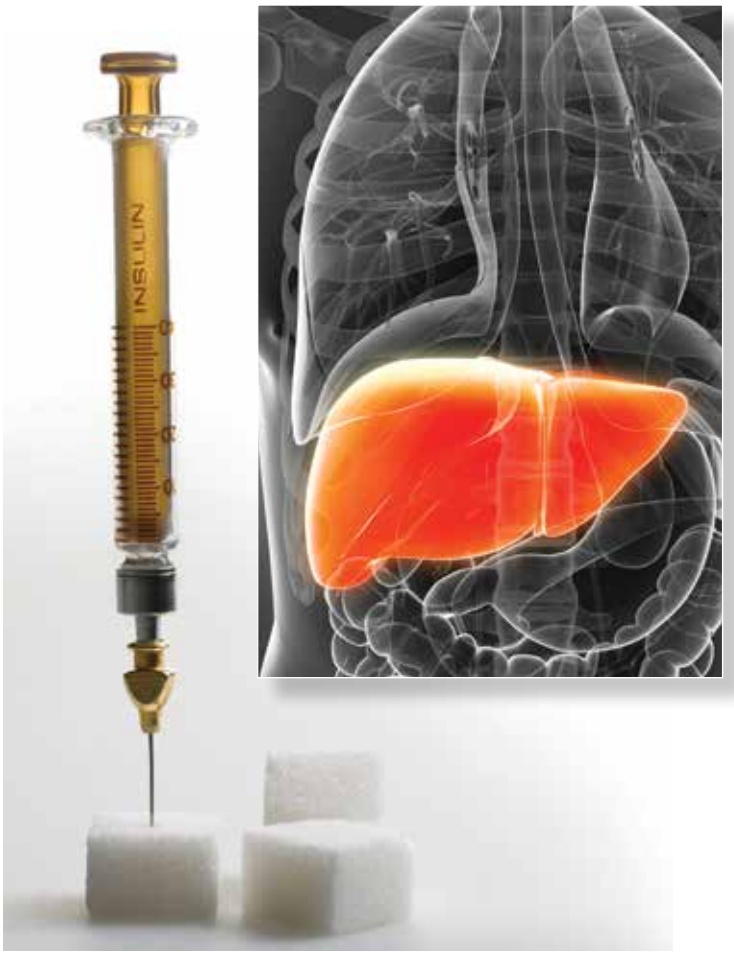
Type 2 diabetes and fatty liver disease

A pathogenic duo with clinical implications



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Nonalcoholic fatty liver disease (NAFLD) is common in people with type 2 diabetes and its subtypes may contribute to significant morbidity and mortality. NAFLD predicts the development of diabetes and vice versa and each condition serves as a progression factor for the other.

Key points

- **Nonalcoholic fatty liver disease (NAFLD) magnifies insulin resistance and its presence increases the risk of type 2 diabetes.**
- **Type 2 diabetes progresses NAFLD, often to nonalcoholic steatohepatitis (NASH) with fibrosis.**
- **Clinical noninvasive tools that enable simple and cost-effective serial assessment of NAFLD severity are increasingly available.**
- **In patients with type 2 diabetes and NAFLD the primary focus of treatment is effective weight management and exercise.**
- **Medications targeting NAFLD in people with type 2 diabetes, especially to potentially prevent or reverse liver fibrosis in those with NASH, require further study.**

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Nonalcoholic fatty liver disease (NAFLD) is a chronic disease that includes a spectrum of liver pathology from simple steatosis to nonalcoholic steatohepatitis (NASH) and, in some cases, progression to cirrhosis and hepatocellular carcinoma (HCC) (Figure 1).[1] Steatosis alone is thought to be a relatively benign condition from a liver point of view; however, NASH can progress to cirrhosis. Cirrhosis due to NASH is usually progressive and can be complicated by liver failure or HCC with the need for liver transplant.[2,3] Traditionally, NAFLD is diagnosed in the absence of other causes of liver disease, including a history of excessive alcohol intake; however, increasingly it is recognised to coexist with other liver diseases and to worsen their prognosis. There is a clear association between NAFLD and diabetes. Studies over recent years have shown that NAFLD predicts the development of diabetes and vice versa and that each condition serves as a progression factor for the other.[3]

Epidemiology of NAFLD and associations with diabetes

NAFLD is common and estimated to be present in about 30% of the western adult population and in about 20% of the Asian population (although with a wide geographical variation in Asian countries of 12.5 to 38%).[4] This prevalence increases to the majority of people in populations with diabetes and obesity.[5] NASH, as the inflammatory and progressive form of the disease, is estimated to be present in 3 to 5% of the general adult population but can be over eight times more common in some cohorts with diabetes and/or obesity. Diabetes is independently associated with liver fibrosis and is an independent predictor of fibrosis progression.[3,6,7] Moderate-to-severe fibrosis has been found in 22 to 60% of patients with type 2 diabetes from tertiary

diabetes centres with steatosis on ultrasound.[3,8] NAFLD is projected to be the leading indication for liver transplantation within the next decade and the increasing prevalence of diabetes is likely to be contributing to this upward trajectory.[3,9] The presence of NAFLD has also been noted to increase the risk of incident diabetes.[3,10]

Pathogenic factors linking NAFLD to diabetes

The increased prevalence of NAFLD in patients with diabetes is related to altered insulin signalling (see Figure 2).[3] Particularly in early type 2 diabetes, insulin deficiency is relative rather than absolute, with high insulin levels that are not enough to overcome levels of insulin resistance in glucose pathways. Insulin acts downstream of many pathways that regulate glucose, lipid and protein metabolism, in addition to cell growth and many other physiological functions. Many of these pathways remain sensitive to insulin, such that these high insulin levels can lead to excessive activation in them. In the formation of hepatic steatosis, relative insulin deficiency leads to excessive lipolysis in adipose tissue and increased free fatty acid delivery to the liver, yet, simultaneously, hyperinsulinaemia upregulates sensitive hepatic lipid synthesis pathways leading to excessive de novo production of lipids.[3]

NAFLD, in turn, will exacerbate insulin resistance and possibly interfere with pancreatic beta cell function, leading to an increased risk of diabetes (see Figure 3).[3,11]

Several mechanisms could contribute to the progression of NAFLD in diabetes. These are likely to include:

- fat overload in the liver leading to the production of toxic fat metabolites, including free fatty acids and free cholesterol
- hyperinsulinaemia overstimulating profibrotic liver pathways
- chronic hyperglycaemia leading to increased advanced glycosylation end products and oxidative stress
- increased absorption and action of endotoxins (or 'bad bacteria') from the gut.[12,13]

So-called 'common soil', including both genetic and environmental factors such as visceral adiposity, diets rich in saturated fat and fructose, lack of exercise, low vitamin D and presence of obstructive sleep apnoea, is also likely to play a part.[2,14,15]

NAFLD and the diabetes phenotype

Given the factors linking both diabetes and NAFLD (as discussed earlier), it would be difficult not to conclude that each condition could alter the course of the other.[3] Studies have not consistently shown an increase in HbA_{1c} in people with diabetes and NAFLD,[16,17] but these patients seem to have higher insulin requirements and/or differential responses to some antidiabetic medications.[18] Diabetes complications may also be exacerbated in the presence of NAFLD.[19] These findings appear most important in patients with NASH and less important in those with isolated steatosis.[3,20]

NAFLD does not only increase the risk of liver-related morbidity and mortality but has also been associated with increased risk of cardiovascular disease and related death, independently of traditional risk factors.[19,21,22] In patients with diabetes, NAFLD has been associated with an increase in the prevalence of macrovascular disease and also perhaps more diffuse coronary artery disease. Increased left ventricular diastolic dysfunction has also been associated with NAFLD in people with diabetes.[3]

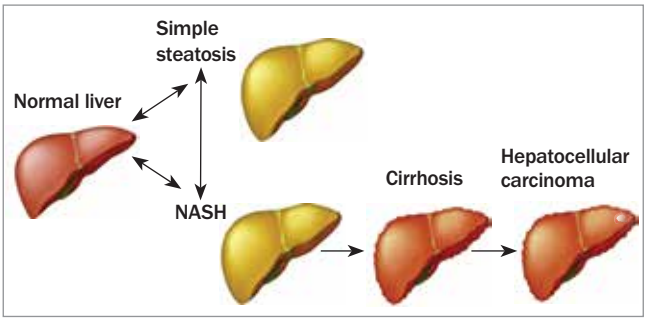


Figure 1. Nonalcoholic fatty liver disease spectrum from simple steatosis to nonalcoholic steatohepatitis (NASH) with varying degrees of hepatocyte damage, inflammation and fibrosis, and which in some cases can progress to cirrhosis and hepatocellular carcinoma.
Adapted from Cohen JC, et al. Science 2011; 332: 1519-1523.[1]

NAFLD may also be associated with increased prevalence and incidence of renal disease, including microalbuminuria and chronic kidney disease, in patients with and without diabetes.[19,23,24] A higher prevalence of retinopathy has also been observed with NAFLD in patients with type 1 diabetes.[25] An elevated prevalence of liver fibrosis secondary to NAFLD has been found in patients with types 1 or 2 diabetes with a past history of foot ulceration.[26]

NAFLD and diabetes have both been associated with an increased risk of HCC and colonic neoplasm.[18] The population risk of HCC attributable to NAFLD is close to 30%.[27] Diabetes is a risk factor for development of HCC in NAFLD, although it is unclear whether diabetes and NAFLD have a synergistic effect on risk of HCC.[28]

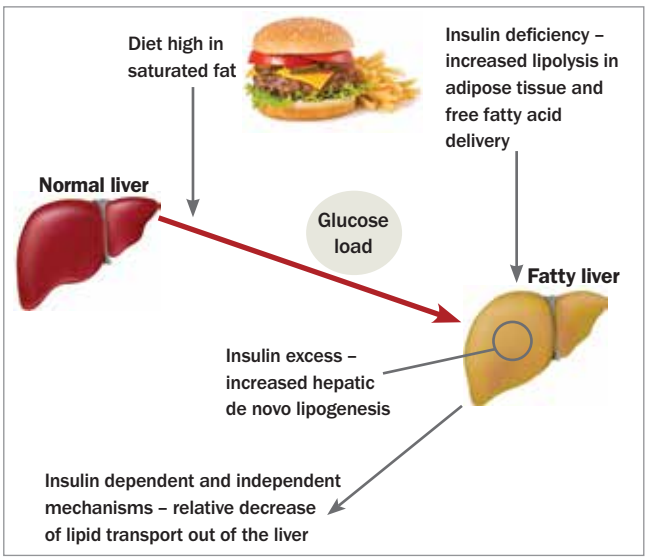


Figure 2. The roles of simultaneous insulin resistance and hyperinsulinaemia that usually coexist in early type 2 diabetes in the development of hepatic steatosis.

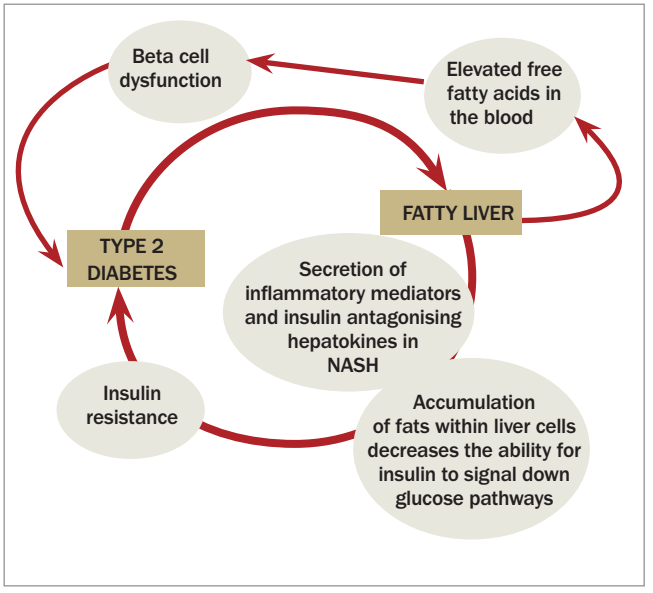


Figure 3. Fatty liver can contribute to diabetes pathogenesis.
Abbreviation: NASH = nonalcoholic steatohepatitis.

Screening patients for NAFLD

Given the high prevalence of NAFLD in people with type 2 diabetes, this diagnosis should be considered in all patients with diabetes. A thorough clinical examination should be carried out yearly in people with diabetes. This includes an assessment for clinical stigmata of chronic liver disease, such as spider naevi, liver palms, excessive bruising, hepatomegaly, ascites and splenomegaly. Indirect markers of significant liver pathology, such as a low platelet count and declining albumin or elevated prothrombin levels, in the absence of other causes, should also be viewed as suspicious. People with persistent elevations in liver enzyme levels or clinical signs of chronic liver disease should be screened for other causes of liver disease (and/or bone disease or muscle pathology if relevant) before the diagnosis of NAFLD is made. Normal levels of liver enzymes do not exclude the diagnosis, as they are often within the reference ranges (derived from populations that included individuals with NAFLD and hepatitis C virus) in patients with biopsy-proven NASH.[3]

The most readily available tool for detection of steatosis is liver ultrasound, which has a sensitivity of up to 94%, although this figure is lower in the presence of obesity, at lower levels of hepatic steatosis and/or in the presence of significant liver fibrosis.[29] Ultrasound also has the advantage of helping to exclude other causes of liver disease and enables screening for portal hypertension or HCC. As such, ultrasound is recommended for any patient with diabetes and persistent elevation in liver enzyme levels and/or signs of chronic liver disease.[3]

Over and above identifying the presence of steatosis, assessment of NAFLD should include an evaluation of severity. Indeed, simple steatosis is unlikely to translate to significant adverse liver-related or perhaps systemic manifestations for the patient, whereas NASH, and particularly NASH with increasing fibrosis, has been shown to have adverse prognostic outcomes.[30] NAFLD severity cannot be determined by liver ultrasound. Liver biopsy remains the gold standard for grading NAFLD pathology, particularly NASH where various degrees of inflammation, hepatocyte injury with 'ballooning' and liver fibrosis may be present. Clearly, as liver biopsy is not feasible or palatable for the sheer number of patients with diabetes and NAFLD, noninvasive assessment is desirable.[3]

Although many biomarkers and algorithms have been proposed, the most clinically useful and cost-effective method for noninvasive assessment of liver fibrosis to date remains the NAFLD fibrosis score (NFS).[31] The NFS has also been shown to independently predict increased mortality, primarily due to cardiovascular death.[32,33] The

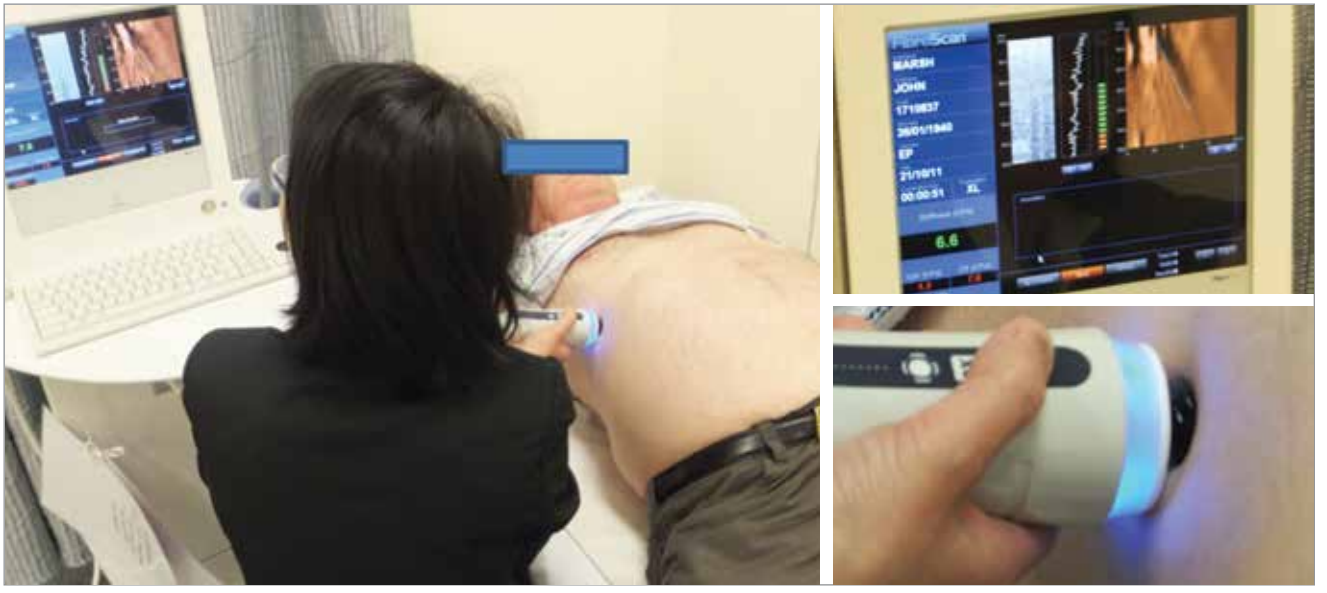
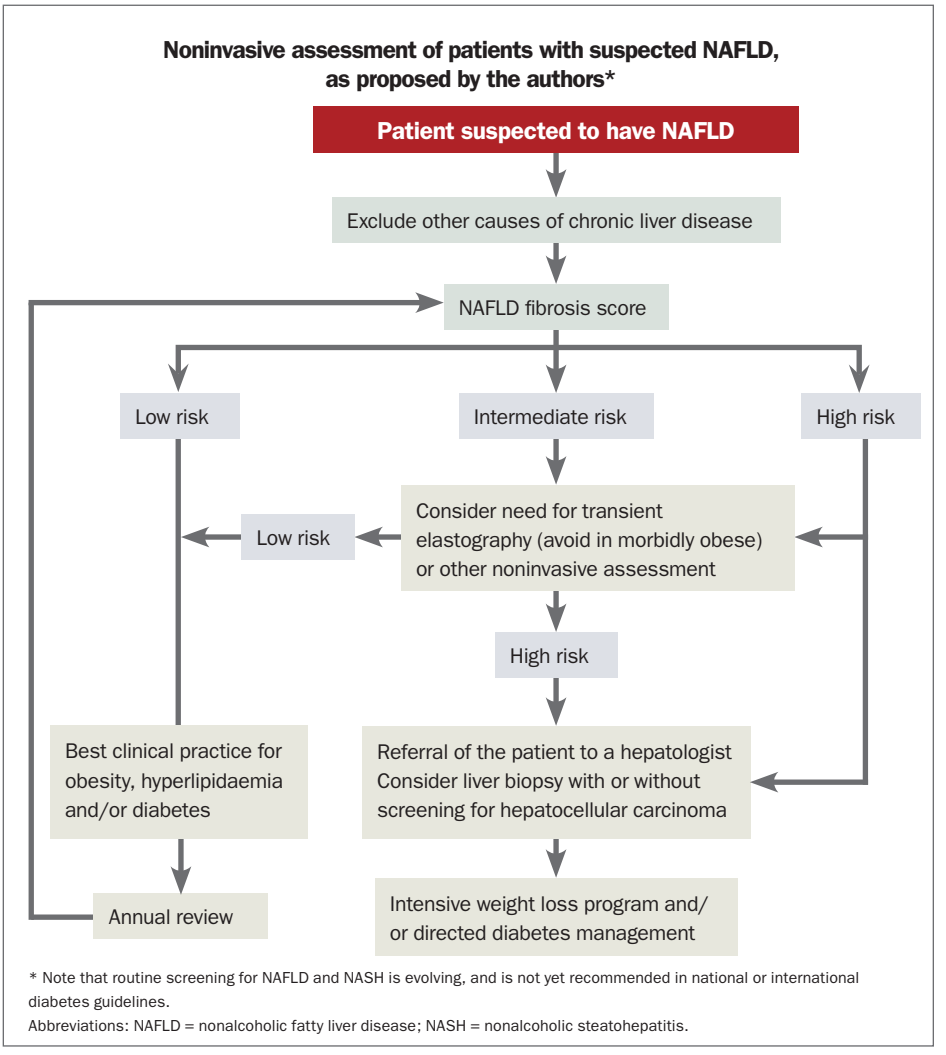


Figure 4. Images of transient elastography.

NFS is a clinical algorithm based on the following clinical parameters: age, body mass index (BMI), presence of diabetes/impaired fasting glucose, aspartate aminotransferase–alanine aminotransferase ratio, blood albumin levels and platelet count. It can easily be calculated by applying a fixed formula but can also be derived by entering patient data into the following website www.nafldscore.com. The calculated NFS is then used to determine whether the patient is low, intermediate or high risk for fibrosis. In a meta-analysis that included 13 studies and more than 3000 patients, a low-risk score was found to have 90% sensitivity and 60% specificity to exclude advanced fibrosis, and a high-risk score had 67% sensitivity and 97% specificity to identify the presence of advanced fibrosis.[22] In other words, a high NFS has a good predictive value for liver fibrosis, although a third of cases will still be missed and further investigations are indicated if clinical suspicion is high despite a low NFS. In addition, caution should be employed when applying this algorithm to patients at the extremes of BMI or age, or in those who may have other conditions that could potentially alter the included laboratory parameters.[34]



* Note that routine screening for NAFLD and NASH is evolving, and is not yet recommended in national or international diabetes guidelines.
Abbreviations: NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis.

Although the NFS is a valuable decision-making tool if a patient is found to be high or low risk, there are a large number of people who are left with an 'intermediate score'. Clearly there is a need for further assessment in this group. Increasingly available at tertiary hospitals is the imaging technique transient elastography[3] (Figure 4). This technology uses pulse-echo imaging acquisitions to measure an elastic shear wave that is propagated through the liver tissue by a vibrationary transducer. The elastic modulus is taken as a measure of tissue stiffness and thus a surrogate measure of liver fibrosis. This technique is highly acceptable to the patient, offers the ability to detect advanced fibrosis and can be used for serial measurement. Elevated BMI can limit its accuracy and/or lead to technical failure, although an XL probe has been developed that can be used in most of these cases.[35] Several groups have recommended transient elastography in patients with intermediate or high-risk NFS to determine the need for liver biopsy[36] (a generic algorithm is shown on this page).

Ultimately, at this stage, these techniques can only be used to assist with counselling patients in regard to whether they should have tailored diabetes management, specialist assessment and/or a liver biopsy.

Management of patients with NAFLD

The most effective treatment for NAFLD to date remains weight loss.[3] Studies have demonstrated improvement of hepatic steatosis with a 5% or greater weight loss by diet and/or weight-reducing pharmacological therapy, but improvement in NASH was shown only when weight loss was at least 7%. Of course, these targets are difficult to achieve by many and bariatric surgery should be considered for patients with diabetes who are obese and have evidence of NASH, particularly those with a BMI of more than 35 kg/m^2 who fail to lose weight by lifestyle measures alone. Exercise appears to offer some benefit and should be incorporated into a lifestyle management plan in patients with diabetes, with intense exercise and resistance training appearing to be of most benefit in those with NAFLD.[3]

All patients with NAFLD and diabetes should be considered for metformin therapy in the absence of contraindications. Although metformin does not appear to have a large impact on liver histology over time, data suggest that it provides some protection against the development of HCC.[37] Glycaemic control should be optimised for the individual. Although little evidence exists, specific antidiabetic agents of interest for people with NAFLD and diabetes include dipeptidyl

peptidase-4 inhibitors and agents associated with weight loss, including glucagon-like peptide-1 agonists (that is, incretin mimetics) and sodium glucose cotransporter-2 (SGLT-2) inhibitors.[3,38] In addition, the use of insulin has been associated with improved fibrosis over time in preclinical and limited human studies. Pioglitazone has the largest evidence base and has been shown to reduce steatosis and inflammation, with variable effects on fibrosis. Concerns about the glitazone drug class, and possible bladder cancer with use of pioglitazone, have limited the prescribing of this medication in recent years.[3,39]

Given the apparent increase in macrovascular risk in patients with NAFLD, particularly those with evidence of NASH and/or fibrosis, close attention to traditional macrovascular risk factors is essential.[3] Patients who are cigarette smokers should be advised to quit. High cholesterol levels should be treated with statin therapy if not contraindicated. Adverse effects of statins on the liver are exceedingly rare and should not be a reason to avoid this therapy in patients with NAFLD.[40] Ezetemibe may also have some beneficial effects on liver histology, primarily on hepatic steatosis.[41] Hypertension should be treated and, as with renal disease, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers appear to be first-line agents.[3,42]

Vitamin E has been shown to improve liver histology at a dose of 800 IU/day but has not yet been studied in patients with diabetes.[39] This therapy can therefore not be routinely recommended in people with diabetes given previous meta-analyses demonstrating a small increase in all-cause mortality with its use.[43] Probiotics and vitamin D supplementation as well as continuous positive airway pressure for treating obstructive sleep apnoea may have some use, although evidence is very limited.[3,13,14,44-46]

Monitoring for complications of liver disease is important in patients with cirrhosis secondary to NASH. People with evidence of advanced fibrosis secondary to NASH on liver biopsy or by noninvasive assessment should be considered for routine surveillance with ultrasound to screen for HCC and/or endoscopy to exclude varices.[3,47-49]

Summary

NAFLD is common in people with type 2 diabetes and may contribute to significant morbidity and mortality. NAFLD magnifies insulin resistance and increases the risk of type 2 diabetes, whereas type 2 diabetes progresses NAFLD, often to NASH with fibrosis. Clinical tools enabling simple and cost-effective serial assessment of NAFLD severity are increasingly available. Diabetes medicines can be tailored in patients with type 2 diabetes and NAFLD, although given current limited treatment data the focus needs to remain on effective and sustained weight loss and regular exercise.[3] It is predicted that in future years methods to screen noninvasively for NAFLD severity in diabetes will become routine and the evidence base supporting NASH treatment with specific lifestyle measures and medicines will be substantiated. **ET**

References

A list of references is included in the website version (www.medicinetoday.com.au) of this article.

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