# Fatty liver disease
## the next epidemic?

**Nonalcoholic fatty liver disease is often seen in patients who are overweight or have type 2 diabetes. Treatment includes reducing insulin resistance, reducing overall energy intake and saturated fat intake and minimising the risk of liver injury from other sources. Identification and management of this often asymptomatic condition is important to prevent progressive liver disease.**

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Obesity has risen at an epidemic rate during the past 20 years.[1] Results of the 1995 National Nutrition Survey indicate that over 50% of Australian adults are either overweight or obese.[2] It is well established that higher levels of body fat are associated with an increased risk for the development of type 2 diabetes, hypertension, dyslipidaemia, gallbladder disease and osteoarthritis.[3]

More recently there has been a surge of interest in the effect of excess bodyweight on the liver. Nonalcoholic fatty liver disease (NAFLD) is an increasingly recognised condition that is often seen in patients who are overweight or diabetic in the absence of significant alcohol use (less than two standard drinks per day for women and less than four standard drinks per day for men). There is a wide spectrum of liver damage, ranging from simple steatosis to steatohepatitis, fibrosis and cirrhosis. The true prevalence of NAFLD in Australia remains to be determined; however, in the United States it has been estimated as 15 to 20% in the general population and higher in obese individuals.[4,5] NAFLD is the most common cause of abnormal liver test results in adults in the United States.[6]

## Who is at risk?

NAFLD can occur at any age; there have been cases of significant liver disease in patients as young as 9 years.[7] Most people with NAFLD will have associated obesity, type 2 diabetes or hypertriglyceridaemia (Table 1).[8]

Overweight and obesity are defined using the body mass index (BMI), and the definitions may

**IN SUMMARY**

- **Nonalcoholic fatty liver disease (NAFLD) comprises a wide spectrum of liver damage ranging from simple steatosis to steatohepatitis, fibrosis and cirrhosis.**
- **Most patients with NAFLD are asymptomatic and have no signs of liver disease at the time of diagnosis. The liver disease is usually discovered incidentally during routine laboratory examination.**
- **Factors associated with a risk of more severe disease include high levels of alanine aminotransferase (ALT), age above 45 years, type 2 diabetes, obesity and hypertension.**
- **There is currently no drug treatment for NAFLD and management consists of treating associated conditions such as obesity and insulin resistance.**
- **Gradual weight reduction of 5 to 10% of bodyweight improves liver enzyme abnormalities and has been shown to improve liver histology.**

**Table 1. Common risk factors for NAFLD**

- Overweight and obesity (see Table 2 for body mass index classifications)
- Visceral adiposity (waist circumference >102 cm in males and >88 cm in females)
- Type 2 diabetes or insulin resistance
- Dyslipidaemia, particularly hypertriglyceridaemia

**Table 2. Classification of overweight and obesity***

| Classification | Body mass index (kg/m²) | |
|---|---|---|
| | Caucasian | Asian |
| Lean | 18.5 to 24.9 | 18.5 to 22.9 |
| Overweight | 25.0 to 29.9 | 23.0 to 24.9 |
| Obese | ≥ 30.0 | ≥ 25.0 |

* Body mass index is calculated by dividing weight in kilograms by the square of height in metres.
Source: International Obesity Taskforce, The Asia-Pacific perspective: redefining obesity and its treatment.[9]

differ between ethnic groups (Table 2).[9] Patients with an Asian background may be at risk of developing NAFLD at a much lower BMI than are Caucasians. Visceral adiposity also contributes to elevated liver enzymes.[10] Patients are at an increased risk with a waist circumference >102 cm in males and >88 cm in females.[11] All of these conditions are associated with insulin resistance (a syndrome characterised by resistance to the physiological effects of insulin), which seems to be fundamental to the pathogenesis of fatty liver disease.[12,13]

A variety of medications (e.g. tamoxifen, corticosteroids, synthetic oestrogens, amiodarone, calcium channel blockers), surgical procedures (e.g. jejunoileal bypass) and other factors (e.g. total parenteral nutrition) are also associated with NAFLD.[14] The pathogenesis of NAFLD in these conditions may differ from that associated with obesity and insulin resistance, and will not be the focus of this review.

## How to make the diagnosis

Although fatigue and upper abdominal discomfort are common complaints, most patients with NAFLD are asymptomatic and have no signs of liver disease at the time of diagnosis. The liver disease is usually discovered incidentally during routine laboratory examination.

### Liver tests

Most patients have mild to moderately elevated serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and the ratio of AST to ALT is usually less than 1. There is currently no specific biochemical or serological test for NAFLD, and a diagnosis is based on characteristic clinical and histological features in a patient who does not consume significant alcohol.

### Excluding other liver disease

Other causes of liver disease should first be excluded by performing serological tests for viral hepatitis, autoimmune disease, Wilson's disease and haemochromatosis. Elevated serum ferritin levels are found in approximately 50% of patients with NAFLD, but the transferrin saturation is usually normal. If uncertainty exists about the significance of elevated iron studies, this should be evaluated further with a test for *HFE* gene mutations to exclude haemochromatosis. Other chronic liver diseases (such as viral hepatitis and primary biliary cirrhosis) may coexist with NAFLD.[15] Data are now emerging to suggest that coexistent NAFLD may act synergistically to accelerate the progression of other chronic liver diseases.[16]

### Liver ultrasound

A liver ultrasound may provide support for the diagnosis of fatty liver, but the changes seen are not specific: cirrhosis has a similar appearance. On ultrasonography, steatosis produces a diffuse increase in echogenicity of the liver compared with that of the kidneys. This test has a sensitivity of 89% and a specificity of 93% in detecting steatosis,[17] but it cannot be used to determine the severity of fibrosis.

### Liver biopsy

The diagnosis of NAFLD can be established only by liver biopsy, which also provides reliable information about the histological extent of the disease and the risk of disease progression. NAFLD is histologically indistinguishable from alcoholic liver disease. Features seen on liver biopsy include steatosis, mixed inflammatory cell infiltration, Mallory bodies (eosinophilic intracytoplasmic inclusions), hepatocyte injury or cell death, and fibrosis (Figure 1a). The presence or absence of a combination of these features in addition to steatosis accounts for the wide spectrum of NAFLD.

## Natural history of NAFLD and predictors of disease severity

Although there are no prospective studies on the natural history of NAFLD, it appears to be determined by the severity of histological damage. Most patients with NAFLD have a benign, nonprogressive course, and patients with steatosis alone on liver biopsy appear to have the best prognosis.[18] In contrast, features of steatohepatitis or liver cell injury are more likely to be associated with progression of liver

continued

fibrosis and a worse prognosis.[4,5] Data from several studies suggest that approximately 20 to 25% of patients with steatosis associated with features of liver cell injury progress to cirrhosis.[5,19,20] Importantly, in patients with NAFLD and severe liver injury (stage 3 or 4 fibrosis), the rate of liver-related death is equal to that of death from coronary artery disease.[19]

## Is a liver biopsy required?

The role of liver biopsy in the management of NAFLD in clinical practice remains controversial. Factors that may be associated with more advanced liver fibrosis are shown in Table 3.[21-23]

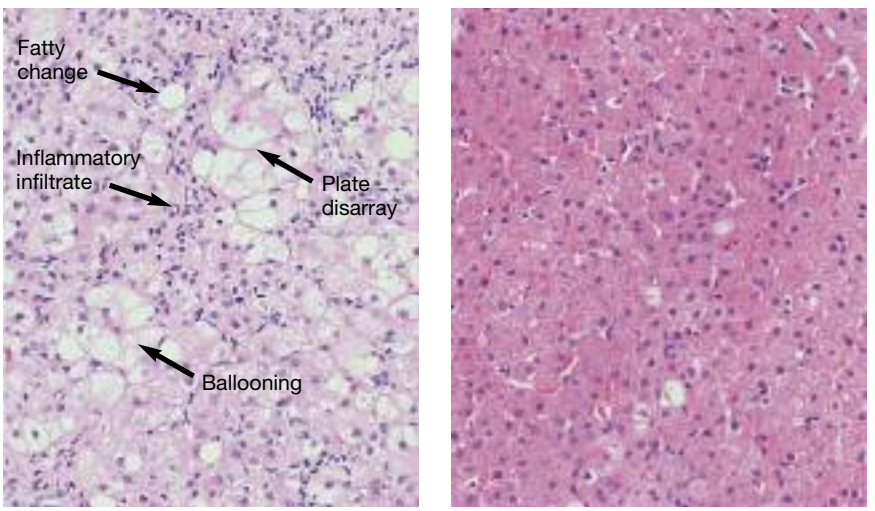
### Table 3. Factors associated with a risk of advanced liver fibrosis

- Older age (>45 years)
- Higher BMI (≥30 kg/m²)
- Presence of type 2 diabetes
- High levels of ALT
- Systemic hypertension

Many gastroenterologists would recommend a liver biopsy for patients with persistently abnormal liver enzymes following attempts to reverse known potential risk factors (see the flowchart on page 45). The presence of factors indicative of more serious liver disease (including hypoalbuminaemia, prolonged prothrombin time, thrombocytopenia or AST>ALT) should prompt early referral to a gastroenterologist for consideration of liver biopsy.

## Theories about the pathogenesis of NAFLD

The pathogenesis of NAFLD remains speculative, and the mechanisms involved in the development and progression of liver injury are still being determined. The retention of triglycerides within hepatocytes may be due to insulin resistance causing alterations in hepatic lipid metabolism. In the development of liver cell injury and fibrosis, a second 'hit' probably occurs in addition to steatosis.[24] This is generally some form of oxidative stress, postulated to result from inflammation, gut-derived endotoxin, micronutrient deficiency or drug-induced mitochodrial injury. Oxidative stress can lead to the production of proinflammatory cytokines, direct cellular damage and fibrosis.




Figures 1a and b. Liver biopsy appearances before and after weight loss. a (left). Before weight loss, there are typical features of steatohepatitis including steatosis (fatty infiltration), hepatocyte ballooning, inflammatory cell infiltration and liver plate distortion due to sinusoidal fibrosis. b (right). In the same patient after a weight loss of 7.1% of bodyweight, the biopsy shows resolution of the steatosis and inflammation.

## Treatment of NAFLD

There is currently no established drug therapy for NAFLD. Treatment is therefore directed initially at controlling the conditions associated with NAFLD and minimising the risk of liver injury from other sources (see the flowchart on page 45).

### Abstinence from alcohol

We recommend abstinence from alcohol because it is uncertain whether even small amounts of alcohol are hepatotoxic in the setting of fatty liver disease. However, this issue remains controversial because there is evidence for a protective effect of low dose alcohol intake against cardiovascular disease in the same set of patients.

### Gradual weight reduction

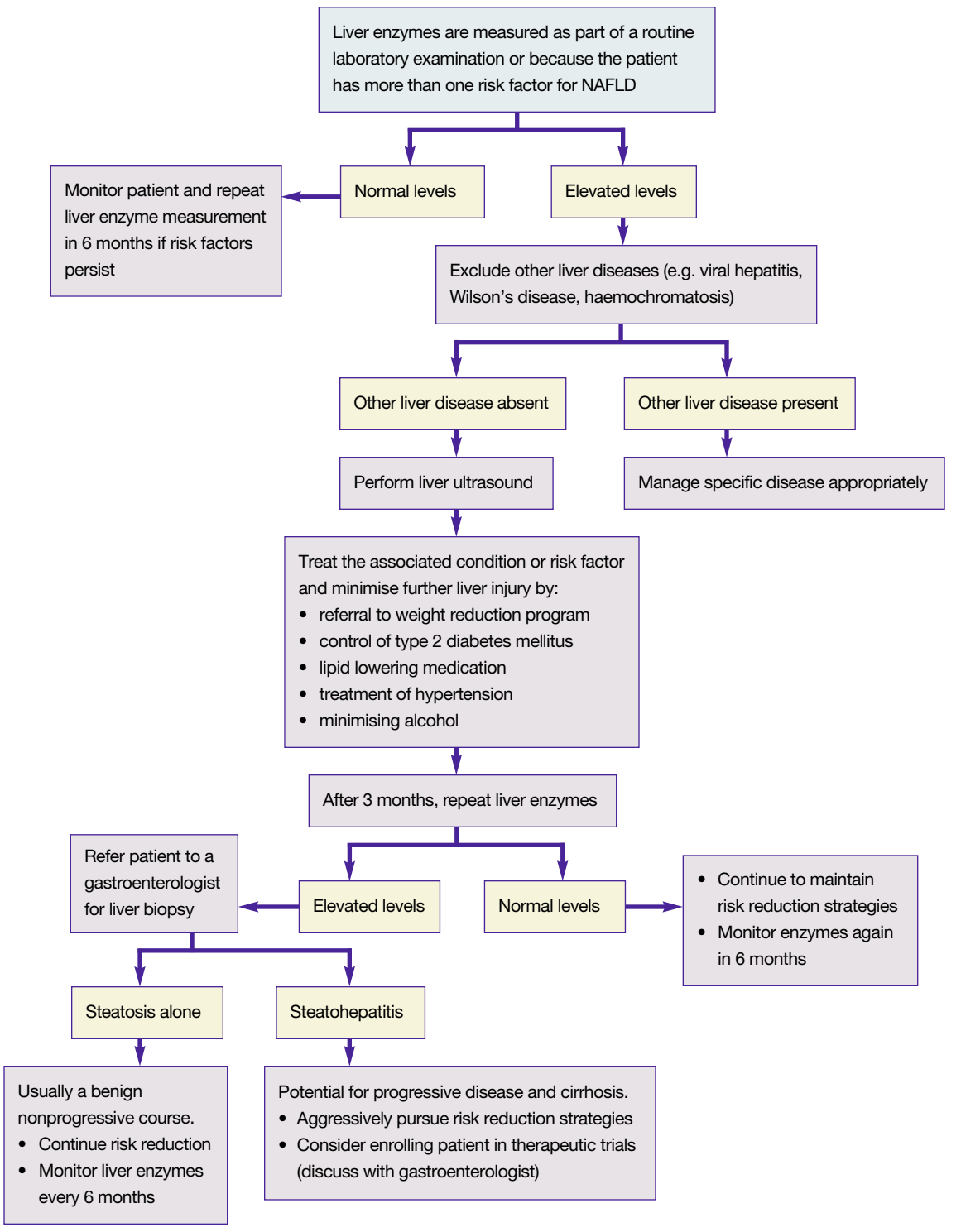
Optimal treatment of diabetes and dyslipidaemia and improvement of insulin sensitivity by active weight reduction are important.

Gradual weight reduction improves liver enzyme abnormalities and has been shown to improve liver histology.[15,25] Too much weight loss too rapidly, as is often seen with many fad diets or radical surgery, may have a negative impact on the progression of liver injury[26] and should be discouraged. However, a gradual weight loss (of 5 to 10% of initial bodyweight over six months) is recommended to improve liver enzymes[25] and insulin resistance,[26] and an improvement in histological features of liver disease has been seen with loss of as little as 5 to 7% bodyweight (Figures 1a and b).

### Pharmacological treatment

Pharmacological treatment strategies aimed at improving insulin resistance (e.g. metformin) and oxidative stress (e.g. vitamin E) are currently being evaluated

## Suggested clinical pathway for the management of NAFLD



in clinical trials. The use of such agents is considered experimental and should not be undertaken in routine clinical practice.

## Strategies for managing weight reduction

It is important that clinicians are able to counsel patients on the basics of a weight-reducing lifestyle with attention to exercise and a well-balanced diet low in saturated fat.

Patients with NAFLD should be discouraged from trying fad diets that promote rapid weight loss over short time frames because this could in fact exacerbate steatohepatitis. The patient should be reassured that a reduction in steatosis may be seen with a weight loss of as little as 5% bodyweight.

Dietary treatment should be focused on improving insulin sensitivity by restricting overall energy intake. The diet should include a low to moderate fat intake of 30% of total energy, preferably as monounsaturated fats.[27] Carbohydrates should have a low glycaemic index and preferably high fibre content.

At least 150 minutes per week of moderately intense exercise should be recommended[28] in addition to incidental

### Strategies for managing weight reduction in NAFLD

- **Do not skip meals**

Even when trying to lose weight, it is important that patients continue to eat three meals a day. Skipping meals, especially breakfast, can lead to higher rates of snacking, fatigue and failure.

- **Reduce the portion sizes of all meals**

Daily energy intake must be restricted to promote weight loss. Recommend that patients cut back on their portion sizes, especially at the evening meal, and choose foods low in saturated fat and added sugar when possible.

- **Increase water intake**

Many patients will not be drinking enough water and may feel hungry when they are in fact dehydrated. Drinking a large glass of water before each meal may also help with satiety.

- **Decrease saturated fat intake and replace with monounsaturated fats**

Overall dietary fat should be reduced to 30% of total energy, with an emphasis on replacing saturated fat with monounsaturated oils. Good sources of monounsaturated fats include olive and canola oils, fish, avocado and nuts.

- **Promote a varied diet with increased fibre choices**

The diet should contain foods from all food groups and aim to include high fibre options such as fruit and vegetables and wholegrain, low glycaemic cereals. High fibre diets increase satiety and help to prevent constipation.

- **Identify behaviours that lead to binge or comfort eating**

Develop strategies to avoid situations where patients may overeat (e.g. when they are stressed, emotional or bored).

- **Increase daily activity**

Daily exercise should be encouraged, including an increase in incidental activity (e.g. using stairs instead of lifts).

- **Avoid further liver injury**

Discuss the consequences of substances or behaviour that may place additional stress on the liver, including excess alcohol, herbal remedies and fad diets involving rapid weight loss.

### Consultant's comment

In their excellent review, Ingrid Hickman and Elizabeth Powell address the importance of fatty liver disorders as a cause of abnormal liver tests in Australia. Current practice indicates that more than half the referrals to liver specialists are for liver test abnormalities that are due to nonalcoholic fatty liver disorders (NAFLD). While most fatty liver disease causes few or no symptoms, fatigue and hepatic discomfort appear to be relatively common complaints in NAFLD, particularly for people who have the more significant (and potentially progressive) disorder of nonalcoholic steatohepatitis (NASH).

Three aspects of fatty liver disease are extraordinarily important. Firstly, a small subset of individuals, particularly those with type 2 diabetes and obesity and older women, often have cirrhosis. The relative risk for cause of death among the 7.5% of the population who have type 2 diabetes is most increased for cirrhosis second only to cancer. Secondly, NAFLD/NASH is a consequence of insulin resistance. Thus we now need to think about type 2 diabetes, cardiovascular disorders, high blood pressure and abnormal liver tests due to fatty disease as all part of one health package. More than 80% of individuals with NAFLD have a strong family history of diabetes, and there is much that can be done to prevent or minimise the impact of this common liver disorder. Thirdly, for preventing diabetes and heart disease, the physiological importance of exercise in correcting insulin resistance should probably be considered as at least equally important as that of diet.

#### Further reading

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activity (such as using stairs instead of lifts).

Patients should be referred to a weight loss specialist who can provide detailed information about dietary composition and the ongoing support required for long term success. This should preferably be a dietitian with an interest in obesity or fatty liver disease, or a centre focusing on healthy weight loss methods (e.g. Weight Watchers). A suggested protocol involves weekly 'weight checks' for 12 weeks (aiming for 0.5 kg weight loss per week) followed by monthly review for 12 months. The box on page 46 lists some common tips used by dietitians to help initiate weight loss. Success with weight loss seems to be related to the initial intensity and frequency of follow up. Monthly review for at least 12 months is required to facilitate long term behavioural changes. Regular exercise is an essential component of a weight loss program that improves insulin sensitivity[28, 29] and enhances weight maintenance.[30]

## Conclusion

NAFLD is a condition of emerging importance, intimately associated with other diseases of affluence such as obesity and type 2 diabetes mellitus. Because of its asymptomatic nature, NAFLD may remain unrecognised for many years and has the potential to develop into progressive liver disease. Research into pharmacological treatment of NAFLD is continuing; however, the primary focus must be to encourage a multidisciplinary approach to weight management and reversal of insulin resistance in 'at risk' individuals. MT

*A list of references is available on request to the editorial office.*

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# Fatty liver disease:
## how to identify and manage it

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