When to suspect it? What to do about it?

Fatty Liver Disease

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The Digestive Health Foundation (DHF) is an educational body committed to promoting better health for all Australians by promoting education and community health programs related to the digestive system.

The DHF is the educational arm of the Gastroenterological Society of Australia, the professional body representing the specialty of gastrointestinal and liver disease in Australia. Members of the Society are drawn from physicians, surgeons, scientists and other medical specialties with an interest in GI disorders.

Since its establishment in 1990 the DHF has been involved in the development of programs to improve community awareness and the understanding of digestive diseases.

Research and education into gastrointestinal disease are essential to contain the effects of these disorders on all Australians.

Guidelines for General Practitioners and patient leaflets are available on a range of topics related to GI disorders. Copies are available by contacting the Secretariat at the address below.

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**BACKGROUND**

- Fatty liver or steatosis means accumulation of fat in the liver, a place where it is not meant to be stored.
- Fatty liver is the commonest reason for abnormal liver tests and hepatic ultrasound results.
- The several causes of fatty liver include excessive alcohol consumption, but by far the commonest is insulin resistance.
- This is usually associated with central obesity.
- **Non-alcoholic fatty liver disease (NAFLD)** is a common disorder that now affects up to one third of the adult population. It is increasingly common in children. The major significance of NAFLD is that:
  1. It is linked to a high risk for type 2 diabetes, metabolic syndrome and resultant cardiovascular disease and some cancers, and
  2. Its form, **non-alcoholic steatohepatitis (NASH)**, can lead to cirrhosis and its complications.

Fatty liver attributable to metabolic factors will be discussed here in the context of NAFLD/NASH. However, it may also co-exist with and worsen liver disease caused by alcohol, hepatitis C, haemochromatosis and some drugs, such as methotrexate. Ways to counter the present epidemic of obesity and fatty liver are an important part of management for all common liver problems.

**DISTINCTION FROM OTHER DISORDERS**

The pathological spectrum of NAFLD/NASH is virtually identical to that of alcoholic liver disease. In fact, NASH was originally defined by the histological features that resemble alcoholic hepatitis, but occurring in patients who have not consumed excessive quantities of alcohol.

Key point:

*The "safe levels" of alcohol intake used to distinguish NAFLD/NASH from alcoholic liver disease are conservative: no more than one standard drink a day (10 g ethanol) for women, or two standard drinks (20 g ethanol) for men. Remember that alcohol and metabolic factors such as obesity can interact to cause more severe liver disease.*

Steatohepatitis may also be caused by other conditions, including rapid and profound weight loss, bulimia, parenteral hyperalimentation (in adults), intestinal blind loop syndrome, lipodystrophy (irrespective of cause) and certain drugs. The latter include:

- Tamoxifen
- Oestrogens
- Corticosteroids
- Amiodarone
- Methotrexate

**PATHOLOGICAL SPECTRUM**

NAFLD encompasses a pathological spectrum from steatosis to cirrhosis; the latter may eventually lead to liver failure. It includes:

- **Simple (or bland) steatosis** - accumulation of fat in the liver without hepatocellular injury, liver inflammation or fibrosis (scarring).
- **Steatohepatitis (NASH)** - steatosis accompanied by hepatocellular injury (ballooning degeneration, Mallory's hyaline), lobular inflammation (with polymorphs), often with hepatic fibrosis.
- **Cirrhosis** - previously termed 'cryptogenic', but with the same risk factors as NASH (obesity, diabetes, metabolic syndrome).
- **Complications of cirrhosis** - portal hypertension (oesophageal varices), liver failure (ascites, jaundice, muscle wasting, encephalopathy), liver cancer (hepatocellular carcinoma, HCC).
HOW COMMON IS NAFLD?

Unexplained liver test abnormalities, particularly alanine transaminase (ALT) elevation, are, in most instances, due to NAFLD. In the 1990s, the prevalence of such unexplained abnormalities was approximately 7-15% in North American adults.

There are no comparable Australian data, but based on the similar prevalence of overnutrition (40-60%), obesity (20-32%) and diabetes (~8%) between Australia and North America, there is reason to believe the prevalence of NAFLD would be similar in this country. A recent school survey in NSW found that 9% of all year 10 boys (far less girls) and more than 40% of obese boys had raised ALT.[Booth M, Okely AD, Denny-Wilson E et al. (2006). NSW Schools Physical Activity and Nutrition Survey (SPANS) 2004: Summary Report. Sydney: NSW Department of Health. www.health.nsw.gov.au]

Hepatic imaging. More informative data on community prevalence of NAFLD come from studies using hepatic ultrasonography or magnetic resonance imaging. The results show that the prevalence of fatty liver in Japan, a country not noted for high obesity rates, is now 29%; this is a real increase (~12%) during the last decade or so. Very similar data from China and Korea in thousands of individuals surveyed indicate that the key change in people who developed steatosis was a modest increase in body mass index (BMI) (median ~1 kg/m²), while the 4% or so who lose steatosis decrease BMI by ~1 kg/m². The dual significance of these observations is that:

(i) visceral adipositiy (central obesity), fat stored within abdominal storage sites, correlates best with NAFLD, not overall obesity, and

(ii) the amount of weight reduction required to reverse NAFLD is small.

Other ultrasound studies conducted in Europe, North America and Asia during the last decade consistently show that the community prevalence of NAFLD exceeds 20%. More alarming still is a large study from the South-Eastern region of the USA which used the highly sensitive approach of proton magnetic resonance spectroscopy to determine hepatic lipid content. This study showed that 45% of Hispanics, 33% of White Americans (42% of men, 24% of women) and 24% of blacks had steatosis; twice as many men were affected as women.

Asian studies indicate that Indians have the highest prevalence of metabolic syndrome, followed by rural Malays and Chinese. It appears likely that between one quarter and one third of the general population have a fatty liver. Based on the importance of obesity and diabetes as risk factors, the unmitigated rise in the obesity/diabetes pandemic, and the existing evidence that fatty liver disease is common among overweight or obese Australian children, it is likely that the prevalence of NASH will continue to increase.

Liver histology. The only way to confirm the diagnosis of fatty liver disease with certainty and to assess its severity is by liver histology. While liver biopsies are not feasible for community studies, autopsy results and hepatic histology from living-related liver donors consistently show the prevalence of significant steatosis is 20-40%.

Even more impressively, 5 of 6 people who undergo bariatric surgery for obesity have NAFLD, and between 10% and 25% of these have NASH. A small proportion have established cirrhosis or severe fibrosis.

WHO HAS NAFLD, AND WHICH NAFLD PATIENTS HAVE NASH?

Metabolic risk factors can be identified in ALL patients with NAFLD. The most reproducible ones are highlighted [BOX 1] (Page 5).

Key point:

Suspect NASH in anyone with unexplained ALT elevation and/or increased echogenicity on ultrasound when there is a history of recent weight gain or expansion of abdominal girth.

It is not possible from routine liver tests or hepatic imaging to distinguish which patients with NAFLD have the more significant liver disease of NASH. However, some factors presage a higher probability that NASH will be complicated by cirrhosis, while other laboratory test results can be a subtle indication of the presence of significant hepatic fibrosis. These factors are summarised in Box 2 (Page 5).
Box 1. Key risk factors for NAFLD

- Central (visceral) obesity (see Table 1 for definitions)
- Glucose intolerance, type 2 diabetes
- Family history of type 2 diabetes
- Family history of fatty liver disease
- Hyperlipidaemia, particularly hypertriglyceridaemia
- Features of metabolic syndrome, e.g., raised blood pressure (see Table 3)

NB: The prevalence of NAFLD increases with age up to 30 years in men, after which it plateaus, and up to 50 years in women. Age is a risk factor for severity of NASH (BOX 2). NAFLD is more common in boys and men up to the age of 50 years, after which the prevalence in women resembles that of men (a similar trend to cardiovascular disease).

Box 2. Factors associated with a higher probability of cirrhosis in patients with NAFLD

- Older age
- ALT raised (versus normal)
- Change in AST:ALT ratio ($\geq 1.0$)
- Low serum albumin
- Low platelet count
- Obesity
- Hyperglycaemia (glucose intolerance) or established diabetes
- Metabolic syndrome (see Table 3), and its severity
- Low serum adiponectin level*

* Low serum adiponectin correlates with onset of diabetes and cardiovascular complications in persons with metabolic syndrome, and appears to distinguish NASH from simple steatosis. However, it is not a routinely available test.
NASH may come to light in the seemingly paradoxical situation of rapid and profound weight loss, for instance during investigation of suspected hepatic malignancy when a patient has hepatomegaly or abnormal liver tests. It is possible that an episode of weight loss can precipitate liver injury in people with steatosis. In an earlier era of more radical forms of obesity surgery (e.g., after jejuno-ileal by-pass), cases of steatohepatitis were diagnosed commonly and occasionally terminated fatally. Individual case reports of subacute liver failure or rapid progression to cirrhosis have been described in persons subjected to repeated episodes of weight loss followed by weight gain. However, present approaches to obesity treatment, including gastric banding, appear to improve (even reverse) NASH rather than precipitate it.

Key point:
The personal history of changes in lifestyle linked to decreased physical activity, weight gain and increase in abdominal girth is critical in assessing someone with abnormal liver tests.

The majority of patients are asymptomatic. They come to medical attention because of abnormal liver tests or an incidental finding of diffusely increased echogenicity (“bright liver”) on hepatic ultrasound; the latter is suggestive of fatty liver, although there are other possible causes, such as cirrhosis.

Patients often complain of:
• fatigue
• right upper quadrant discomfort

Pain attributable to fatty liver disease is unusual.

Some patients have hepatomegaly. The consistency of the liver is usually firm (“rubbery”), but not hard; it may be slightly tender. Peripheral stigmata (spider naevi, palmar erythema, Dupuytren’s contractures) associated with this form of liver disease are uncommon.

Anthropometric measurements: All doctors should now routinely take and record fundamental measurements of body composition. After weighing the patient (in kg) and measuring their height in metres (m), body mass index (BMI) is readily calculated:

\[
\text{BMI} \ [\text{kg/m}^2] = \frac{\text{weight} \ [\text{kg}]}{\text{height} \ [\text{m}]}^2
\]

In addition, a measurement of central obesity should be taken, such as waist circumference or waist: hip ratio. Waist circumference is measure with the patient standing, halfway between lower rib cage and iliac crest. Normal values for waist circumference, and categories of over-nutrition by BMI are presented in Table 1.

A recommended approach to primary care investigation of someone suspected to have NAFLD is outlined in Figure 1.
Figure 1. An approach to diagnosis and specialist referral in cases of NAFLD

ALT RAISED (any value)

CONSIDER: central obesity, obesity, diabetes, metabolic syndrome

CONSIDER: HBV, HCV, alcohol, medications

YES: Then perform Hepatic ultrasound

YES: (Manage Accordingly)

Diffuse hyperechogenicity (LIKELY NAFLD)

UNLIKELY NAFLD

NORMAL

EVIDENCE OF CIRRHOSIS (low albumin or platelets, portal hypertension on imaging)

YES:
Refer to gastroenterologist or hepatologist

NO:
6 month lifestyle adjustment (physical activity, diet)

REPEAT ALT

RAISED:
Refer to gastroenterologist/hepatologist, or obesity service (BMI >35kg/m², or diabetes service

ALT NORMAL

Reinforce good lifestyle and dietary habits. Monitor blood pressure, blood glucose, cancers
Liver biochemistry ("liver function tests"):

- ALT and gammaglutamyltranspeptidase (GGT) elevations are the commonest disturbances.
- The value for ALT is usually greater than AST.
- If AST is greater than ALT, this could indicate cirrhosis, or alcoholic liver disease.
- Minor abnormalities of serum albumin and bilirubin may indicate cirrhosis.

*Note that disproportionate elevation of GGT, or an elevated MCV on full blood count, should raise concerns about excessive alcohol intake.*

Elevated serum ferritin is very common (~60% of cases) in patients with NAFLD, but iron overload (indicated by the serum transferrin saturation, or iron stain on liver biopsy) is rare. In cases with a family history or where there is clinical concern about genetic haemochromatosis, HFE gene testing can be performed.

Test of insulin resistance:

These are essential. Simple tests that may indicate insulin resistance include:

- fasting blood glucose (FBG)
- serum insulin
- C-peptide levels (see below).

Asian-Pacific guidelines for NAFLD recommend that a minimal requirement is FBG. If this is elevated (≥5.6 mmol/L), an oral glucose tolerance test (GTT) should be performed according to the 2005 recommendations of the International Diabetes Federation. More detailed assessment of insulin resistance ideally requires a dynamic rather than static tests. An acceptable compromise for the excessive cost of multiple serum insulin measurements is to perform a 75G oral GTT.

In addition to blood glucose determinations at time 0 (FBG), 30, 60, and 120 minutes, insulin levels can be determined fasting and at 120 minutes; failure to return to normal values indicates insulin resistance. C-peptide reflects the rate of pancreatic insulin secretion; serum levels are often raised in patients with NASH. It may be a useful marker for interventions designed to improve insulin sensitivity, but this remains to be determined.

Blood count:

Low platelet count is common in cirrhosis.
Serum lipids: Measurement of fasting serum lipids is also important. Elevated cholesterol and triglyceride levels are commonly detected, usually with a disproportionate elevation of serum triglyceride. In accordance with underlying insulin resistance, low HDL and high LDL cholesterol are frequently noted.

Hepatic imaging: About two-thirds of patients with significant steatosis will have an abnormal hepatic ultrasound (US) examination. However, the usual pattern of increased echogenicity is non-specific; it may also be observed with significant fibrosis, irrespective of the cause. CT scanning is probably as sensitive as US, the finding being increased radioluency. However, no form of hepatic imaging can distinguish between steatosis and steatohepatitis. Subtle signs of cirrhosis can sometimes be observed with hepatic imaging, including dilated portal vein, presence of retroperitoneal varices, nodular liver edge and consistency, but the sensitivity of any imaging modality for detection of cirrhosis is low.

Liver biopsy: A liver biopsy should be considered when the diagnosis of NASH is uncertain. The diagnostic accuracy of contemporary blood tests and hepatic imaging for hepatobiliary disease are such that this is unlikely to apply in the vast majority of cases of suspected chronic liver disease. On the other hand, only liver biopsy can reliably distinguish between cases of steatosis, NASH and NASH with advanced fibrosis or cirrhosis. Since the latter is the main determinant of prognosis, biopsy can be helpful in clarifying the severity of liver disease as a guide to motivating patients to embark on lifestyle change or obesity therapy.

Conversely, a nihilistic case can be made for not usually performing liver biopsy in cases of NAFLD because there is not yet specific therapy. The development of non-invasive approaches to estimate inflammatory activity and fibrotic severity in NAFLD may further decrease the applicability of liver biopsy. As a result of these uncertainties, there are currently no consensus guidelines amongst specialists in the field on who and when to biopsy.

### Table 2. Some other conditions associated with NAFLD, and the impact on disease severity

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>OVERWEIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallstones</td>
<td>None (predisposing factors in common)</td>
</tr>
<tr>
<td>Polycystic ovarian syndrome</td>
<td>Often mild</td>
</tr>
<tr>
<td>Hypopituitarism and hypothalamic disorders</td>
<td>Often severe</td>
</tr>
<tr>
<td>Sleep apnoea</td>
<td>None (predisposing factors in common)</td>
</tr>
<tr>
<td>Gout</td>
<td>None; consider metabolic syndrome</td>
</tr>
<tr>
<td>Lipodystrophy</td>
<td>A cause of NASH</td>
</tr>
</tbody>
</table>
NATURAL HISTORY AND PROGNOSIS: DOES ANYONE EVER DIE OF FATTY LIVER DISEASE?

In the absence of steatohepatitis, steatosis rarely causes fibrosis or progressive liver disease. In contrast, NASH with fibrosis may be associated with progression to cirrhosis.

The proportion of patients with NAFLD in the community who have cirrhosis is not known. Amongst those referred to liver clinics and selected for biopsy, about 25% have NASH with significant fibrosis. Like hepatitis C, NASH with fibrosis appears to be a slowly progressing liver disorder. In one community study, ~5% NAFLD patients developed cirrhosis over 10 years. Among patients reviewed in hospital-based liver clinics, progression to cirrhosis is higher, about 20% over 10 years, and the mortality of those with advanced fibrosis/cirrhosis is ~12% over 10 years.

Obesity and fatty liver disorders have been associated with the development of hepatocellular carcinoma (HCC). The exact risk is not known, but it appears to be lower than for other causes of cirrhosis. Diabetes, and possibly obesity, insulin resistance and fatty liver could act synergistically to increase the already substantial risk of HCC with chronic HBV or HCV infection, or heavy alcohol exposure.

Although the overall morbidity and mortality attributable to NAFLD remain rather low compared with other liver diseases, it is important to note that the magnitude of increased relative risk from liver disease in patients with type 2 diabetes is second highest to cancer. Further, liver disease was the third ranked cause of death in one US community study of patients with NAFLD, compared with ~13th in age and gender-matched controls.

Key point:
These observations indicate that attempts to identify significant liver disease in persons with fatty liver are likely to be worthwhile, particularly if something can be done to reverse NAFLD.

Finally, it needs to be reiterated that patients with NAFLD have central obesity and insulin resistance. They are therefore at increased risk, not only of cirrhosis, but also of diabetes, cardiovascular mortality, and certain cancers (breast, bowel and renal).

Attempts to improve the health of such individuals, as well as regular monitoring for these other disorders, are clearly vital. Anecdotal experience is that insight into this “health package” provides useful leverage in bringing about the behavioural changes in physical activity and eating required to correct weight disorders, insulin resistance and NAFLD.

WHAT CAUSES NAFLD?

The steatosis of NAFLD is related to insulin resistance. Opinions vary as to whether insulin resistance comes first, causing steatosis by well-understood mechanisms, or whether steatosis comes first and initiates insulin resistance. Whichever applies, it is important for practitioners to be able to describe to those who consult them the nature and importance of insulin resistance.

Insulin resistance is the condition of decreased tissue sensitivity to the actions of insulin. One consequence is a compensatory increase in insulin secretion by pancreatic beta cells, so that serum insulin levels are high, rather than absent, as in type 1 diabetes. Correspondingly, raised serum C-peptide levels reflect the increased rate of pancreatic insulin secretion. In peripheral tissues, exemplified by skeletal muscle, insulin resistance impairs uptake of glucose and fails to suppress hormone-sensitive lipase. The latter effect results in continuous post-prandial hyperlipaemia, with transport of lipids to the liver where they are taken up and stored. In the liver, high insulin levels drive the local synthesis of new fatty acids in the process of lipogenesis, which is also stimulated by high glucose levels. The high insulin levels also impair fatty acid oxidation. The net effect of these processes is to trap fat in the liver.
WHY DO SOME CASES OF NAFLD PROGRESS TO NASH AND CIRRHOSIS?

The factors that determine transition of steatosis to steatohepatitis are unclear, and remain the subject of intense research.

Favoured hypotheses are that a second, injurious mechanism is required, and this could be triggered by excessive oxidative stress in the liver, or by mobilisation of cytotoxic and pro-inflammatory cytokines, like tumour necrosis factor-alpha (TNF-α). An alternative (but not mutually exclusive) concept of NASH pathogenesis is that there are quantitative differences from benign steatosis in the amount of fat ‘partitioning’ into liver, and that fat itself (for example, free fatty acids) causes liver cell injury and promotes the damaging, pro-fibrotic inflammatory response. The process whereby excessive fat storage in non-adipose tissues causes tissue injury is called lipotoxicity. The practical implication is that reversal of the factors (obesity, insulin resistance) that lead to disordered lipid partitioning will heal the liver disease, irrespective of whether steatohepatitis has complicated steatosis. Genetic factors are likely to modify individual predisposition to NASH. These could operate at a several levels to increase the amount and type of fat trapped in fatty livers, the tissue response (injury, inflammation) and the fibrotic outcome to that fat.

The factors associated with more severe forms of NAFLD (Box 2) are likely to work as follows:

Increasing age is associated with a higher risk of insulin resistance, with more prolonged exposure to steatosis, and with a more fibrotic response to liver inflammation.

Obesity may cause more severe and more prolonged insulin resistance, as well as an endless source of fatty acids for hepatic uptake.

Hyperglycaemia and diabetes favour hepatic lipid synthesis because short chain carbohydrates are the ideal substrate for fatty acid synthesis.

Finally, metabolic syndrome (summarised in Table 3) and its attendant low serum adiponectin levels are associated with more severe NASH because of the combination of visceral obesity, glucose intolerance, and the lack of adiponectin as a ‘counter regulatory’ hormone (or adipokine) that shuts off hepatic lipogenesis and promotes fatty acid oxidation.

**Key point:**

The practical message is that measures to counter metabolic syndrome are clearly indicated in people with NASH.

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**Table 3. Components of the metabolic syndrome**

The metabolic syndrome is defined by ‘central obesity’ (see Table 1 for normal values according to gender and ethnicity) plus any two of the following:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting serum triglycerides raised</td>
<td>≥1.7 mmol/L, or receiving treatment for this lipid abnormality</td>
</tr>
<tr>
<td>Fasting serum HDL low</td>
<td>≤1.03 mmol/L in men; ≤1.29 mmol/L in women, or receiving specific treatment for this lipid abnormality</td>
</tr>
<tr>
<td>Raised blood pressure</td>
<td>Systolic BP ≥ 130 or diastolic BP ≥85 mm Hg or receiving treatment for hypertension</td>
</tr>
<tr>
<td>Fasting blood glucose (FBG)</td>
<td>≥5.6 mmol/L# or previously diagnosed type 2 diabetes</td>
</tr>
</tbody>
</table>

*The definition proposed by the International Diabetes Federation (Lancet 2005) is given. Note that there are many definitions of metabolic syndrome, and these are subject to revision. Microalbuminuria and hyperuricaemia are sometimes regarded as minor criteria, and some authors regard polycystic ovarian syndrome as part of the syndrome.

# If FBG is ≥5.6 mmol/L, a glucose tolerance test is strongly recommended, but is not necessary to define the syndrome.
At present, cases should be assessed on an individual basis. A pragmatic approach is that, in the absence of features to suggest more severe liver disease, a period of lifestyle modification (increased physical activity, dietary modification to achieve some weight loss) for 3-6 months is recommended first. If this is associated with normalisation of ALT or resolution of US findings, this removes the imperative to proceed with a liver biopsy. Consideration of liver biopsy can also be given to those with risk factors for cirrhosis, as outlined in Box 2. Laparoscopic cholecystectomy and bariatric surgery provide opportunities to obtain a liver biopsy under safer and more acceptable circumstances for patients with suspected fatty liver disease.

**WHEN TO REFER TO A SPECIALIST**

The usual reasons to consider specialist referral are:

- **The diagnosis is not certain**
- **The GP or patient is concerned about the severity of liver disease**
- **Advice is required about pharmacological management of associated conditions or liver complications**
- **More complex management decisions are needed, for example, obesity therapy, or drug treatment of type 2 diabetes**

**SOME ASSOCIATED DISORDERS, AND HOW TO DEAL WITH THEM**

The common medical disorders associated with NAFLD are obesity, type 2 diabetes, hyperlipidaemias and cardiovascular disease, including hypertension and coronary heart disease.

The practitioner should also bear in mind that insulin resistance, the key risk factor for NAFLD, also increases the risk of breast, colon and several other cancers, enhancing the need to implement appropriate cancer screening tests. A few simple principles can guide the general practitioner concerned about fatty liver disease in a person with metabolic disorders.

**Overweight and obesity.** Correction of these predisposing conditions is the essence of intervention against fatty liver diseases. The presence of NAFLD should only strengthen the resolve of affected persons and their GP to do something about the underlying weight and lifestyle issues. The presence of liver disease should not impact on therapy for obesity, including use of lipase inhibitors (which can improve liver disease) and consideration of bariatric surgery. In some circumstances, interventions that reverse obesity can cure diabetes, metabolic syndrome and NASH. A specialist can provide guidance as to the likely severity of NAFLD in individual cases, and whether more invasive investigation (such as liver biopsy) is advisable before surgery.

**Type 2 diabetes** should be managed on usual lines, with careful attention to correction of visceral obesity, inactivity and hyperlipidaemia, as well as glycaemic control. While there are no agreed guidelines on selection of pharmacotherapy for poorly controlled diabetes in a person with NAFLD, diabetologists and primary care physicians may want to consider use of a thiodiazinedione (‘glitazone’) for possible additional benefits against NASH (discussed later). Consultation with a gastroenterologist/hepatologist could be useful. Most anti-diabetic agents have rarely (less than one
case per 10,000 persons exposed) been associated with instances of drug-induced liver injury. It is therefore important to note that underlying liver disease does NOT increase the risk of drug-induced liver disease.

**Hyperlipidaemia.** Hypertriglyceridaemia should respond to dietary and lifestyle modification. If not, a fibrate such as gemfibrozil can be considered (but not in combination with a ‘statin’). If hypercholesterolaemia is also present, this should be treated with a ‘statin’ if appropriate dietary measures fail to correct the abnormality. The indication for drug intervention is stronger if there are other cardiovascular risk factors (smoking, hypertension, diabetes, family history).

As for antidiabetic drugs, the presence of abnormal liver tests does NOT increase the very low risk of adverse hepatic reactions to statins. Further, hepatologists no longer recommend frequent ALT monitoring in persons taking statins, even those with NAFLD, because elevations are nearly always transient and do not predict more significant liver injury.

**Hypertension, cardiovascular disorders.** These should be treated along the usual lines. The presence of NAFLD or even NASH is not a contraindication to drug therapy or interventions required for coronary heart disease, other than that the risk of post-operative complications after cardiac by-pass surgery is increased for someone with cirrhosis.

**Other associations.** In addition to the medical and personal impact of the predisposing conditions commonly associated with NAFLD/NASH, several other disorders can be associated with fatty liver (see Table 2), probably because of shared aetiogical factors. Management of gallstones and gallbladder disease is along usual lines, except that the presence of cirrhosis greatly increases the risks of cholecystectomy; expert advice may be helpful in cases of doubt. Fatty liver complicating polycystic ovarian syndrome is usually mild, possibly reflecting the age and gender distribution of such cases. Conversely, NASH in association with hypothalamic and hypopituitary disorders is often severe; involvement of a liver specialist in such cases is advised. The association between gout and NAFLD reflects the co-association with metabolic syndrome and has no special management or prognostic implications. Lipodystrophies, irrespective of cause are often associated with NAFLD/NASH; in this case, fatty liver disease (and insulin resistance) resolves with leptin replacement therapy.

**IS FATTY LIVER IN THE CONTEXT OF HEPATITIS C IMPORTANT?**

Fatty liver is found in at least 40% of patients with chronic HCV infection. In HCV genotype 2 and 3 infections, the virus appears to play a direct role, but with HCV genotype 1 and 4 infections, steatosis is attributable to obesity, insulin resistance and type 2 diabetes, thus resembling NAFLD.

The clinical consequences are important. Obesity, steatosis and insulin resistance are associated with a higher rate of cirrhosis, and are also strongly associated with suboptimal responses to interferon-based antiviral therapy. Conversely, research from Brisbane has shown that ALT levels and steatosis improve with dietary changes and improved physical activity in overweight people with hepatitis C. It is therefore important that these measures be considered in shared care of patients with hepatitis C.
WHAT SHOULD WE RECOMMEND ABOUT MANAGEMENT OF FATTY LIVER?

In the absence of type 1, 2 or 3 evidence, strategies for managing patients with fatty liver disease are currently based on what is known about correcting the underlying factors, particularly obesity (or visceral obesity) and insulin resistance.

It is a reproducible observation that successful programmes to counter these metabolic risk factors produce impressive reversal of NAFLD, including restitution of normal liver tests, correction of steatosis and reversal of steatohepatitis and liver fibrosis.

The initial approach is for the GP, specialist, dietician or other expert (personal trainer, physical therapist) to motivate and educate the affected person (or people) to undergo lifestyle changes. How to bring about the desired behavioural changes is the subject of ongoing research, and will need to consider cost-efficacy and translation into public health policy to PREVENT NAFLD in children and adults, as well as to intervene in those already affected.

Key point:
Management of NAFLD should include BOTH increasing physical activity and healthy eating. Primary care physicians can play a pivotal role in engaging at-risk patients and their families in these lifestyle adjustments. NAFLD serves as an additional motivating factor when recognized as a ‘barometer of metabolic disease’.

OBJECTIVES (AND ENDPOINTS) OF LIFESTYLE INTERVENTION

Physical activity. Increasing physical activity improves insulin sensitivity, even in the absence of weight loss. It has also been shown that combining enhanced physical activity with an energy-restricted diet is more effective in promoting weight loss and reversal of fatty liver disease than diet alone.

Key point:
The recommended minimal period of aerobic exercise (e.g., fast walking) to prevent or reverse NAFLD is 140 minutes/day, spread over at least 4 days a week.

Diet. Dietary prescription for NAFLD/NASH is based upon reversing insulin resistance, an intervention that has been shown to delay the onset of type 2 diabetes. In the absence of evidence specific to fatty liver disease, it is reasonable to use a similar dietary approach as for diabetes prevention, and this would be similar to “heart healthy” guidelines.

Key point:
The primary aim should be correction of central obesity and thus of insulin resistance. So the focus should be on waist circumference and modest weight reduction, rather than on restitution of normal BMI. Even a modest reduction (0.5 to 3 kg) may be sufficient to reverse fatty liver.

• The initial target should be no more than 0.5 kg/week
• Rapid weight loss accomplished with ‘crash’ or ‘fad’ diets may result in further deterioration of liver function, particularly with repeated cycles of weight gain and weight loss.
• Weight loss reduces steatosis, liver cell injury and inflammation.
• However, it needs to be sustained in order to reduce the severity of hepatic fibrosis and to prevent diabetes and other metabolic complications.
Many motivated patients will respond to simple dietary guidelines that include modest reductions in energy (caloric) intake, lowering the amounts of saturated fat, total fat and simple (high glycaemic index) carbohydrates, effectively by increasing the proportion of fresh fruit and vegetables and dietary fibre from these and other sources (cereal, selected breads, rice and pasta products). Further information on healthy eating is available from a number of sources, including the NHMRC ‘Dietary Guidelines for Australian Adults’:


**Key point:**

*In managing obese patients or those refractory to simple lifestyle and dietary advice, the general practitioner may need to refer to a dietician or obesity service.*

**Alcohol:** Minimalising alcohol consumption is important. Abstinence may not be necessary; there is evidence for beneficial effects of very low level alcohol intake. However, abstinence should be considered in those who have difficulty keeping below toxic thresholds. Alcohol consumption aggravates induction of steatosis and worsens oxidative stress in the liver, thereby enhancing cellular injury. Interestingly, obesity and insulin resistance are now known to be important risk factors for fibrotic progression in alcoholic liver disease.

**Key point:**

*This reflects the fact that many patients with heavy alcohol consumption have risk factors for NASH (obesity, insulin resistance, glucose intolerance), and the metabolic factors and alcohol toxicity act synergistically to cause liver disease.*

**Drug therapy for NASH:** At present there is no accepted drug treatment for NASH. Steatosis alone is benign and apart from lifestyle adjustment, no further therapy is required. In cases of NASH, particularly with cirrhosis, obesity, diabetes and hyperlipidaemia should be managed along usual lines in an attempt to normalise blood glucose and serum lipids.

The most logical drugs to consider against NASH are insulin sensitising agents, in an attempt to correct the fundamental underlying pathophysiology. Metformin, pioglitazone and rosiglitazone have shown promise in open or small controlled studies, but the glitazones are associated with unacceptable weight gain (about 4% overall at 12 months) and rapid relapse of steatohepatitis after discontinuing the drug. Further large scale clinical trials are continuing. There has also been interest in vitamins C and E, betaine and other antioxidants, but none are of proven benefit in NASH. At present, *ad hoc* drug treatment for NASH is not recommended.
CONCLUDING MESSAGES

Fatty liver disease is part of the obesity and diabetes pandemic. Fortunately, the majority of cases are benign, but cirrhosis can occur particularly in those with obesity and type 2 diabetes. GPs should suspect NAFLD in anyone with abnormal liver function tests (specifically, raised ALT) or diffusely increased echogenicity on hepatic ultrasound when metabolic risk factors, particularly central obesity, are present.

The diagnosis of NAFLD requires exclusion of alcoholic liver disease, hepatitis C, complications of medications and other common liver diseases. Patients who do not already have diabetes are at risk of developing this and other complications of metabolic syndrome; monitoring of blood pressure, blood sugar and screening for common cancers is therefore indicated. A primary care and community focussed approach to obesity prevention is needed to combat escalating rates of NAFLD and diabetes. Conversely, the management of affected people centres on appropriate early recognition, counselling and life-style intervention, or obesity therapy in more advanced and refractory circumstances.