-up of up to 32 months and this revealed that people who underwent RYGB had a histological improvement in steatosis, fibrosis and inflammation following the surgery (Hafeez and Ahmed, 2013). In one particular study from 2010, the researcher followed 116 people with morbid obesity and NAFLD for a mean period of 18.6 months post-bariatric surgery and observed a complete regression of NAFLD in 83% of the cohort (Weiner, 2010). However, several studies have shown that some people can experience worsening of existing fibrosis or develop incident fibrosis following bariatric surgery (Hafeez and Ahmed, 2013). Further research in this area is required to clarify the exact role of bariatric surgery in the treatment of NAFLD and currently there are no data available on whether it reduces the long-term risk of progression to established liver cirrhosis.

Do anti-diabetes drugs help with NAFLD?

Metformin is an effective treatment for type 2 diabetes and is known to promote insulin sensitivity in part by reducing hepatic glucose production. Some clinical studies have shown that metformin leads to an improvement in liver enzyme levels during the first year of treatment, compared with dietary measures alone; however, this improvement does not seem to be maintained beyond the first year (Schwimmer et al, 2005). In addition, a systematic review of eight randomised controlled trials did not find any histological benefit of metformin on liver biopsy specimens (Shyangdan et al, 2011).

Thiazolidinediones, such as pioglitazone, act on the nuclear transcription factor peroxisome proliferator-activated receptor-gamma and result in increased insulin sensitivity. Several small studies have demonstrated that these agents are associated with normalisation of both biochemical and histological features in people with a diagnosis of NASH (Boettcher et al, 2012). However, it has also been noted that these abnormalities are likely to return on cessation of the drugs and there are currently no data to suggest a beneficial effect on the progression of liver disease.

Are antioxidants or vitamin supplements effective?

Vitamin C has been studied in the context of paediatric NAFLD and no clear benefit was demonstrated when it was given on its own (Harrison et al, 2003). The most robust data on vitamin E in NAFLD come from the PIVENS (Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis) study, which demonstrated improvement in histological parameters including the level of steatosis, but not fibrosis, in 43% of the vitamin E group compared with 19% of the placebo group (Sanyal et al, 2010). Normalisation of liver enzymes was also noted; however, levels

returned to baseline on cessation of treatment. A recent systematic review looking at administration of omega-3 polyunsaturated fatty acids revealed a significant reduction in hepatic fat content, although it is unclear what the most effective dose or treatment duration is (Parker et al, 2012). As yet, there are no data to suggest that this treatment has a positive effect on long-term progression of liver disease.

Conclusion

NAFLD was once considered to be a relatively uncommon condition that was largely benign; however, it is now widely considered to be the most common cause of chronic liver disease in much of the developed world and a significant proportion of people with the condition will progress to advanced stages of liver disease. It is important that healthcare professionals who care for people with diabetes are aware of NAFLD, as it confers a significantly increased risk of CVD, serious liver disease, CKD and all-cause mortality, in addition to making it more difficult to achieve good glycaemic control in many individuals by causing extreme insulin resistance. There are currently no treatments available that have proven efficacy in halting or slowing the progression of liver disease in people with NAFLD. The incidence of NAFLD has rapidly increased over the past 30 years, largely as a result of the ongoing epidemic of obesity and type 2 diabetes. Further research is required to identify new treatments that may be able to help these individuals. ■

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"It is important that healthcare professionals who care for people with diabetes are aware of non-alcoholic fatty liver disease, as it confers a significantly increased risk of cardiovascular disease, serious liver disease, chronic kidney disease and all-cause mortality, in addition to making it more difficult to achieve good glycaemic control in many individuals by causing extreme insulin resistance."