Non-alcoholic fatty liver disease and diabesity

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Article points

1. Non-alcoholic fatty liver disease (NAFLD) is a spectrum of conditions that is caused by a build up of fat within the liver cells, and its prevalence is increasing with increasing obesity and type 2 diabetes rates.
2. There is no one definitive treatment for NAFLD, but lifestyle changes such as weight loss, increased physical activity and better control of type 2 diabetes are useful tools.
3. There is a need for better understanding and prevention of NAFLD aetiology, better non-invasive biomarkers to diagnose NAFLD and, finally, a better understanding of a definitive NAFLD treatment.

Key words

- Metabolic syndrome
- Non-alcoholic fatty liver disease
- Steatosis

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Non-alcoholic fatty liver disease (NAFLD) is a spectrum of conditions that is caused by a build up of fat within the liver cells. Although the specific mechanisms are not clearly understood at present, the risk factors for NAFLD include obesity, dyslipidaemia and type 2 diabetes. Potentially a lesser known complication of diabesity, NAFLD is increasing in prevalence in the UK and worldwide. This article discusses the link between NAFLD and diabesity, and an overview of the diagnosis, management and prognosis on NAFLD.

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of conditions that is caused by a build up of fat within liver cells. It is defined when the fat content of the liver is more than 5% of the liver volume. The most common form of NAFLD is simple fatty liver, also known as hepatic steatosis. This can develop into necro-inflammation or non-alcoholic steatohepatitis (NASH), which is a subgroup of NAFLD where steatosis co-exists with liver-cell injury and inflammation (steatohepatitis) (Ratziu et al, 2010). NASH can be severe and lead to cirrhosis and hepatocellular carcinoma.

Prevalence

NAFLD is the most common liver disease in Western countries (Bedgoni et al, 2014). The overall prevalence of NAFLD may be underestimated, as many individuals remain asymptomatic. The prevalence of NAFLD reported in the general population is 20–30% in Europe and 27–34% in the USA (World Gastroenterology Organisation, 2012).

Risk factors for NAFLD include dyslipidaemia, obesity, type 2 diabetes and insulin resistance, all of which are components of metabolic syndrome (Marchesini et al, 2001; American Gastroenterological Association, 2002; Marchesini et al, 2003; Hamaguchi et al, 2005), which is thought to be the trigger for NAFLD. Therefore, NAFLD is becoming an increasing problem to public health worldwide as the prevalence of obesity and type 2 diabetes also increase.

In England alone, almost a quarter of working-age people are now obese, a proportion which has increased since the early 1990s (Health Survey for England, 2013). A review article by Machado et al (2006) has shown a very high prevalence of NAFLD in 1620 asymptomatic morbidly obese people; the prevalence of steatosis was 91% and the prevalence of NASH was 37%. However, in this particular study, NASH was not associated with BMI. The prevalence of type 2 diabetes, another risk factor for NAFLD, in England has also risen and has nearly doubled from 2.4% to 5.8% between the 1990s and 2012 (Health Survey for England, 2013). A large Italian study conducted by Targher and colleagues (2007) of 2839 people with type 2 diabetes showed the prevalence of NAFLD was as high as 70%. NAFLD has a strong association with metabolic syndrome, but studies have also shown that NAFLD is associated with coronary, cerebrovascular and peripheral vascular disease (Targher et al, 2007; Ratziu et al, 2010).

End-stage NASH attributes to 30–75% of cryptogenic (where the cause is unknown) cirrhosis of liver (Ratziu et al, 2010). With no symptoms and negative test results, it is imperative to recognise the key risk factors that can lead to NASH for its prevention and diagnosis: at least one major risk factor as well as other risk factors (see *Box 1*).

Box 1. Metabolic risk factors of end-stage non-alcoholic steatohepatitis (Ratziu et al, 2010).

BMI >25 kg/m^2 **and/or**

- Waist circumference of >94 cm in men and >80 cm in women (Caucasian).
- Arterial hypertension >135/85 mmHg.
- Fasting serum glucose >6.1 mmol/L.
- Serum triglycerides >1.7 mmol/L.
- HDL-cholesterol <1.1 mmol/L in men; <1.3 mmol/L in women.
- Serum ferritin >350 µg/L.
- First-degree relative with obesity and/or diabetes.

Although obesity and type 2 diabetes have been identified as major risk factors for NAFLD (Larter et al, 2010; Musso et al, 2010; Neuschwander-Tetri, 2005), the pathogenesis for how they interact is unclear. There is a "two hit" concept of NASH pathogenesis, which dissects two processes leading to NASH. The first process includes liver steatosis, which is associated with insulin resistance, central obesity and triglyceride accumulation in the liver. The second process involves pro-inflammatory pathways within the hepatocytes leading to liver fibrosis and cirrhosis (Farrell et al, 2012; Abd El-Kader and El-Den Ashawy, 2015).

Diagnosis

Diagnosis of NAFLD should be assessed individually, based on clinical history and biochemical tests. Secondary causes of fatty liver such as alcohol, drugs and other liver disorders (e.g. hepatitis C) must be excluded prior to establishing a diagnosis of NAFLD (see *Box 2*). Alcohol history is crucial because it is not always possible to distinguish NAFLD and alcoholic liver disease by liver biopsy. The European Association for the Study of Liver (EASL) and the American Gastroenterology Association (AGA) have suggested NAFLD be diagnosed only when consumption of alcohol is ≤30 g/day (or 21 units/week) for men and ≤20 g/day (or 14 units/week) for women (Bedogni et al, 2014); any amount more than stated would possibly lead to development of alcoholic liver disease (Bellentani et al, 2000).

Box 2. Causes of fatty liver.

- Most common:
  1. Alcohol.
  2. Insulin resistance.
  3. Disorder of lipid metabolism.
  4. Hyperlipidaemia.
- Less common:
  1. Drugs, for example:
     - Amiodarone.
     - Prednisolone.
     - Tamoxifen.
     - Highly active antiretroviral therapy.
  2. Total parenteral nutrition.
  3. Severe weight loss:
     - Jejunoileal bypass.
     - Gastric bypass (less common).
     - Severe starvation.
  4. Refeeding syndrome.

Biochemical diagnosis

NAFLD is one of the commonest causes of incidental abnormal liver function test (LFT) in primary care. Many patients seen in primary care have no signs and symptoms of liver disease except abnormal liver transaminases, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transpeptidase (gamma-GT). The classical pattern of developing liver steatosis would be that the ALT level exceeds that of AST. Although liver transaminases, especially ALT, have long been used as a marker of liver abnormality, it is not a good measure for the severity of liver disease. Approximately 80% of people with NAFLD could have normal liver enzymes and over 80% of people with either steatohepatitis or fibrosis could have normal ALT (Mofrad et al, 2003; Koehler et al, 2012).

A study in Nottingham by Skelly et al (2001) looked at the use of liver biopsy to assess abnormal liver function when all serological tests were negative. Approximately 20% of patients with abnormal ALT had established fibrosis in liver biopsy. Another study, one of the first large community studies completed in the UK to assess asymptomatic individuals who have abnormal LFTs

Page points

1. Diagnosis of non-alcoholic fatty liver disease (NAFLD) should be assessed on individual cases and based on clinical history and biochemical tests. It is important to discount other causes of fatty liver, especially alcohol.
2. NAFLD is one of the commonest causes of incidental abnormal liver function test in primary care.
3. However, approximately 80% of people with NAFLD could have normal liver enzymes and over 80% of people with either steatohepatitis or fibrosis could have normal liver function test results.

Page points

1. Liver ultrasonography is a common, non-invasive method to assess fatty liver.
2. The gold standard to diagnose non-alcoholic fatty liver disease (NAFLD) is liver biopsy, but this method is flawed by sampling errors and intra- and inter-observer variability.
3. Alternative techniques such as transient elastography and magnetic resonance spectroscopy may provide more sensitive testing for NAFLD, although they both have disadvantages over liver biopsy.

during routine blood tests by GPs in Birmingham, showed 7.6% of people who had NAFLD but were asymptomatic in fact had advanced liver fibrosis (Armstrong et al, 2012). This is a worrying finding, as this cohort of patients would have a higher risk of developing liver cirrhosis, which can be fatal if the liver fails. Therefore it is clear that relying on biochemical abnormalities alone is a poor marker and not the most effective way to assess severity of NAFLD.

Non-invasive diagnosis

Liver ultrasonography is a common, non-invasive method to assess fatty liver. It has a sensitivity of approximately 85% and a specificity of 94% (Hernaez et al, 2011). It is widely available for use by primary care physicians as a first-line screening procedure for NAFLD. Other radiological modalities used to diagnose liver steatosis are computerised tomography (CT) and magnetic resonance imaging (MRI) scans. They have higher sensitivities than ultrasonography in diagnosing advanced liver disease and work either by direct assessment of liver parenchyma or by indirectly detecting signs of portal hypertension. However, these two modalities are not able to assess severity of fibrosis or steatohepatitis of the liver.

Liver biopsy: The gold standard

The gold standard to diagnose NAFLD is liver biopsy. It helps to risk stratify patients who are at risk of developing liver cirrhosis or hepatocellular carcinoma. This is an invasive procedure and has potential complications. Moreover, the use of liver biopsy is limited to secondary and tertiary care. At present, although liver biopsy seems to be the gold standard for diagnosing NAFLD, this method is flawed by sampling errors and intra- and inter-observer variability (Bedossa et al, 2003; Papastergiou et al, 2012). Even an optimal (25 mm long) biopsy specimen has a 25% rate of discordance for fibrosis staging (Bedossa et al, 2003).

Future diagnostic techniques

Recently, there has been an emergence of new non-invasive techniques to assess liver fibrosis and cirrhosis. Although some may not be able to replace liver biopsy, they may provide enough information to avoid unnecessary liver biopsies. Transient elastography (TE) is now widely used in Europe and the UK. It is non-invasive, portable and easily reproducible (Fraquelli et al, 2007). TE is performed using an ultrasound-based machine with a portable probe that measures the elasticity within the liver by inducing low-frequency elastic shear waves that propagate within the liver. The volume of liver measured using this method is at least 100 times bigger than a liver biopsy. The speed of the shear wave directly relates to liver stiffness, which is measured in kilopascals (kPa). Values for an individual with normal liver function would be <5.5 kPa, whereas someone with liver cirrhosis would have a reading of ≥12.5 kPa (Sandrin et al, 2003). Meta-analyses have confirmed its validity as a tool to diagnose severe fibrosis and liver cirrhosis non-invasively (e.g. Friedrich-Rust et al, 2008), and it can be done repeatedly to measure the progression of disease. Unfortunately, TE can not be used in individuals who are obese, have active liver inflammation, narrow rib spaces and ascites (Ozkurt et al, 2014).

Magnetic resonance spectroscopy (MRS) is a sensitive modality to assess for liver steatosis by quantifying intracellular triglyceride in the liver. It is more sensitive at quantifying excess hepatic triglyceride than surrogate serum markers. This method is non-invasive and is a specialised technique associated with MRI. MRS has been validated giving good correlation with triglyceride concentration in liver biopsy and it is also easily reproducible (Szczepaniak et al, 2005). This technique to assess NAFLD remains promising, its use is currently limited to research although it has been used in asymptomatic people with type 2 diabetes (e.g. Sanchez et al, 2015). Similar to other imaging modalities, MRS is not able to assess severity of liver fibrosis and inflammation.

Risk stratification

It is essential to risk stratify individuals who may be at risk of developing NASH or advanced liver fibrosis. Screening for type 2 diabetes is essential as there is a strong link between NAFLD and diabetes. Individuals with type 2 diabetes should, therefore, receive regular 6-monthly checks on their liver function. Worsening results from liver function tests (e.g. three times the upper limit of normal ALT level) should lead to a referral to

secondary care for further management, especially for individuals who have risk factors for insulin resistance as they can have a higher prevalence of NASH and advanced fibrosis compared to individuals who have type 2 diabetes and obesity only (de Lédinghen et al, 2006).

There has been a push in recent years to develop non-invasive biomarkers that could accurately reflect liver biopsy findings, and there are a few simple scoring systems to help assess the severity of liver fibrosis in NAFLD. Fibrosis-4 is a model that was developed to predict liver fibrosis in people with HIV/hepatitis C virus co-infection (Sterling et al, 2006). It consists of a formula based on a combination of biochemistry results including age, AST and ALT levels and the platelet count:

$$\text{FIB-4} = \frac{(\text{age} \times \text{AST level})}{(\text{platelet count} \times \sqrt{\text{ALT level}})}$$

It has a good negative predictive value of 90% for advance fibrosis (Sterling et al, 2006) compared to other scoring systems, but it requires some calculation. A simpler method that is now used in many community studies is the BARD score (Harrison et al, 2008). This is based on a scoring system consisting of three variables:

- AST:ALT ratio ≥0.8 (score 2).
- BMI ≥28 kg/m^2 (score 1).
- The presence of diabetes (score 1).

The possible BARD score ranges from 0 to 4 points. The assessment of the AST:ALT ratio ≥0.8 has a negative predictive value of 96% for advance liver disease, and over 20% of patients with normal ALT can avoid having a liver biopsy based on an AST:ALT ratio <0.8 (McPherson et al, 2013). A BARD score of ≥2 points was associated with an odds ratio for advanced fibrosis of 17 and a negative predictive value of 96% (Harrison et al, 2008). This simple scoring system would be a useful tool in primary care to risk stratify patients and determine referral to secondary care.

Management of NAFLD

General treatment

At present, there is no definitive treatment for NAFLD. The main aim of treating NAFLD is to reverse any liver injuries caused by the accumulation of fatty tissue. Hence, the most important management for all types of NAFLD is to address lifestyle changes such as weight loss, increased physical exercise and better control of type 2 diabetes and dyslipidaemia (Thoma et al, 2012). So far, there is a lack of evidence and no consensus for the optimal weight loss in people with NAFLD, especially NASH, but modest weight loss regardless of reduction in body fat could significantly reverse liver steatosis (Petersen et al, 2005). A large randomised controlled trial in the US showed that intensive lifestyle changes and weight reduction of ≥7% body weight over 48 weeks led to significant improvements in steatosis, lobular inflammation and NASH compared to a weight reduction of <7% (Promrat et al, 2010).

International consensus based on diabetes trials have suggested that people with NAFLD should do at least 150 minutes per week of moderate-intensity exercise, at least 75 minutes per week of vigorous-intensity exercise and muscle strengthening exercise twice a week (Ratziu et al, 2010). The efficacy of these implementations should be followed up every 6 months and, if ineffective, pharmacological treatment should be considered.

Pharmacological treatment

In general, drugs to target metabolic disorders, such as antihypertensives, statins and anti-diabetes medications, should be given as needed. Medication that has a mode of action through the liver should be considered carefully for people who are at risk of developing advanced fibrosis.

Unfortunately, there is no definitive pharmacological treatment for NASH. There have been a few trials using insulin-sensitising medication such as metformin and thiazolidinediones to treat NASH, but they did not show improvement in liver fibrosis during long-term follow up. Studies using metformin in NASH were limited to small sample sizes and did not show benefit in liver histology following this treatment (Nair et al, 2004; Haukeland et al, 2009; Loomba et al, 2009). Thiazolidinediones, such as pioglitazone and rosiglitazone (which was withdrawn in the UK in 2011), used for the treatment of NASH showed improvement in serum transaminase levels and liver histological parameters (Aithal et al, 2008), but a larger study by Ratziu and colleagues (2008) demonstrated no improvement in liver fibrosis or

Page points

1. Scoring systems are used to risk stratify individuals suspected of having non-alcoholic liver disease (NAFLD); the BARD score tends to be used in community settings.
2. At present, there is no definitive treatment for NAFLD, but the main aim of treating NAFLD is to reverse any liver injury due to the accumulation of fatty tissue.
3. The most important management pathways for all types of NAFLD is to address lifestyle changes, such as weight loss, through increased physical exercise and encourage better control of type 2 diabetes and dyslipidaemia.

Page points

1. Possible new and upcoming therapies for non-alcoholic steatohepatitis include dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor analogues and vitamin E.
2. Longitudinal studies have shown that long-term mortality in non-alcoholic fatty liver disease (NAFLD) increases from simple steatosis to cirrhosis.
3. NAFLD prevalence will continue to rise and so to will the burden of managing NAFLD in primary and secondary care.

Table 1. Pooled data of studies with an average follow-up of 5 years or more for people with non-alcoholic fatty liver disease (Angulo et al, 2010).

Diagnosis	*n*	Cirrhosis prevalence*	Liver deaths	Overall deaths	Average F/U (years)
NAFLD (overall)	798	6%	3.8%	25.6%	15.2
Simple steatosis	342	0.7%	0.9%	32.5%	15.6
NASH	205	10.8%	7.3%	40.5%	15.5
Cirrhotic in NAFLD	252	100%	18.3%	24.6%	10.25

NAFLD=non-alcoholic fatty liver disease; NASH=non-alcoholic steatohepatitis; F/U=follow-up.
*Cirrhosis prevalence includes all participants diagnosed with cirrhosis at both baseline and during follow-up.
NAFLD denotes the inclusion of individuals with simple steatosis and individuals with NASH.

NAFLD activity score. The use of pioglitazone long term did not show further histological benefit after the initial benefit in the first year of treatment. Moreover, pioglitazone has been shown to cause a significant weight gain in the duration of treatment, which detracts from its long-term benefit (Sanyal et al, 2010).

Vitamin E is an anti-oxidant and anti-inflammatory agent thought to decrease oxidative cell damage. A large trial of 247 people with NASH who did not have diabetes was conducted. Vitamin E, pioglitazone and placebo were compared and vitamin E 800 IU/day was shown to significantly improve liver histological parameters, including NASH but not fibrosis, compared to placebo (Sanyal et al, 2010). The safety of the long-term use of vitamin E remains unclear but the American Association for the Study of Liver Disease (AASLD) had recommended the use of vitamin E in people without diabetes who have biopsy-proven NASH (Chalasani et al, 2012).

Possible new and upcoming therapies for NASH include dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor analogues. These pharmacological treatments are already established for the treatment of type 2 diabetes. So far, animal studies have shown DPP-4 inhibitors such as sitagliptin may be effective in the prevention and treatment of NASH (Jung et al, 2014). Human studies using a DPP-4 inhibitor (e.g. sitagliptin [Yilmaz et al, 2012]) and GLP-1 receptor analogues (e.g. liraglutide [Ohki et al, 2012] and exenatide [Kenny et al, 2010]) are limited, but they have shown promising results in the treatment of people with diabetes and NASH, including reversal of liver fibrosis.

Coffee consumption has been suggested to reduce progression of liver fibrosis in NASH especially in the people with lower insulin resistance (Molloy et al, 2012; Bambha et al, 2014). The underlying mechanism in coffee remains unclear and further longitudinal studies are needed to assess it as therapy for NAFLD.

Prognosis

Overall prognosis for steatosis alone is good. Longitudinal studies have shown that long-term mortality in NAFLD increases from simple steatosis to cirrhosis (Angulo, 2010 [see *Table 1*]). People who have NASH have the highest overall mortality, and there is a need to identify this group to ensure stricter monitoring and management.

Conclusion

It is not surprising that the rise in a more sedentary lifestyle with less physical activity and the emergence of convenience foods have led to an epidemic of obesity and type 2 diabetes. Consequently, an increase in NAFLD has also been observed, and the burden of managing NAFLD in primary and secondary care will continue to rise. There is a need for better prevention and knowledge of NAFLD aetiology, better non-invasive biomarkers to diagnosis NAFLD and, finally, a better understanding of a definitive NAFLD treatment.■

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Non-alcoholic fatty liver disease and diabesity

Online CPD activity

Visit www.diabetesonthenet.com/cpd to record your answers and gain a certificate of participation

Participants should read the article "Non-alcoholic fatty liver disease and diabesity" by Lam and Babu (2015) published in *Diabesity in Practice* volume 4 issue 2 (which can also be found at **http://bit.ly/1HUMkK0**) before answering the multiple choice questions below. There is ONE correct answer to each question. After submitting your answers online, you will be immediately notified of your score. A pass mark of 70% is required to obtain a certificate of successful participation; however, it is possible to take the test a maximum of three times. A short explanation of the correct answer is provided. Before accessing your certificate, you will be given the opportunity to evaluate the activity and reflect on the module, stating how you will use what you have learnt in practice. The CPD centre keeps a record of your CPD activities and provides the option to add items to an action plan, which will help you to collate evidence for your annual appraisal.

1. What is the threshold fat content of the liver, above which non-alcoholic fatty liver disease (NAFLD) is defined? Select ONE option only.

A. 1%
B. 5%
C. 10%
D. 25%
E. 33%

2. Which is the COMMONEST liver disease in Western countries? Select ONE option only.

A. Alcoholic liver disease
B. Autoimmune liver disease
C. Chronic hepatitis B infection
D. Chronic hepatitis C infection
E. NAFLD

3. According to Targher et al (2007), what is the prevalence of NAFLD in people with type 2 diabetes? Select ONE option only.

A. 10%
B. 30%
C. 50%
D. 70%
E. 90%

4. Which of the following is SPECIFIC to nonalcoholic steatohepatitis (NASH) but not NAFLD? Select ONE option only.

A. A finding of normal liver function tests
B. An absence of physical symptoms
C. Liver cell inflammation
D. The presence of deranged liver function tests
E. The presence of fat in liver cells

5. A 49-year-old obese, Caucasian man has type 2 diabetes. A liver ultrasound has shown he has a "fatty liver". Which of the following is an ADDITIONAL risk factor for the development of NASH? Select ONE option only.

A. Blood pressure 130/80 mmHg
B. First-degree relative with obesity
C. HDL-cholesterol 2 mmol/L
D. Serum triglycerides <1.7 mmol/L
E. Waist circumference 90 cm

6. Which of the following drugs, if any, is recognised as a potential cause of a fatty liver? Select ONE option only.

A. Aspirin
B. Flucloxacillin
C. Losartan
D. Naproxen
E. Tamoxifen
F. None of the above

7. Which of the following liver function test results MOST likely represent NAFLD? Select ONE option only.

	ALT	AST	AlkPhos	GGT
A	Normal	Normal	Normal	Normal
B	Normal	Normal	Raised	Normal
C	Normal	Raised	Raised	Slightly raised
D	Raised	Significantly raised	Slightly raised	Raised
E	Raised	Slightly raised	Normal	Raised

ALT= alanine aminotransferase; AST=aspartate aminotransferase; AlkPhos=alkaline phosphatase; GGT=gamma-glutamyl transpeptidase.

8. According to Armstrong et al (2012), what approximate percentage of ASYMPTOMATIC people with NAFLD have ADVANCED liver fibrosis? Select ONE option only.

A. <1%
B. 8%
C. 16%
D. 32%
E. 64%

9. A 55-year-old woman has type 2 diabetes, NAFLD and a BMI of 25 kg/m^2. Which of the following is the most appropriate non-invasive investigation to assess her liver for fibrosis? Select ONE option only.

A. Biopsy
B. CT scan
C. Magnetic resonance spectroscopy
D. Transient elastography
E. Ultrasound

10. According to current evidence, which of the following, if any, is the MOST effective drug treatment for NASH? Select ONE option only.

A. Exenatide
B. Metformin
C. Pioglitazone
D. Sitagliptin
E. Vitamin E
F. None of the above

Armstrong MJ, Houlihan DD, Bentham L et al (2012) Presence and severity of non-alcoholic fatty liver disease in a large prospective primary care cohort. *J Hepatol* **56**: 234–40

Targher G, Bertolini L, Padovani R et al (2007) Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. *Diabetes Care* **30**: 1212–8