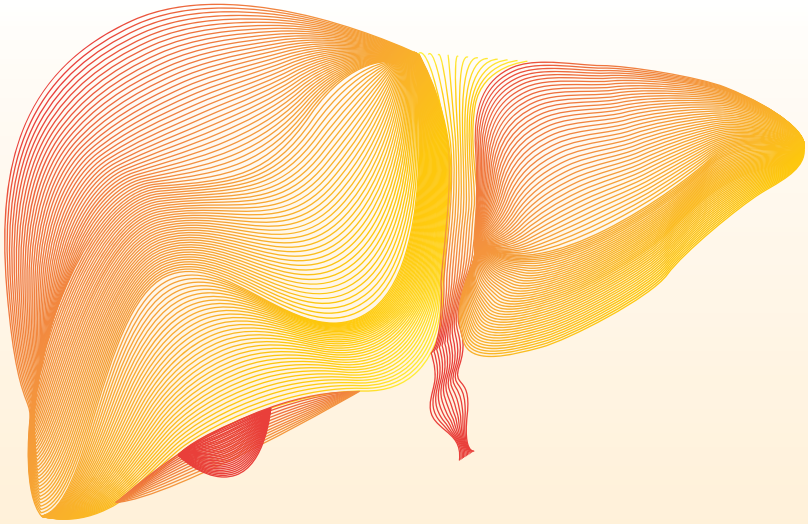
Non-alcoholic fatty liver disease is on the rise in tandem with growing levels of obesity and diabetes

Suzanne Norris



The hidden dangers of a fatty liver

PATIENTS WITH DIABETES are usually very well informed about the importance of keeping glucose levels under tight control to prevent macrovascular and microvascular complications. Disease management advice includes maintaining good blood pressure and cholesterol levels, not smoking, being active, maintaining a healthy diet and not gaining weight.

Patients living with diabetes are also aware of the importance of the requirement for annual checks such as kidney, eyes and foot reviews. However, few patients understand or are aware that they also carry a risk of developing liver cirrhosis as a consequence of diabetes due to fatty liver, a risk that is present even in non-drinkers.

What is non-alcohol fatty liver?

Fatty liver, or non-alcoholic fatty liver disease (NAFLD) is a term used to describe a condition caused by the build-up of fat in liver cells. NAFLD infers no significant alcohol intake (daily alcohol consumption less than 30g/day for men and less than 20g/day for women), and no secondary causes such as hereditary metabolic disorders and exposure to steatogenic medications such as tamoxifen.[1] NAFLD may develop as:

- **Simple steatosis:** The accumulation of fat in the liver without damage or inflammation. It may slowly progress to liver inflammation and scar tissue (fibrosis) over many decades
- **Non-alcoholic steatohepatitis (NASH):** This is a condition where fat in the liver causes inflammation, resulting in cellular damage to the liver cells, switching on of fibrosis genes, resulting in fibrosis. NASH is considered to be the more progressive and aggressive subtype of NAFLD and can lead to the development of fibrosis and cirrhosis.

The presence of fibrosis is the most important determinant of liver outcome.[2] Over a 10-year follow-up period, 21-28% of patients with NASH compared to just 4% of patients with simple steatosis developed cirrhosis and related complications such as hepatocellular carcinoma (HCC).[3]

A particular concern for NASH patients is that NASH is associated with a greater than 10-fold risk of liver-related death, and a doubling of cardiovascular risk. Cardiovascular disease is the leading cause of death in NAFLD patients.[4]

How common is fatty liver?

Fatty liver is a common condition that affects up to 30% of the population. It is the most common cause of chronic liver disease in developed countries. Up to 10% of the general population may be affected by the more severe inflammatory form NASH. Prevalence estimates range from 22% to 45% of adults and 15-20% children in western countries,[5] increasing in parallel with that of obesity and diabetes. In Ireland, approximately 43% of Irish over-50 year olds are overweight (BMI $\geq$ 25kg/m^2), with a further 36% classified as obese (BMI $\geq$ 30kg/m^2); just 21% have a normal BMI.[6]

According to an epidemiological study published in *The Lancet* in 2016,[7] the incidence and prevalence of obesity in Ireland is increasing at a more rapid rate than in other European countries, and if maintained, Ireland will be the most obese country in Europe by 2025. Additionally, it is estimated that there are 190,000 people in Ireland living with diabetes, with type 2 diabetes accounting for 90% of all cases.

In 2010, the Institute of Public Health predicted that the prevalence of type 2 diabetes in Ireland will increase from 4.5% in 2007 to 5.9% by 2020.[8] This represents a significant number of diabetes patients at risk of liver disease from NAFLD, in the absence of effective screening and intervention approaches.

What are the consequences of fatty liver?

For most patients, the condition remains as uncomplicated steatosis or NASH. However, in approximately one third of patients with NASH, scarring can continue to progress to irreversible liver damage or cirrhosis. Patients with cirrhosis may

develop life-threatening complications such as liver failure and are at higher risk of liver cancer.

If cirrhosis is present, laboratory tests evaluating liver failure should be performed (INR, bilirubin, albumin), patient assessed for decompensated liver failure (presence of ascites, encephalopathy), and the patient screened for oesophageal varices and HCC.

Patients with fatty liver also have a higher risk of heart disease, even in the absence of diabetes, and cardiovascular disease (CVD) is the leading cause of death in NAFLD patients.[4] It should not be surprising that NAFLD plays a role in the genesis of CVD.

The normal glucose and lipid homeostasis within the liver becomes disturbed with the accumulation of liver fat, resulting in hepatic insulin resistance, increased fasting glucose levels and an atherogenic lipid profile.[9] Weight gain in NAFLD patients exacerbates the cardiovascular risk profile. Additionally, the fatty liver produces inflammatory pro-atherogenic cytokines, hyper-coagulable factors and adhesion molecules, which play a role in myocardial dysfunction and atherosclerosis.[10]

However, data presented in 2016 strongly suggest that NAFLD confers an increased risk for CVD over and above its association with traditional cardiac risk factors. In a cross-sectional analysis of 5,671 patients attending a CVD primary intervention clinic,[11] the presence of NAFLD was associated with greater cardiovascular risk independent of smoking, age, sex, diabetes and hypertension. The evidence therefore suggests NAFLD increases CVD risk.

Who is at risk for fatty liver?

Fatty liver is typically associated with the following:

- Obesity (especially central abdominal fat)
- High cholesterol
- Type 2 diabetes
- High blood pressure
- Insulin resistance.

Hypogonadism, hypothyroidism, and obstructive sleep apnoea have also been linked with fatty liver. The presence of hypertension, insulin resistance, high triglyceride levels and high waist circumference are all associated with a higher risk of NASH and a more progressive disease course. Consequently, primary care doctors and nurses caring for patients at risk for NAFLD – type 2 diabetes patients, patients with high cholesterol values, patients with features of the metabolic syndrome – need to be aware of fatty liver disease and the risk of cirrhosis to allow for early referral to hepatology for early intervention.

New research is suggesting a genetic involvement in the development of fatty liver. The best-characterised genetic association is with the PNPLA3 gene, initially identified from genome-wide association studies and confirmed in multiple cohorts as a modifier of NAFLD severity.[12,13]

Some patients therefore may be more genetically susceptible to developing fatty liver disease. This is borne out by the phenomenon of 'lean' fatty liver disease patients with normal BMI who are non-diabetic. These patients account for less than 7% of all NAFLD cases.

How is fatty liver diagnosed?

The majority of diabetes patients with NAFLD are asymptomatic or have non-specific symptoms such as fatigue, non-specific RUQ (right upper quadrant) discomfort, or arthralgia. Because of the concern of the potentially huge burden of undiagnosed liver disease due to fatty liver in at-risk patients, the European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO) jointly produced clinical practice guidelines and recommendations for the diagnosis, treatment and follow-up of patients with NAFLD in 2016.[1]

These clinical practice guidelines strongly recommend that the progressive form of NAFLD (ie. NASH) should be identified in patients at risk (age > 50 years, type 2 diabetes or metabolic syndrome). The guidelines also strongly recommend that for type 2 diabetes patients, the presence of NAFLD should be screened irrespective of liver enzyme levels, since type 2 diabetes patients are at high risk of liver disease progression.[1]

ALT levels

Although an elevated ALT can indicate hepatic inflammation in patients with NAFLD, patients with advanced fibrosis frequently have normal LFTs. Almost three quarters of diabetes patients with NAFLD and half of diabetes patients with NASH have normal ALT levels. In three large studies, 30%-60% of biopsy-proven NASH patients had normal ALT values.[14,15] Consequently, normal LFTs in diabetes patients should not reassure the clinician that there is no evidence of NASH or fibrosis.

Ultrasound

Abdominal or liver ultrasound is commonly the means by which a fatty liver is identified. Ultrasound is a widely available and inexpensive diagnostic tool for the presence of fat in the liver, but sensitivity is poor when the fat content is less than 20% of the liver,[16] or in patients with BMI > 40kg/m^2.

Additionally, the ultrasound characteristics of fatty liver such as increased brightness and echogenicity may also be seen with advanced fibrosis and early cirrhosis. Despite these limitations, it is commonly the first test to identify the presence of fatty liver, but cannot identify or quantify fibrosis.

Fibroscan

Vibration controlled transient elastography (Fibroscan) is an ultrasound-based technology which measures liver stiffness and correlates with liver fibrosis. With the patient lying on his back, right arm elevated above the shoulder, the Fibroscan probe is placed in the RUQ and 10 readings of liver stiffness are taken (normal values ranging from 2.5-6.5kPa).

A median result is derived and available immediately, which makes it a very attractive diagnostic tool for fibrosis assessment at clinic. From the patient's perspective, the procedure is painless, quick and easy to repeat over time. Several studies have compared paired liver biopsies and Fibroscan results in more than 1,000 patients and have shown that Fibroscan is reliable in distinguishing advanced fibrosis from mild or no fibrosis.[17]

A further advantage of the Fibroscan assessment is the simultaneous detection and quantification of hepatic steatosis, based on a physical parameter called controlled attenuation parameter or CAP.[18] Values range from 100-400dB/m, with normal values below 220dB/m. Recent studies of paired liver biopsies and CAP scores have reported that for the diagnosis of steatosis > 5%, steatosis > 33% and steatosis > 66%, AUROCs for CAP were 0.79, 0.84, and 0.84, respectively.[19]

The simultaneous evaluation of both liver stiffness and fat quantification in the same liver volume is very useful in assessing NAFLD patients. In one recent study of 1,918 Chinese type 2 diabetes patients assessed by Fibroscan, 73% had CAP scores above the upper limit of normal, and 18% had liver stiffness scores indicative of advanced fibrosis/cirrhosis.[20]

Fibroscan assessment is therefore a very attractive non-invasive method of assessing liver fibrosis. It also has the advantage of tracking changes over time and changes in response to treatment. Where non-invasive assessments yield uncertainty regarding the degree of fibrosis, liver biopsy may be necessary.

What is the treatment for fatty liver?

The main focus of treatment is lifestyle intervention including diet, exercise (aerobic and resistance), and behavioural

change.[21] Relatively small amounts of weight loss reduce liver fat and improve hepatic IR.

A number of small studies have reported that in overweight/obese NAFLD, 7-10% weight loss sustained over 48 weeks results in significant improvement of liver enzymes, reduction in liver steatosis and inflammation, and is associated with significant reduction in histologic severity of NASH. Therefore, lifestyle intervention can improve and reverse NASH, provided significant weight loss is achieved.

However, a systematic review of the available lifestyle modifications in NAFLD reported that less than 50% of patients achieve the necessary weight loss goal of > 7% in the clinical trial setting.[22,23] Food choices based on the Mediterranean diet are recommended considering the additional beneficial effect on cardiovascular outcomes.

Scientific evidence suggests that the anti-oxidant vitamin E may also have beneficial liver impact,[24] but may be associated with an increase in prostate cancer in men older than 50 years in one large study of 35,000 patients,[25] and a 20% increased risk of haemorrhagic stroke.[26]

GLP1 analogues such as liraglutide have reported significant weight loss in patients with type 2 diabetes.[27] In the Lira-NAFLD study,[28] researchers reported that six months of liraglutide 1.2mg daily dose in patients with inadequately controlled type 2 diabetes induced a significant reduction in liver fat, body weight and HbA1c, and that this effect was driven by the liraglutide-induced reduction in body weight. However, the study did not report whether reduction in liver fat content reduced hepatic fibrosis, and further studies are needed.

What happens now?

NAFLD is the most common cause of liver disease worldwide. Because of the burden of disease, it is important to identify which patients are likely to have increased morbidity and mortality related to NAFLD. The 2016 European clinical practice guideline document recommends that the aggressive form of NAFLD (NASH) should be identified in patients at risk – type 2 diabetes or metabolic syndrome, and age > 50 years.[1]

With an estimated 190,000 people in Ireland living with diabetes, it is neither practical nor feasible to perform liver biopsies on such large numbers of patients, and non-invasive screening methods are pragmatic and validated approaches. Given the potentially life-threatening complications of unrecognised and undiagnosed advanced liver disease (cirrhosis, liver failure, HCC), awareness of liver health in diabetes patients is critical and should be incorporated in diabetes care pathways.

Causes of fatty liver

- Obesity (especially central abdominal fat)
- High cholesterol
- Type 2 diabetes
- Insulin resistance
- Hypogonadism, hypothyroidism and obstructive sleep apnoea

Suzanne Norris is professor in gastroenterology and hepatology at the School of Medicine, TCD, and a consultant hepatologist, at St James's Hospital, Dublin

Prof Norris will be delivering a session on NAFLD at DICE 2018 (see more on pg. 26)

For information on NAFLD and Fibroscan assessment please see: **www.liverwellness.ie**

References

1. EASL-EASD-EASO Clinical Practice Guidelines for the Management of Non-alcoholic fatty liver disease, European Association for the Study of the Liver, European Association for the Study of Diabetes and European Association for the Study of Obesity. J Hepatol 2016;64:1388-1402

2. Rinella M. Nonalcoholic fatty liver disease a systematic review. JAMA 215;313(22):2263-2273

3. Pais R, Charlotte F, Fedchuk L, et al. LIDO Study Group. A systematic review of follow-up biopsies reveals disease progression in patients with non-alcoholic fatty liver. J Hepatolo 2013;59(3):550-556

4. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. NEJM 2010;363:1341-1350

5. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther 2011;34:274-285

6. Healthy Ireland Survey Report 2015. http://health.gov.ie/wpcontent/uploads/2015/10/Healthy-Ireland-Survey-2015-Summary-of-Findings.pdf

7. NCD Risk Factor Collaboration. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet 2016; 387:1377-1396

8. ICGP A practical guide to integrated type 2 diabetes care. httpa://www.icgp.ie/go/about/policy

9. Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes, cardiovascular disease, or cirrhosis. Nat Rev Gastroenterol Hepatol 2013;10:330-344

10. Vanni E, Marengo A, Mezzabotta L, Bugianesi E. Systematic complications of nonalcoholic fatty liver disease: when the liver is not an innocent bystander. Semin Liv Dis 2015;35:236-249

11. Pais R, Giral P, Khan JF, et al. Fatty liver as an independent predictor of early carotid atherosclerosis: results from a large transversal and longterm follow-up. J Hepatol 2016;65:95-102

12. Valenti L, Al-Serri A, Daly AK, et al. Homozogosity for the patatin-like phospholipase-3/adiponutrin 1148M polymorphism influences liver fibrosis in patients with nonalcoholic fatty liver disease. Hepatology 2010;51:1209-1217

13. Liu YL, Patman GL, Leathart JB, et al. Carriage of the PNPLA3 rs738409 C>G polymorphism confers an increased risk of nonalcoholic fatty liver disease associated hepatocellular carcinoma. J Hepatol 2014;61:75-81

14. Mofrad P, Contos MJ, Haque M, et al. Clinical and histological spectrum of nonalcoholic fatty liver disease associated with normal ALT values. Hepatology 2003;37(6):1286-1292

15. Amarapurkar DN, Patel ND. Clinical spectrum and natural history of nonalcoholic fatty liver steatohepatitis with normal ALT values. Trop Gastroenterol 2004;25(3):130-134

16. Dasarthy S, Dasarthy J, Khiyami A, et al. Validity of real time ultrasound in the diagnosis of hepatic steatosis: a prospective study. J Hepatol 2019;51(6):1061-1067.

17. Friedrich-Rust M, Ong MF, Martens S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterology 2008;134(4):960-974

18. Sasso M, Miette V, Sandrin L, et al. The controlled attenuation parameter (CAP): a novel tool for the non-invasive evaluation of steatosis using Fibroscan. Clin Res Hepatol Gastroenterol 2012;36(1):13-20

19. de Ledinghen V, Vniol J, Capdepont M, et al. Controlled attenuation parameter (CAP) for the diagnosis of steatosis: a prospective study of 5323 examinations. J Hepatol 2014;60:1026-1031

20. Kwok c, et al. Gut 2016;65:1359-1365

21. Marchesini G, Petta S, Dalle Grave R. Diet, weight loss, and liver health in nonalcoholic fatty liver disease: pathophysiology, evidence, and practice. Hepatology 2016;63(3):2032-2043

22. Promrat K, Kleiner DE, Niemeier HM, et al. Randomised controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology 2010;51:121-129

23. Franz MJ, VanWormer JJ, Crain AL, et al. Weight loss outcomes: a systematic review and meta-analysis of weight loss clinical trials with a minimum 1 year follow up. J am Diet Assoc 2007;107:1755-1767

24. Sanyal AJ, Mofrad PS, Contos MJ, et al. A pilot study of Vit E versus Vit E and pioglitazone for the treatment of nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol 2004;2:1107-1115

25. Klein EA, Thompson IM, Tangen CM, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 2011;306:1549-1556

26. Schurks M, Glynn RJ, Rist PM, et al. Effects of vitamin E on stroke subtypes:meta-analysis of randomised controlled trials. BMJ 2010;341:c5702

27. Davies MJ, Bergenstal R, Bode B, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes. The SCALE Diabetes Randomised Clinical Trial. JAMA 2015;314)&):687-699

28. Petit JM, Cerceuil JP, Loffroy R, et al. Effect of liraglutide therapy on liver fat content in patients with inadequately controlled type 2 diabetes. The LIRA-NAFLD study. J Clin Endocrinol Metab 2016;doi:10.1210/jc.2016-2775