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Practical approach to the diagnosis and management of people with fatty liver diseases

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Key learning points

- 1 In the appropriate metabolic setting, a primary diagnosis of non-alcoholic fatty liver disease (NAFLD) can be made with relative ease.
- 2 A complete history (including family history of diabetes) and examination as well as tests to exclude viral hepatitis are part of the initial evaluation of persons with suspected NAFLD.
- 3 Assessment for other features of the metabolic syndrome (e.g. hypertension, dyslipidaemia, central obesity) is mandatory and helpful as a basis for practical management.
- 4 Criteria for the diagnosis of obesity and overweight are different across racial groups.
- 5 Lifestyle intervention with diet and increased physical activity is the cornerstone of management in NAFLD/NASH.
- 6 Liver biopsy should be considered: (i) in those with warning signs of advanced liver disease; or (ii) in those with clinical features associated with advanced hepatic fibrosis (diabetes, age 45 years, significant overweight or obesity [body mass index ≥ 28 kg/m²]), particularly if liver tests have failed to normalize after attempts at lifestyle adjustment.
- 7 Pharmacotherapy, particularly with insulin-sensitizing agents, show great promise but at present application should be limited to clinical trials.
- 8 In patients with type 2 diabetes and NAFLD, insulin-sensitizing agents could be considered as first-line drug therapy, although further weight gain may be an issue.

Abstract

The spectrum of non-alcoholic fatty liver diseases (NAFLD) encompasses simple hepatic steatosis, steatohepatitis and cirrhosis (Chapters 1 and 2). NAFLD is the hepatic manifestation of the insulin resistance or metabolic syndrome (Chapter 5). Thus, in the appropriate setting, a primary diagnosis of NAFLD can be made with relative ease on the basis of a history, physical examination and a basic panel of biochemical assessments. In persons with liver disease from other

causes, the presence of insulin resistance may adversely influence the progression of liver injury (Chapter 24). A liver biopsy is the only method at present that can distinguish simple steatosis from steatohepatitis. The latter represents a progressive form of liver injury that, in a proportion, may lead to advanced hepatic fibrosis. The initial approach to the management of NAFLD is to institute a programme of lifestyle intervention comprising weight-reduction strategies and enhanced physical activity. The simultaneous identification and appropriate treatment of other components of the

metabolic syndrome is crucial to reduce hepatic as well as cardiovascular morbidity and mortality. Failure to normalize liver tests after a period of 3–6 months is an indication to consider liver biopsy. To date, no universally accepted algorithms exist to identify persons with a high likelihood of having significant hepatic fibrosis and who may benefit from knowledge of their histopathology. Among the published studies, obesity, older age (over 45 years), the presence of type 2 diabetes, or the presence of warning signs of cirrhosis should prompt serious consideration for biopsy. In those with more advanced stages of disease confirmed by biopsy, aggressive lifestyle intervention strategies and enrolment in clinical trials of pharmacotherapy need to be considered.

Introduction

If current trends continue, primary care physicians and gastroenterologists will need to manage an increasing case-load of persons with NAFLD. Thus, an appreciation of the modes of clinical presentation, the optimal tools for diagnosis and therapeutic options is essential. Given the near epidemic proportions of the problems of diabetes, overnutrition and obesity in industrialized and developing nations, primary care physicians will also bear the brunt for case management. While drug therapies may eventually have a role in management, lifestyle intervention is likely to be more feasible and cost effective for the more than 50% of the population of many countries who are already overweight or obese, as well as specifically for the 10–20% of this group who have concomitant NAFLD/NASH. Thus, up-grading of skills by gastroenterologists, hepatologists and specialist medical societies, of patients, the community and government is a central issue for the prevention and control of NAFLD. The role of the specialist physician is likely to remain the identification and management of patients with NASH as opposed to benign forms of NAFLD (see Chapter 14), and particularly those with advanced hepatic fibrosis. Some patients with NASH may be suitable for pharmacotherapies as well as requiring follow-up for the development of liver-related morbidity and mortality.

This chapter presents a practical approach to diagnosis and management of fatty liver disorders. However, as emphasized thematically throughout the book, NAFLD is the *hepatic* manifestation of the metabolic

syndrome, a systemic disorder with many health implications for type 2 diabetes, heart and other vascular disease, and as well as for cirrhosis. A complete metabolic assessment and appropriate therapy of associated conditions is therefore an essential part of individual patient care.

Diagnosis of fatty liver disease

For a more detailed account of the clinical features, investigation and management of persons with NAFLD, the reader is referred to Chapters 13 and 16. The focus of this chapter is a practical road map for clinicians caring for people with fatty liver disorders.

In the past, NAFLD has been primarily recognized in those presenting with abnormal liver tests. It is likely that this bias will continue because physicians are alerted by abnormal pathology results. However, it is now recognized that the full spectrum of NAFLD from steatosis to steatohepatitis, cirrhosis and liver-related morbidity can also occur in those with entirely ‘normal’ liver enzymes by conventional criteria [1]. This raises an important semantic and practical issue of ‘normal’ versus ‘reference ranges’ for liver biochemistry. Two recent publications have assessed the prevalence of elevated aminotransferase (AT) levels in the cohort of subjects from the Third US National Health and Nutrition Survey (NHANES III, 1988–94) (see also Chapter 3). In one report, the data set was evaluated in 15 676 subjects aged 17 years and older and the prevalence of AT elevation (men: aspartate aminotransferase (AST) > 37 IU/L, alanine aminotransferase (ALT) > 40 IU/L; women: AST or ALT > 31 IU/L) was 7.9%. Aminotransferase elevations unrelated to alcohol consumption, hepatitis B and C or haemochromatosis (presumed NAFLD) occurred in 5.4% of the cohort [2]. In contrast, when the data set was subanalysed including only the 8232 participants who had a fasting morning examination, and using the cut-off of ALT > 43 IU/L as elevated, the prevalence of presumed NAFLD after excluding other common causes was 2.8% [3].

To add to the debate, a recent retrospective cohort study from Milan assessed reference ranges for serum ALT levels in 6835 blood donors who were negative for hepatitis B and C markers and HIV. Based on 3927 persons who satisfied the criteria of normal body mass index (BMI), normal serum cholesterol, triglyceride and glucose levels and no concurrent medications, median

Table 15.1 Clinical presentations of patients with NAFLD.

1	Features of the metabolic syndrome*
2	Abnormal liver biochemistry
3	Abnormal hepatic imaging suggestive of fatty infiltration
4	Non-specific symptoms (fatigue, abdominal discomfort)
5	Upper gastrointestinal bleeding (portal hypertension), liver failure or liver cancer

* See Table 15.2.

serum ALT was 11 IU/L, while values were 6, 9, 15 and 26 IU/L for the 5th, 25th, 75th and 95th percentiles, respectively. Based on these data, healthy ranges for serum ALT values, defined as those below the gender-specific 95th percentile, were 30 IU/L for men and 19 IU/L for women [4]. Using the above revised cut-offs for 'abnormal' ALT, Ruhl and Everhart [3] found the prevalence of presumed NAFLD to be 12% for men and 14% for women. Thus, reference ranges for serum AT from many laboratories may not reflect the expected 'normal' values in healthy adults. Physicians therefore need to be alerted to the possibility that significant liver injury may occur in subjects with NAFLD who have AT levels within the 'reference' range, but which are clearly outside the 'normal' range for healthy adults.

With this caveat in mind, patients with NAFLD may present in one of five ways (Table 15.1). NAFLD is now accepted as the hepatic manifestation of the metabolic (or insulin resistance) syndrome (Table 15.2) [5–8] (see also Chapter 5). Thus, while abnormal biochemistry or imaging will alert the physician to follow diag-

nostic pathways for the assessment of liver disease, it is now prudent that all persons presenting with any feature of the metabolic syndrome be assessed for fatty liver disease as well as for other less classic features of the syndrome (as opposed to 'definitional criteria' specified elsewhere in the book) (see Chapter 5); the latter include hyperuricaemia, obstructive sleep apnoea and polycystic ovarian syndrome [9].

In those presenting with abnormal liver biochemistry or imaging suggestive of fatty liver disease, certain clues in the history and physical examination should raise the suspicion of metabolic liver disease (Table 15.3). Of particular importance, questioning regarding recent increases in weight, lifestyle changes and of a family history of NAFLD or type 2 diabetes is mandatory in any patient assessed for abnormal liver biochemistry or a 'bright' liver on ultrasound suggestive of NAFLD. In a recent study of 66 patients with NASH [5], 33 had abnormalities of glucose tolerance, while 13 of 33 (39%) of the remainder had a family history of type 2 diabetes in one or more first-degree relative. In another report [10], 16 of 90 (18%) patients with NASH had a first-degree relative with the condition.

Likewise, an acute phase elevation in serum ferritin that is not associated with increases in transferrin saturation is present in up to 40% of patients with NAFLD; this common finding should therefore alert the physician to the possible diagnosis of NASH [11–15]. Similarly, in patients with non-replicative forms of viral hepatitis, the presence of abnormal liver biochemistry and/or presence of 'rubbery' hepatomegaly should alert the clinician to the presence of NAFLD rather than chronic viral hepatitis. Finally, it is increasingly

Table 15.2 Diagnostic criteria for the insulin resistance syndrome. Modified from the World Health Organization criteria [8].

Component	Definition
Diabetes mellitus, impaired glucose tolerance <i>and/or</i> insulin resistance, together with two or more of the following:	
Raised arterial blood pressure	140/90 mmHg, or documented use of antihypertensive therapy
Raised serum triglycerides	≥ 1.7 mmol/L
<i>and/or</i> low serum HDL-cholesterol	< 0.9 mmol/L for men; < 1.0 mmol/L for women
Central obesity	Waist : hip ratio > 0.90 (for men) waist : hip ratio > 0.85 (for women) <i>or</i> body mass index > 30 kg/m ²
Microalbuminuria	Urinary albumin : creatinine ratio (20 mg/g) <i>or</i> urinary albumin excretion rate (20 µg/min)

HDL, high-density lipoprotein.

Table 15.3 Clinical clues to the diagnosis of NAFLD.*Unexplained abnormal liver tests with:*

Recent weight gain, expanding waistline, change of lifestyle (unemployment, retirement, disability)
Type 2 diabetes or impaired glucose tolerance
Family history of type 2 diabetes or NAFLD
Obesity (particularly central [visceral] obesity)
Dyslipidaemia (elevated triglyceride, low high-density lipoprotein)
Other features of the insulin resistance syndrome or its complications: arterial hypertension, ischaemic heart disease, vascular disease
Raised serum ferritin with normal transferrin saturation
Other liver diseases and the presence of 'metabolic' risk factors
Non-replicative forms of viral hepatitis B or C

recognized that metabolic (fatty) liver disease may be associated with accelerated disease progression in those with liver diseases from any aetiology, including alcoholic liver disease [16] and viral hepatitis [17,18]. Hence, physicians should not be dissuaded from a diagnosis of NAFLD as an additional and modifiable liver disorder in persons with other forms of liver disease and the presence of metabolic risk factors (see Chapters 23 and 24).

The alcohol history must be carefully evaluated in persons with abnormal liver biochemistry. This involves both repeated questioning of the index person, and also of close family members. For clinical research, significant alcohol consumption needs to be excluded. 'Significant' consumption is variously defined as 140 g/week and 20 g/day in men and 10 g/day in women. In clinical practice, it is likely that there is a large proportion of individuals in whom liver disease may be caused by the combination of toxic levels of alcohol consumption and metabolic fatty liver disease (see also Chapter 2). In these persons, alcohol intake should be reduced to the safe levels suggested above (or discontinued completely if it is unlikely that self-control can limit intake to safe levels), concomitant with other dietary approaches aimed at reducing insulin resistance. The importance of lifetime alcohol exposure (versus recent levels of intake) is discussed in Chapter 24.

Abnormal imaging, typically a hyperechoic liver on an ultrasound performed for another indication, is often the first clue to the presence of NAFLD. Conversely, a

'bright' liver on ultrasound may bring useful confirmatory information in a person with suspected NAFLD. However, it should be emphasized that the presence of fat, fibrosis or elevated hepatic iron stores can have an identical sonographical appearance. The sensitivity of sonography for the detection of hepatic fatty infiltration in a recent study was 67%, specificity was 77% and the positive predictive value was 67% [19]. However, ultrasound had 100% sensitivity for the detection of more extensive hepatic steatosis, as defined by 33% of cells showing steatosis [20].

In NAFLD, presentation with symptomatic liver disease (ascites, variceal bleeding, encephalopathy, hepatocellular cancer) has been infrequent. The large burden of NAFLD in industrialized nations [3], and the fact that NASH-associated cirrhosis has an identical prognosis to cirrhosis from chronic hepatitis C [21] (see also Chapter 3), suggests that there is significant case ascertainment bias in attributing liver disease to end-stage NAFLD.

Recent reports indicate that in patients presenting with cryptogenic or obesity-related cirrhosis, NAFLD is likely to be the underlying aetiological cause in approximately two-thirds of cases (see Chapter 14) [22,23]. Further, in current practice, NASH-associated liver failure may present in the later decades (7th and 8th) in individuals with other comorbid conditions, and is therefore often overlooked. For instance, insulin resistance, diabetes and diabetic metabolic control can be significantly worsened by the presence of advanced hepatic fibrosis or cirrhosis, which impairs insulin clearance. In the future, it is likely that NAFLD-associated liver failure may present in earlier decades, given the epidemics of obesity and diabetes affecting young adults and children (see Chapter 19). Advocacy to improved physician and patient awareness of the hepatic consequences of the metabolic syndrome is therefore important.

Patients with the earlier stages of NAFLD may present with non-specific symptoms (see Chapter 13) including fatigue and right upper quadrant pain. The latter is usually a dull discomfort, sometimes compared to a toothache, and often associated with hepatic tenderness so that the person does not feel comfortable lying on the right side. Rarely, more severe pain may be a clue to hepatic pathology. While fatigue is very common, a thorough psychosocial and medical history, as well as a complete physical examination, is required before attributing it to NAFLD. Other common dis-

orders (depression, anaemia, sleep disorders) need to be considered (see also Chapter 14). Unless liver failure has supervened, the physical examination may be normal or only reveal hepatomegaly; the texture of the liver is firm but not hard ('rubbery'), and this is occasionally associated with some tenderness.

When to diagnose NAFLD

While conventionally considered a disease of exclusion, it is important for physicians to consider a positive diagnosis of NAFLD based on the history and physical examination. Features of the metabolic syndrome in association with abnormal liver biochemistry and serum lipids or a 'bright' liver on ultrasound are present in the vast majority of patients. Often the major clue for considering NAFLD as a diagnostic possibility is the presence of overweight or obesity and, more importantly, central obesity and a family history of diabetes. There is clear evidence that the risk of cardiovascular morbidity and mortality in relation to anthropometric variables differs across ethnic groups. Thus, given the enormous cross-cultural migrations that have taken place to regions such as North America and Australia in recent decades, physicians should be aware of ethno-specific cut-offs for anthropometric criteria (Table 15.4) (see also Chapter 18).

Clearly, a discrete panel of laboratory tests needs to be considered in patients presumed to have NAFLD. Diabetes should be excluded with a fasting blood glucose. Appropriate therapy must be instituted if this is present. Tests of insulin resistance (e.g. the homeostasis model assessment (fasting glucose [mmol/L] \times fasting insulin [units]/22.5) or impaired glucose tolerance based on a glucose tolerance test, while not routinely used in clinical practice, should be strongly considered. This is because NAFLD is rarely if ever present in the absence of insulin resistance (see Chapter 5). Estimation of serum lipids and serology for viral hepatitis B and C is mandatory. In the Anglo-Celtic population, consideration must also be given to the performance of iron studies, as haemochromatosis may occur in up to 1 in 300 of the population and may present with non-specific symptoms. As indicated earlier, serum ferritin is increased in approximately 40%, but haemochromatosis is easily excluded in most cases by the percentage iron saturation of transferrin, together with genetic testing (C282Y, H63D). In those

Table 15.4 Measuring components of adiposity. (After World Health Organization [24] and International Diabetes Institute [25].)

Category	Anthropometric criteria
<i>Overweight</i>	
White	BMI \geq 25 kg/m ²
Asian	BMI \geq 23 kg/m ²
Pacific Islander	BMI \geq 26 kg/m ²
<i>Obese</i>	
White	BMI \geq 30 kg/m ²
Asian	BMI \geq 25 kg/m ²
Pacific Islander	BMI \geq 32 kg/m ²
<i>Central obesity</i>	
White	WC > 102 cm (men) WC > 88 cm (women)
Asian	WC \geq 90 cm (men) WC \geq 80 cm (women)
Pacific Islander	Not determined

BMI, body mass index; WC, waist circumference.

with pointers in the clinical history or baseline biochemistry (e.g. a positive family history of Wilson's disease or marked elevations in AT levels), other tests may be indicated including tests for autoimmune liver disease, Wilson's disease and coeliac disease (see Chapter 21). Where the clinical history, examination and baseline biochemistry is suggestive of NAFLD, hepatic imaging by ultrasound can be a useful and relatively inexpensive test that will show appearances consistent with steatosis in two-thirds of cases. However, hepatic imaging cannot distinguish steatosis from steatohepatitis and cirrhosis.

A significant conceptual advance in understanding the pathogenesis and progression of chronic liver disease is the knowledge that liver disease of any aetiology can be significantly worsened by the presence of insulin resistance (NAFLD) [17,26,27]. From a clinical perspective, therefore, the assessment of any form of liver disease should include a consideration of modifiable metabolic cofactors, including obesity, insulin resistance, diabetes and features of the metabolic syndrome. Thus, it is incumbent on the physician treating an obese or diabetic patient with chronic hepatitis C or alcoholic liver disease to ensure control of diabetes and lifestyle modification to improve central obesity, lipid disorders

and other features of the metabolic syndrome. Control of these factors may contribute to reducing disease progression separately to effective treatment of the underlying liver disease (see also Chapter 24).

When to consider a liver biopsy

While a liver biopsy can ultimately confirm a diagnosis of NAFLD and determine its severity, for the vast majority of patients seen in the primary care setting, biopsy is not required for patient assessment and the institution of appropriate management, at least in the first instance.

The aims of liver biopsy for persons suspected to have NAFLD are threefold. First, a biopsy can confirm the histological diagnosis of fatty liver disease and exclude other disorders. In a recent study of 36 asymptomatic patients with non-specific persistent liver test abnormalities, the presumptive prebiopsy diagnosis was altered in 14% of cases and influenced the frequency of subsequent monitoring in 36% [28]. Likewise, biopsy may help in the diagnosis of surreptitious alcohol abuse by demonstrating 'florid' changes (see Chapter 2) [26].

Secondly, liver biopsy is currently the only available method to distinguish between simple steatosis and steatohepatitis (see Chapter 2). As outlined in Chapters 3, 13 and 14, this distinction is not simply a matter of semantics, as steatohepatitis can progress in a proportion of individuals to advanced hepatic fibrosis, liver failure and, rarely, liver cancer. Finally, a biopsy provides information on the stage of hepatic fibrosis in NASH, the most crucial determinant of long-term outcomes (see Chapter 3). Such information is particularly important in the light of data indicating the difficulty of clinical criteria to identify advanced fibrosis or compensated cirrhosis [21,29–31]. Thus, in a recent study of 23 persons with NASH-associated cirrhosis, only 26% had an AST : ALT > 1 and four were 36 years of age or younger [21].

While there are several cogent reasons for considering liver biopsy in persons with presumed NAFLD/NASH, it is neither feasible nor appropriate to biopsy all patients, except in the setting of a clinical research agenda. To date, no universally accepted algorithms exist to identify patients who have a high likelihood of deriving benefit from the information provided by a liver biopsy (e.g. more aggressive lifestyle interven-

tion, careful monitoring, enrolment in clinical trials). Among the published studies, a few clinical features have consistently suggested an increased likelihood of advanced stages of hepatic fibrosis. These are older age, obesity and type 2 diabetes [15,30,32–34]. Less consistent findings in those with advanced fibrosis include an elevated ALT, hypertriglyceridaemia, hypertension and female gender [11,30,33]. The use of non-invasive markers to predict fibrotic severity of NAFLD/NASH is considered in more detail in Chapter 3, and has been updated (to June 2004) in Chapter 24.

The issue of whether female gender predisposes to advanced hepatic fibrosis is particularly vexed. Currently, it is unclear if this represents case ascertainment bias, the possibility that males with NAFLD die of other disorders, or as yet unknown factors. Until large (more than 300 persons) validated cohort studies are published, it seems prudent to consider liver biopsy in subjects with suspected NAFLD who are 45 years of age or older, diabetic and significantly overweight or obese (BMI ≥ 28 kg/m² for white people). The presence of additional features of the metabolic syndrome, including hypertension and hypertriglyceridaemia, should lower the threshold for considering liver biopsy in these individuals. In addition, certain features suggestive of cirrhosis, irrespective of the presence of other criteria, should prompt consideration for early liver biopsy. These include a hard liver edge, an AST : ALT ratio > 1, a low platelet count or serum albumin and imaging findings suggesting portal hypertension (dilated portal vein, hepatofugal blood flow in portal vein, splenomegaly).

While a liver biopsy is being considered in individuals who meet the above criteria, an equally important issue is the timing of the biopsy. Most experts in the field would consider it valuable to embark on or recommend a 3–6 month trial of lifestyle intervention in an attempt to normalize AT levels before proceeding to liver biopsy, unless there are warning signs to suggest advanced hepatic fibrosis (Fig. 15.1). This view is endorsed by the editors.

Management of NAFLD

At present there are no consensus guidelines for the management of patients with NAFLD/NASH. This situation is likely to change over the coming decade with improved understanding of the pathophysiology

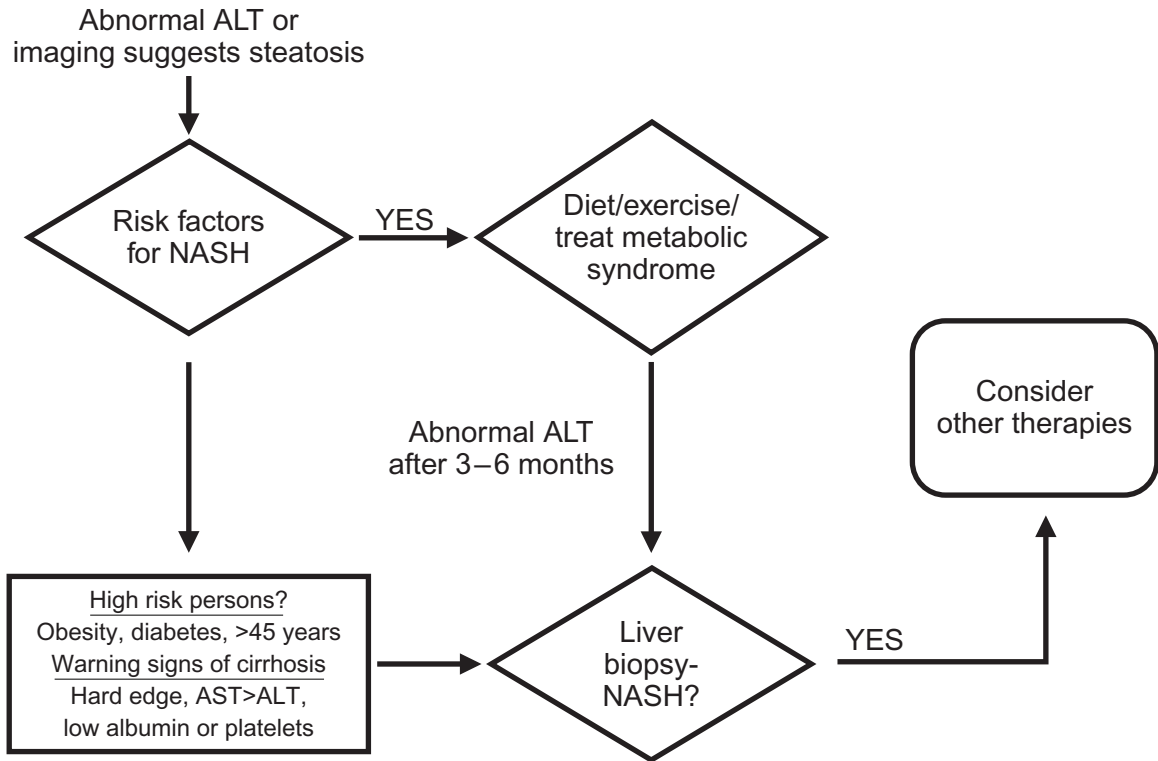


Fig. 15.1 A practical approach to the diagnosis and stepwise therapy of non-alcoholic fatty liver diseases (NAFLD).

of NAFLD and the completion of evidence-based lifestyle modification and pharmacotherapeutic trials for management of these disorders. In broad terms, therapy should target:

- 1 Components of the metabolic syndrome
- 2 Steatohepatitis
- 3 Advanced liver disease (screening for treatable complications of portal hypertension, e.g. large esophageal varices, gastric arterio-venous ectasia).

Patients with NAFLD are at risk of both liver-related and non-liver-related (particularly vascular) morbidity and mortality. In those with earlier fibrotic stages of NAFLD at diagnosis, non-liver disease-related end-points are likely to predominate, while in those with advanced hepatic fibrosis, liver disease-related end-points are likely to have a major impact (see Chapters 3 and 14) [21–23,35,36]. Thus, a thorough assessment for individual components of the metabolic syndrome and appropriate therapy of underlying diabetes, hypertension or dyslipidaemia is warranted.

Because insulin resistance is near universal in persons with NAFLD/NASH, strategies to lower insulin resistance are a logical first step. Given the prevalence of NAFLD in industrialized and developing nations (see Chapters 3, 5 and 18), and the cost and potential untoward adverse effects of drug therapy (Chapter 16), pharmacotherapy is likely to remain a second choice for a disease that is, in large part, lifestyle based [37,38]. As cited in a recent editorial on diabetes prevention, which could apply equally to persons with NAFLD, three types of interventions are possible.

- 1 Interventions that limit fat accumulation in the body (the reduction of central obesity is associated with less insulin resistance; see Chapter 4)
- 2 Strategies that uncouple obesity and insulin resistance (reducing insulin resistance and thereby preventing or delaying β -cell failure)
- 3 Interventions that directly preserve β -cell mass and/or function, thereby preventing or delaying the metabolic consequences of diabetes [39].

Among these, three recent large studies indicate that lifestyle intervention with diet and exercise can reduce the risk of diabetes in high-risk subjects. Further, they are at least as effective as drug therapy with metformin [40–42]. Clearly, therefore, lifestyle intervention can reduce insulin resistance and we believe it should be the first-line treatment of NAFLD/NASH.

In light of the above cogent considerations of pathophysiology, a recent review of the literature found that there are surprisingly few data to support or refute the recommendation for weight reduction as an effective therapy [43]. Among 517 potentially relevant studies, only 15 met the inclusion criteria of reporting histology, serum AT levels or hepatic imaging in obese subjects who had undergone weight reduction. Further, these 15 studies included only one randomized and two randomized controlled trials, and only three included more than 50 persons [43]. Although, all 15 studies reported improvement in liver outcomes (histology, serum AT levels or hepatic imaging), in one study hepatic histology worsened in those with weight loss that exceeded 1.6 kg/week [43,44]. This analysis infers that there is a great need for lifestyle programmes in subjects with NAFLD which include robust markers of liver disease progression, including histology. The results then need to be correlated with potential non-invasive markers, including AT levels, hepatic imaging and potential serum markers suggested as fibrotic markers among persons with hepatitis C [45–47].

Until such evidence-based data are available, it seems prudent to recommend a sustainable programme of diet and exercise aimed at both weight loss and subsequent weight maintenance and increased physical activity. However, rapid weight loss, in excess of 1 kg/week, should be avoided [44]. In order to achieve these goals, a multidisciplinary approach is essential. This could include a dietitian and/or a physical therapist [40–42, 48,49]. Involvement of the family and personal supports of the index case are crucial for establishing long-lasting lifestyle change.

Based on the National Heart Lung and Blood Institute (NHLBI) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) expert panel guidelines, the initial target for weight loss should be 10% of baseline weight within a period of 6 months (0.5–1 kg/week) [50]. This can be achieved through a variety of strategies. Based on the Diabetes Prevention Programme (DPP) study [51], guidelines include phys-

ical activity of moderate intensity (e.g. brisk walking at least 5 days/week, 30 min per occasion, 150 min/week) and a low-energy low-fat diet (less than 30% of energy intake). While the composition of dietary formulations in relation to weight loss and NAFLD have not been examined, it would appear prudent to decrease saturated fats and to increase polyunsaturated fats and antioxidants (particularly vitamin C), and to add complex carbohydrates rich in fibre (e.g. 15 g/day), fruit and vegetables [52]. Guidelines for appropriate diets include the American Heart Association (AHA) heart-healthy diet [53] and for those with diabetes, the American Diabetes Association (ADA) diet [54]. Such interventions and public health promotion programmes should ideally begin in childhood as this group represents the future burden of disease to the community.

Surgical therapies for weight reduction

Absorptive or restrictive (gastric banding) procedures are increasingly being used as therapy for weight reduction (see Chapters 16 and 20). Procedures such as jejunio-ileal bypass are contraindicated in patients with NAFLD/NASH; they may lead to worsening of liver disease and hepatic decompensation. Procedures such as banding are probably safer [33], but significant safety issues remain in those with NAFLD/NASH and hepatic fibrosis, because weight loss of up to 4.5 kg/month can occur and this may be associated with worsening of liver injury [43,44].

Pharmacotherapy of NAFLD

Several small studies of pharmacotherapy in NASH have been completed, and large-scale trials are underway (see Chapters 16 and 24). Application of pharmacotherapy to NAFLD/NASH may need to be lifelong, thereby incurring a considerable cost to the community and a burden of adverse effects such as weight gain. Thus, a critical issue is the targeting of therapy to patients most likely to benefit in terms of liver-related disease end-points. At present, no algorithms have been prospectively validated for the identification of individuals at high risk for disease progression. Even if such a cohort could be identified, cirrhosis in NASH may be slowly progressive. Hence, to demonstrate cost efficacy (cost per quality year of life saved from liver disease-related morbidity or mortality), long-term

Table 15.5 Potential pharmacotherapeutic agents for use in NAFLD.

Drug class	Examples
Weight loss drugs	Orlistat, phentermine, sibutramine
<i>Insulin-sensitizing medications</i>	
Biguanides	Metformin
PPAR γ agonists	Rosiglitazone, pioglitazone
PPAR α/γ agonists	Raraglitazone
PPAR α agonists	Clofibrate
<i>Lipid-lowering agents</i>	
Triglyceride	Gemfibrozil,* clofibrate, probucol*
HMG CoA reductase inhibitors	Atorvastatin
Antioxidants	Vitamin E, betaine, probucol, N-acetylcysteine
Other hepatoprotective drugs	Ursodeoxycholic acid

* Not available in USA.

studies spanning decades may be required. Given the scope of the epidemic of NAFLD, it is prudent for the clinician to evaluate any new drug treatment study in relation to whether institution of lifelong therapy is likely to alter liver disease end-points, and the associated costs and potential detriments of such treatment. There is a pressing need for clinical studies and consensus guidelines in this field.

A variety of therapeutic strategies have been attempted in patients with NAFLD. These are categorized and discussed in detail in Chapter 16 and summarized in Table 15.5. Of the agents studied, drugs that effect weight loss such as orlistat, in addition to that obtained by diet and exercise, may be of benefit, at least during the weight loss rather than weight maintenance phase of NAFLD/NASH therapy [55,56] (and see Chapter 24). Use of insulin-sensitizing agents hold the most promise; however, large-scale clinical trials are awaited and these agents cannot be recommended, particularly as they facilitate weight gain [57]. Of drugs in this class, metformin reduces hepatic lipid in both animal and human studies [58,59]. It is cheap, has a long history of use in clinical practice, does not cause hypoglycaemia even in non-diabetic persons and has an excellent safety profile in those without advanced liver or renal disease. It is not yet known whether it affects progression of NAFLD.

Peroxisome proliferator activator receptor γ (PPAR γ) agonists are potent insulin-sensitizing agents in clinical use for the last decade. The recently published Troglitazone in Prevention of Diabetes (TRIPOD) study [60]

clearly demonstrates that in women with impaired glucose tolerance (insulin resistance), diabetes incidence in the treated group was approximately 55% lower than in placebo controls. Further, protection from diabetes was closely related to the degree of reduction in endogenous insulin resistance, and persisted 8 months after study medication was ceased. The results point to the efficacy of this class of compounds to reduce insulin resistance, which is thought to underlie NAFLD. Three small studies of the use of this class of compounds have been reported [57,61–63] (and see Chapter 24). As expected, they showed improvements in serum AT levels, hepatic steatosis, inflammatory scores, ballooning and zone 3 fibrosis. However, adverse effects were reported including elevations in serum ALT and weight gain (67% of subjects). Thus, while PPAR γ agonists are likely to be of benefit to patients with NAFLD, their routine use is neither recommended nor licensed. If possible, patients with NAFLD and significant hepatic fibrosis on biopsy should be enrolled into clinical trials. In patients with type 2 diabetes and NAFLD, these agents could be considered as first-line pharmacotherapy, after lifestyle modification. However, even with the newer agents (rosiglitazone, pioglitazone), physicians should remain vigilant to the possibility of rare but sometimes serious hepatotoxicity such as occurred with troglitazone.

While insulin resistance appears to be essential for NAFLD, oxidative stress has been demonstrated both in animal models [64–66] and humans with NAFLD [7,67–70]. It represents either the cause or consequence

of liver injury in NAFLD and may be an important determinant of disease progression and inflammatory recruitment [71]. Thus, antioxidants have been studied in small cohorts with NAFLD. Vitamin E perhaps holds the most promise, but again, its routine use awaits large-scale randomized studies (see Chapter 16). While this compound has no significant adverse effects and is cheap, the optimal regimen for clinical use is not known (studies have used 400–1200 IU/day). These compounds may have a role because of their low toxicity profile in children with NAFLD (see Chapter 19).

Management of advanced liver disease in those with NAFLD

This is no different to that for patients with advanced liver disease from other causes who develop ascites, encephalopathy or variceal bleeding. In those with low platelet counts (less than $100 \times 10^9/\text{mL}$) or other evidence of portal hypertension (see above), endoscopy should be considered and prophylactic β -blocker therapy instituted if large varices are evident. Hepatocellular cancer does occur in subjects with NASH and cirrhosis, but the incidence in obese persons with cirrhosis remains controversial [21,23,34]. Those with multiple risk factors (previous hepatitis B or C virus infection, alcohol, older men) may be at greatest risk. Primary liver tumours in the setting of NASH should be treated by the usual approaches. While patients with NASH and hepatic decompensation need to be considered for hepatic transplantation, the underlying metabolic milieu favours recurrence in the transplanted liver [72]. These matters are discussed in Chapters 2 and 17.

Conclusions

Hepatic steatosis and lipid-mediated liver injury may be primary (NAFLD) or, more commonly, given the prevalence of obesity in our population, a contributing factor to liver disease from other causes (e.g. alcoholic liver disease, viral hepatitis). In both circumstances, steatosis can cause or worsen liver disease. In the appropriate metabolic setting, physicians need to consider NAFLD/NASH or comorbid steatosis in the setting of dual liver disorders as a primary diagnosis. Once a diagnosis of probable NAFLD/NASH has been made on clinical and laboratory grounds, lifestyle inter-

vention incorporating both diet and physical activity should be instituted for a trial period of 3–6 months. In those with warning signs or predictors of advanced liver disease, liver biopsy should be considered, particularly if liver tests fail to normalize. In those with significant fibrosis, more intensive lifestyle intervention and pharmacotherapy can be considered. At this time, the latter can only be endorsed in the setting of clinical trials. After lifestyle intervention, insulin-sensitizing agents should be considered as first-line therapy in those with type 2 diabetes and NAFLD/NASH. An essential role for the physician in the management of NAFLD/NASH remains the identification and appropriate treatment of individual components of the metabolic syndrome that may contribute to hepatic as well as cardiovascular morbidity and mortality.

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