26 Non-alcoholic fatty liver disease

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Introduction

In the past few years an increasing amount of research effort has been expended on various aspects of non-alcoholic fatty liver disease (NAFLD) for at least two main reasons. First is the recognition that NAFLD is extremely common, and second the accumulating body of evidence that a proportion of patients with NAFLD can progress to cirrhosis, liver failure and hepatocellular carcinoma. With respect to prevalence, although some high profile reviews have suggested that up to 24% of the general population suffer from NAFLD in various countries,[1] a more evidence-based estimate has come from two analyses of data from the third National Health and Nutrition Examination Survey (NHANES III) carried out between 1988 and 1994 in the USA. These reports have suggested that between 3–6% of the US population have some degree of NAFLD with the diagnosis based on raised aminotransferases in the absence of any alternative etiologies.[2,3] Evidence that this diagnostic label is reasonable has come from a large histological survey of 354 consecutive patients presenting with abnormal liver function tests of unknown etiology. "Abnormal" was defined as either an alanine transaminase (ALT), a γ-glutamyl transferase or an alkaline phosphatase more than twice the upper limit of normal for at least 6 months. Two-thirds of the patients had NAFLD, one-third with simple steatosis and one-third with more advanced disease – non-alcoholic steatohepatitis (NASH) either with or without fibrosis.[4]

Natural history of non-alcoholic fatty liver disease

In marked contrast to patients with alcoholic steatohepatitis, the short-term prognosis of patients with NAFLD is largely excellent. There has been a recent case report of three patients presenting with subacute liver failure[5] and isolated reports of patients developing hepatic failure following obesity surgery.[6,7] However, given the prevalence of fatty liver, these cases appear to be rare exceptions. Although information from a large scale, prospective study examining the natural history of NAFLD in an inception cohort of patients is currently lacking, the available data suggest that the long-term prognosis of patients with NAFLD depends critically on the histological stage of disease at presentation (Figure 26.1). With respect to clinical follow up studies, the largest retrospective study thus far reported on 132 patients with NAFLD of a variety of stages followed up for a median of almost 9 years. While 25% of patients with NASH (± fibrosis) on their index biopsy developed "clinical" evidence of cirrhosis and 11% died a "liver" death, only 3·4% (2/59) with simple fatty liver developed clinical cirrhosis, one of whom (1·7%) died from a liver-related cause.[8] In another study of patients with simple non-alcoholic fatty liver followed for a median 11·5 years, none had clinical evidence of disease progression.[9] With respect to histological follow up studies, to date six paired liver biopsy studies have been reported.[9–14] In most of the included cases the second biopsy was done for normal "clinical" indications, rather than as part of a study protocol and therefore the reported progression rates are almost certainly an overestimate. However, with this proviso the evidence is similar to that in the clinical studies, i.e. the risk of progression differs markedly between patients with simple steatosis and those with NASH ± fibrosis. Of the 14 patients with simple steatosis,[9,14] 3 (21%) developed grade 1 (out of 4) fibrosis (follow up 4.5–15·6 years), while 38% of the 50 patients with NASH[10–14] had an increase in their fibrosis score with 16% progressing to grade 3 (bridging) or 4 (cirrhosis) fibrosis (follow up 1·0–15·7 years).

Further evidence that some patients with NAFLD can progress to cirrhosis has been provided by a study of patients with apparently "cryptogenic" (of no known cause) cirrhosis.[15] The prevalence of the most established risk factors for NAFLD, obesity and diabetes, was over 70% in these patients, which was identical to that seen in the patients with NASH. The cryptogenic patients were, on average, 13 years older than the NASH patients, providing indirect evidence that at least some cases of cryptogenic cirrhosis result from longstanding NASH. These results were confirmed by a subsequent study using a similar strategy to look for NAFLD risk factors in patients with cirrhosis of different aetiologies awaiting liver transplantation.[16] More recently, Ratziu and

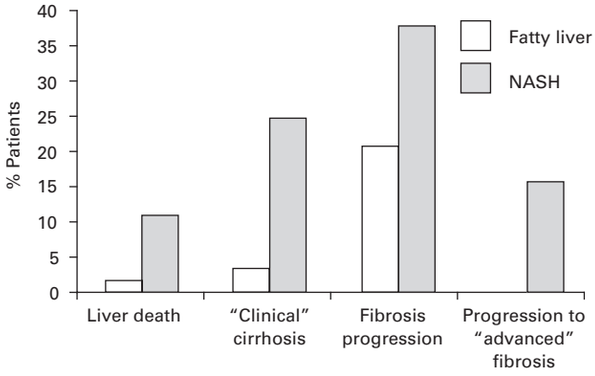

Figure 26.1 Natural history of non-alcoholic fatty liver and non-alcoholic steatohepatitis (NASH).[8–14] Follow up ranged from 1 to 15 years in the different studies. Advanced fibrosis: bridging fibrosis or cirrhosis

colleagues have reported on the natural history of patients with obesity-related cryptogenic cirrhosis.[17] They compared the natural history of 27 patients with obesity-related cirrhosis with that of 85 patients with chronic hepatitis C-related cirrhosis matched for age and sex at the time of diagnosis. Over a median 2·2-year follow up 33% of patients with cryptogenic cirrhosis died a "liver" death compared with only 24% of the hepatitis C cases, with mean time to death in the cryptogenic patients only 9 months compared with over 2 years in the hepatitis C patients. Moreover, the risk of hepatocellular carcinoma (HCC) – 25% – was similar in the two groups of patients. This observation is consistent with several other case reports and series over the past 2 years,[18–20] which, taken together, provide strong evidence that the NAFLD-related cirrhosis is associated with a risk of developing HCC that appears to be of a similar magnitude to the risk associated with alcohol and HCV-related cirrhosis, intermediate between the risks associated with cirrhosis due to autoimmune diseases and chronic hepatitis B infection.[20] This offers at least one plausible explanation for the recently reported linear association between the risk of liver cancer and body mass index (BMI).[21] The difference between the prognosis of patients with simple steatosis compared with those with NASH ± fibrosis has clear implications for both the investigation and subsequent management of patients with suspected NAFLD.

Investigation of patients with suspected non-alcoholic fatty liver disease

The most important issue to consider when devising a protocol for the investigation of patients with suspected NAFLD is to consider which (if any) patients warrant a liver biopsy. This question is best answered by considering the arguments for and against taking a liver biopsy in the investigation of patients with suspected liver disease in general. The first potential justification is that it helps to establish a diagnosis. In a patient presenting with abnormal liver function tests (LFTs) in association with the classic risk factors for NAFLD – obesity, type 2 diabetes mellitus (DM), hypertension and/or dyslipidemia – and an ultrasound showing steatosis, the diagnosis of NAFLD can almost certainly be made with relative confidence without a liver biopsy after the other common causes of abnormal LFTs have been excluded by careful history taking (for alcohol intake and hepatotoxic drugs) and a standard liver "screen" including serological markers for hepatitis B and C infection, autoantibodies, serum ferritin, ceruloplasmin and α-1 anti-trypsin phenotype. As discussed above, several studies have reported that up to two-thirds of patients presenting with unexplained abnormal liver blood tests will have NAFLD[4,22,23] and it seems likely that this proportion will be even higher in patients with established risk factors for NAFLD. Much has been written about how much alcohol intake is "allowed" for a diagnosis of NAFLD. The only study to have examined this issue has reported that "light" to "moderate" alcohol intake reduces the risk of steatosis and NASH in morbidly obese patients undergoing obesity surgery,[24] possibly by reducing insulin resistance and the risk of type 2 DM.[25] In the absence of strong evidence to the contrary, it therefore appears reasonable to suggest that a weekly alcohol intake at or below currently recommended "sensible" limits (21 units for men, 14 units for women) is compatible with a diagnosis of NAFLD.

The second justification for a liver biopsy in patients with suspected liver disease is that the histology will provide prognostic information. As discussed above, this is certainly the case for patients with suspected NAFLD given the different prognoses of simple steatosis and more advanced forms of the disease. Although a number of clinical and biochemical parameters are undoubtedly associated with an increased risk of advanced disease, as yet no factor or combination of factors has been identified that has sufficient sensitivity and specificity to replace biopsy for reliable disease staging. With respect to the various imaging modalities, a recent study comparing ultrasonography, magnetic resonance imaging (MRI) and computed tomography (CT) in patients with biopsy-proven NAFLD has shown that all three modalities are excellent at quantifying the severity of steatosis, but none can accurately distinguish between steatosis and NASH ± fibrosis.[26]

The third reason is that it changes management strategy. For patients with suspected NAFLD, the observations indicating different prognoses for the different stages clearly suggest that different management strategies are appropriate. For patients with simple steatosis, the commonly associated

Table 26.1 Factors predicting advanced fibrosis (bridging or cirrhosis) in biopsy series of patients with or at risk of non-alcoholic fatty liver disease

Factor	Predictive cut-off	Reference
Age	≥ 45 years	29
	≥ 50 years	13
Type 2 diabetes	Presence	29
Hypertension	≥ 140/90 mmHg or on treatment	24
Body mass index	≥ 28 kg/m^2	13
	> 31·1 kg/m^2 (men) 32·3 kg/m^2 (women)	29
ALT	≥ × 2 upper limit of normal	13
	> upper limit of normal	24
AST/ALT ratio	> 1	29
Triglycerides	≥ 1·7 mmol/l	13
C-peptide	> upper limit of normal	24
Metabolic syndrome	Presence of ≥ three features (see Table 26.3)	28

ALT, alanine transaminase; AST, aspartate transaminase

conditions should be sought and treated appropriately. In view of their benign prognosis, these patients should probably be discharged back to their primary care physicians. In contrast, patients with NASH ± fibrosis, with their increased propensity for disease progression, require long-term follow up. Advanced cases (bridging fibrosis or cirrhosis) should be entered into appropriate screening programs for esophageal varices and HCC. C5 In a recent case series of patients with HCC it was reported that patients with NAFLD-related cirrhosis were less likely to have undergone HCC surveillance and had larger tumors at diagnosis compared with patients whose cirrhosis was attributable to other aetiologies.[27] Finally, in the next few years when evidence supporting the use of newer therapies may be provided by currently ongoing randomized clinical trials (RCTs), liver biopsy may be required to determine which patients are suitable candidates for these "second-line" therapies which will be primarily indicated for patients with potentially progressive forms of NAFLD.

Risk factors for advanced non-alcoholic fatty liver disease

If we accept that determining disease severity is critical to the future management of a patient with probable NAFLD, and given the large number of such patients currently presenting to liver outpatient departments, it is important to consider the clinical and biochemical factors that have been associated with an increased risk of advanced disease. While not a replacement for liver biopsy, these factors can help to identify those patients most likely to have advanced NAFLD in whom liver biopsy is probably justified. Several studies in different groups of patients have identified a number of independent clinical and laboratory predictors of advanced fibrosis that can be used to aid the decision of whether or not to biopsy a patient with suspected NAFLD (Table 26.1).[13,24,28,29] Other than the ALT and the aspartate transaminase (AST), almost all of the predictive factors can essentially be considered to be part of the metabolic syndrome, with the presence of the syndrome *per se* associated with an odds ratio of 3·5 (CI 1·1 to 11·2) for advanced fibrosis in the most recent study of 163 patients with biopsy-proven NAFLD.[28] Age (greater than 45 or 50 years) has been identified as risk factor for advanced fibrosis in some,[13,29] but not all,[24] studies. This may also be explained, at least in part, by the increased risk of the metabolic syndrome with increasing age.[28] On the basis of these data, it is reasonable to restrict liver biopsy to patients with at least some, if not all, of these risk factors. It has been suggested that biopsy should be reserved for patients whose abnormal LFTs persist after correction of some of the predictive factors. However, at present there is no evidence that patients whose LFTs respond to these maneuvers are less likely to have advanced disease than patients whose LFTs fail to improve.

General management strategies

There are no published large RCTs of therapies for NAFLD on which to base definitive treatment recommendations. Encouraging results from pilot studies of several treatment modalities have been reported over the past few years and many are currently being tested in large RCTs with histological improvement as their appropriate primary

Table 26.2 Therapeutic strategies for NAFLD/NASH with evidence of benefit from human studies

Strategy	Specific treatment
Weight loss	Calorific restriction
	Calorific restriction and exercise
	Weight-reducing surgery
Insulin sensitization	Troglitazone
	Pioglitazone (+vitamin E)
	Rosiglitazone
	Metformin
	Iron depletion[a]
Lipid lowering	Gemfibrozil
	Probucol[a]
Antioxidant	Betaine[a]
	Probucol[a]
	Iron depletion[a]
Hepatoprotection	Betaine[a]

[a]Treatments with more than one potential beneficial effect.
NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis

endpoint (Table 26.2). Until results from these trials become available, it seems sensible to direct management strategies for patients with NAFLD at the commonly associated conditions, obesity, type 2 DM, dyslipidemia and hypertension, now considered to be the main features of the metabolic syndrome.[30] C5 These strategies will undoubtedly reduce the risk of patients dying from a cardiovascular cause and may also improve the underlying liver disease. In addition to managing the metabolic syndrome, since several drugs have been recognized as causes of NAFLD (for example amiodarone, tamoxifen),[31] these agents should be stopped if possible, since their withdrawal usually leads to resolution of the hepatic pathology.[31] With respect to alcohol intake, for reasons outlined above,[24] it is reasonable to advise patients to drink alcohol within currently recommended "sensible" limits.

Management of the metabolic syndrome

Over the past 4 years several studies have reported that the majority of patients with NAFLD will have some, if not all, features of the recently characterized metabolic syndrome.[32–35] The Third Report of the National Cholesterol Education Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III (ATPIII)) has recently provided a working definition of the syndrome based on a combination of five factors – central obesity, hypertension, abnormal glucose tolerance, hypertriglyceridemia and low high-density lipoprotein (HDL) cholesterol (see Table 26.3 for definitions).[36] Subjects with three or more of these factors are considered to have the metabolic syndrome. Since patients with this syndrome have a 30% increased risk of cardiovascular death in the absence of type 2 DM, and a 40–70% increased risk of cardiovascular death in the presence of type 2 DM,[37] patients with the metabolic syndrome require treatment of the syndrome regardless of the severity of any associated NAFLD. First-line management of patients with the metabolic syndrome consists of lifestyle interventions with weight loss, increased exercise and smoking cessation as the primary goals. A large randomized placebo-controlled trial in over 3000 overweight non-diabetic individuals showed that intensive dietary and lifestyle modification directed at achieving modest weight loss (7%) and including exercise (150 minutes per week) reduced the incidence of type 2 DM by 58% (95% CI 48% to 66%) over a mean 2·8 year follow up.[38] The incidence of type 2 DM over 100 patient-years was: control 11, lifestyle intervention 4·8 and the NNT (the number of patients needed to be treated with intensive lifestyle intervention rather than a placebo for three years to prevent one case of type 2 DM) was 7. Ald If the individual components of the syndrome persist despite these lifestyle modifications they should be treated according to conventional guidelines, since the treatment of type 2 DM, hypertension and dyslipidemia occurring either in isolation[39–41] or in combination[42–44] has been shown in large RCTs to result in significant reductions in mortality. Recently evidence has been provided by the Heart Protection Study Collaborative Group that statin therapy reduces the risk of major vascular events (major coronary event, stroke or revascularization) in patients with diabetes irrespective of their initial cholesterol concentration.[44] Patients who have history of cardiovascular disease or adequately treated hypertension *and* are aged 50 years or more, have type 2 DM or a 10-year coronary heart disease risk of ≥ 5% estimated by the Joint British Societies Risk Prediction Chart/Programme and no contraindication, should take aspirin 75 mg daily.[45] Although direct evidence from RCTs is currently lacking, there are good theoretical reasons to believe that treatment strategies directed at components of the metabolic syndrome may have beneficial effects on the livers of patients with NAFLD. C5 As our understanding of the pathogenesis of NAFLD increases it is likely that the choice of therapy for hypertension, type 2 DM and dyslipidemia will be influenced by their perceived or established beneficial hepatic effects.

Treatment directed at achieving weight reduction

There is a sound theoretical basis for believing that strategies aimed at achieving and maintaining weight reduction in patients with NAFLD will improve hepatic histology. Excessive adipose tissue and the associated insulin

Table 26.3 Components of the metabolic syndrome[a] (ATP III recommendations)[36]

Component	Defining level
Glucose intolerance	Fasting glucose ≥ 6·1 mmol/l or known type 2 diabetes mellitus
Central obesity	Waist circumference > 102 cm (men); > 88 cm (women)
Hypertension	≥ 130/85 mm Hg or on treatment
Hypertriglyceridemia	Fasting triglyceride > 1·7 mmol/l or current use of fibrates
Low HDL-cholesterol	< 1·0 mmol/l (men); < 1·3 mmol/l (women)

[a]Metabolic syndrome is defined by the presence of three or more of these features.
HDL, high density lipoprotein; ATP, Adult Treatment Panel

resistance is the primary source of free fatty acids (FFA) coming into the liver. The combination of an increased hepatic supply of FFA and hyperinsulinemia leads to the accumulation of triglyceride and the development of steatosis – the so-called "first-hit" in NAFLD.[46] The increased hepatic FFA oxidation coupled with the adverse mitochondrial effects of the cytokine tumor necrosis factor (TNF)-α, also secreted by adipose tissue, results in oxidative stress – the most likely "second hit" required for steatosis-related hepatocyte injury and associated inflammation.[46] The hyperinsulinemia associated with obesity along with several other "adipocytokines" secreted by adipose tissue including leptin, angiotensinogen and norepinephrine may also contribute to obesity-related hepatic fibrosis via their effects on hepatic stellate cells.[47]

Unfortunately, despite the sound rationale, at present the evidence that weight loss in patients with NAFLD leads to improved liver histology, rather than biochemistry, is largely anecdotal[48,49] and, with one exception,[50] restricted to uncontrolled case series. Importantly, several of these series have demonstrated that too rapid weight loss (usually following surgery) can lead to an increase in hepatic necroinflammation and/or portal fibrosis despite a reduction in steatosis and an improvement in liver blood tests.[51,52] The majority of studies using diet to achieve weight loss relied on simple calorie restriction with no studies examining the value of specific diets. This may be an area for future study since both the saturated fat content of the diet and the fiber intake are known to influence insulin resistance,[53] and a diet high in saturated fat appears to be a risk factor for NASH in obese individuals.[54] The value of exercise in achieving and maintaining weight loss is now well established and the only controlled study of weight loss that has achieved an improvement in histology in treated patients (only steatosis was significant) combined 3 months of increased exercise with moderate calorie restriction.[50] The addition of exercise to calorie restriction makes physiological sense, since exercise reduces the FFA and triglyceride content of skeletal muscle cells resulting in a reduction in insulin resistance.

As regards "non-lifestyle" interventions for obesity, there are currently three drugs available as adjuncts to dietary therapy in weight reduction: phentermine, sibutramine and orlistat.[53] The National Heart, Lung, and Blood Institutes (NHLBI) and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) guidelines for the management of obesity currently recommend that pharmacotherapy be added to lifestyle modification for patients with a BMI ≥ 30 kg/m^2 and no comorbidity, and ≥ 27 kg/m^2 for patients with obesity-related comorbidity. As yet there is no evidence from RCTs that any of these agents are beneficial in the management of NAFLD. However, a recent observational study of 6 months of orlistat therapy in patients with NASH has shown improvement in both steatosis and fibrosis,[55] and large RCTs are currently ongoing. C5 In addition patients with morbid obesity (BMI ≥ 35 kg/m^2) may be candidates for weight-reducing surgery; either proximal gastric bypass or laparoscopically placed adjustable gastric banding. Jejuno-ilieal bypass has been abandoned, mainly due to the high frequency of severe NASH and subsequent liver failure. As discussed previously, liver failure[6,7] and a deterioration in histology[51,52] has been reported to occur in association with the rapid weight loss that follows gastric bypass surgery and patients therefore require careful assessment and monitoring prior to and following this procedure.

In the absence of data from RCTs, at present it seems appropriate to advise obese patients with NASH to lose weight by combining moderate calorie restriction with increased exercise. Based on the NHLBI-NIDDK guidelines they should aim to lose 10% of their baseline weight at a rate of 500 g–1 kg/week. Patients should be advised against more rapid weight loss in view of the risks of exacerbating liver damage. Diet should be based on a normal "heart-healthy" diet or a standard diabetic diet where indicated.[53] The use of adjunctive pharmacotherapies should be considered for markedly obese patients (BMI ≥ 30 kg/m^2) who fail to lose weight despite these measures. For less obese patients with NASH they should only be used in the context of a clinical trial. Morbidly obese patients may be considered for surgery and require careful monitoring in view of the potential risk of precipitating liver failure.

Treatment directed at associated diabetes mellitus/insulin resistance

In overweight patients with NAFLD and type 2 DM, tight glycemic control with metformin is recommended since this has been shown to reduce the risk of diabetes-related microvascular complications, diabetes-related death and all-cause mortality.[39] This beneficial effect is greater than that obtained with either insulin or sulfonylureas.[39] There is,

however, currently no evidence that improving glycemic control with metformin or any other agent leads to an improvement in hepatic histology in diabetic patients with NASH. Despite this, recent reports that insulin resistance is a universal finding in patients with NASH,[32,35,56] along with increasing evidence that insulin resistance and the associated hyperinsulinemia may play a role in the pathogenesis of advanced NAFLD[47] has led to pilot studies of metformin and other insulin-sensitizing agents in NAFLD patients with and without diabetes. A further attraction of these drugs in NAFLD is that they appear to exert their insulin-sensitizing effect by reducing hepatic and muscle steatosis.[57,58] C5 Whilst there is, as yet, no direct evidence that the use of insulin or sulfonylureas has any adverse effect on the liver of diabetic patients, the putative role of insulin in the pathogenesis of steatosis and fibrosis in NAFLD suggests that these agents should be avoided if glycemic control can be achieved with other treatment modalities. C5

Metformin

Metformin is a member of the biguanide class of drugs. It appears to improve insulin resistance by reducing the fat content of liver and muscle through activation of the enzyme adenine monophosphate (AMP)-dependent protein kinase that results in increased mitochondrial FFA oxidation and decreased FFA and very-low-density lipoprotein (VLDL) synthesis.[57] In the *ob/ob* mouse, an animal model of fatty liver, metformin reverses hepatomegaly and steatosis and improves liver biochemistry.[59] Intrahepatic expression of TNF-α and several TNF-α inducible factors are also reduced by metformin in this model. In two recent pilot studies, metformin given for 3–6 months to non-diabetic patients with NASH was associated with a significant improvement in ALT, glucose disposal, BMI, and hepatomegaly (assessed by CT) compared with non-compliant patients.[60,61] B4 Large RCTs of metformin are currently ongoing in Europe and North America.

Thiazolidinediones

Thiazolidinediones are a new class of anti-diabetic drug that act as agonists for peroxisome proliferator activated receptor γ (PPARγ) and improve insulin sensitivity at least in part via anti-steatotic effects in liver and muscle.[58] They also exert anti-inflammatory effects *in vitro*[62] and antifibrotic effects *in vitro* and *in vivo*.[63] Pilot studies have been carried out with three members of this class of drug in patients with NAFLD. In the first, troglitazone was given to 10 patients with NASH for 3–6 months[64]; one patient had type 2 DM and three had cirrhosis. ALT levels improved in nine patients and, although features of NASH remained in the post-treatment liver biopsies, the grade of necroinflammation improved in five patients and deteriorated in only one patient. Troglitazone has, however, been associated with rare cases of severe hepatotoxicity and has now been withdrawn from the market. The second thiazolidinedione, rosiglitazone, does not appear to be associated with hepatotoxicity. In a recent uncontrolled pilot study in 22 patients with NASH including 7 with type 2 DM, 48 weeks of therapy led to improved insulin sensitivity and ALT levels, with the histological fibrosis score improving in 8 patients, deteriorating in 3 and remaining unchanged in 11.[65] B4 Of some concern was the observation that 67% of patients gained weight with a mean increase of 7·3%. Pioglitazone, the third member of this class of drug, has also been shown to improve steatosis and liver cell injury (ballooning and Mallory's hyaline) in non-diabetic patients with NASH when given for 6 months in combination with vitamin E.[66] A1c In this randomized study no significant changes were observed with vitamin E alone. In a further pilot study of 18 non-diabetic NASH patients, pioglitazone, given for 48 weeks improved histology on two-thirds of patients.[67] Importantly one patient in two of these studies had therapy withdrawn as a result of a rising ALT. Therefore concern over the safety of these drugs remains a significant issue that can only be addressed by currently ongoing large RCTs.

IκB kinase inhibitors

Recent evidence from animal models demonstrating a role for IκB kinase (IKK) in insulin resistance and an improvement in fat-induced skeletal muscle insulin resistance with salicylate,[68] an IKK inhibitor, suggests that selective IKK inhibition may be the next therapeutic strategy directed at improving insulin sensitivity. Since IKK inhibition will also reduce the expression of several NFκ-B-dependent proinflammatory cytokines and adhesion molecules, once developed, these inhibitors may be particularly useful for the treatment of NASH.

At present there is not enough evidence to support the routine use of antidiabetic agents in non-diabetic patients with NASH, although such evidence may be forthcoming from ongoing RCTs. At present, for patients with NASH and type 2 DM, it would seem reasonable to suggest that, where treatment with oral hypoglycemic agents is indicated for "conventional" reasons, insulin sensitizers such as metformin are the preferred drugs, particularly in obese patients.

Treatment directed at associated lipid abnormalities

Dyslipidemia, particularly hypertriglyceridemia is present in between 20% and 80% of patients with NAFLD. As with weight loss and insulin sensitizers, there is good scientific

rationale supporting the use of fibrates – the conventional triglyceride-lowering agents – in patients with NAFLD. C5 Fibrates are agonists for PPAR-α receptors, transcription factors that upregulate the transcription of genes encoding a variety of FFA oxidizing enzymes in mitochondria, peroxisomes and endoplasmic reticulum.[69] The use of potent PPAR-α agonists ameliorates liver injury in the methionine-choline deficient (MCD) animal model of NASH and PPAR-α "knockout" mice develop more severe disease.[70] Several observational studies have examined the effect of lipid-lowering agents on parameters of liver function in patients with NAFLD. However, in the only small observational study in which there was histological follow up, 1 year of clofibrate therapy had no effect on liver biochemistry or histology.[71] Combined PPAR-α/PPAR-γ agonists have recently been developed and have been shown to improve insulin sensitivity and reduce hepatic steatosis in fat-fed rats.[72] These agents have great potential for the treatment of NAFLD and the results of clinical trials are awaited with interest. There is no rationale for the use of HMG CoA reductase inhibitors ("statins") in the treatment of NAFLD. However, they should be prescribed for the "conventional" indications including type 2 DM regardless of cholesterol concentration.[44] Importantly there is no evidence that patients with NAFLD are more likely to suffer from statin-induced idiosyncratic hepatotoxicity.

Antihypertensive therapy

Hypertension should be sought and treated appropriately in patients with NAFLD, particularly those with type 2 DM in whom tight blood pressure control (< 140/80 mmHg) with an angiotensin converting enzyme (ACE) inhibitor or a β-blocker significantly reduces the risk of cardiovascular morbidity, sudden death, stroke and peripheral vascular disease.[42,43] No studies have specifically examined the effect of different antihypertensive agents on the livers of hypertensive patients with NAFLD. However, recent evidence that angiotensin 2 receptor antagonists and ACE inhibitors are antifibrotic in animal models of hepatic fibrosis,[73] suggests that these agents are worth examining in clinical trials. In the meantime, in the absence of contraindications, these drugs may be considered as the drugs of choice for hypertensive patients with NAFLD. C5

Liver-specific therapies

In view of the difficulties in achieving weight loss in patients with NASH, the concern over the potential toxicity of insulin-sensitizing agents, and the apparent lack of efficacy of hypolipidemic drugs, it is not surprising that investigators have begun to examine the effects of alternative forms of therapy for patients with NASH. The rationale for these studies, most of which are at the animal model or "pilot" stage, has been based either on reducing the severity of the putative second hits – oxidative stress and endotoxin-mediated cytokine release[44] – or on the use of general hepatoprotective agents.

Antioxidants

The accumulating body of evidence supporting a role for oxidant stress in the pathogenesis of NASH[44] has lead to trials of several agents, whose potential beneficial effects might be attributed, at least in part, to their antioxidant effects. In a recent placebo-controlled RCT, probucol, a lipid-lowering agent with antioxidant properties, led to a significant reduction in ALT and AST in 30 patients with biopsy-proven NASH.[74] Alc No histological follow up was done. Betaine is required for the hepatic synthesis of *S*-adenosylmethionine, which, in addition to being an important donor of methyl groups, is a precursor of glutathione (GSH), an important intracellular antioxidant. Betaine given to seven patients with NASH for 1 year led to a significant improvement or normalization of serum ALT levels and to improved or unchanged histological parameters (steatosis, necroinflammation and fibrosis).[75] B4 Vitamin E, (α-tocopherol), is a lipid-soluble antioxidant particularly effective against oxidative attack on membrane phospholipids. Vitamin E (400–1200 IU/day) given to 11 children with NAFLD for 4–10 months, led to a significant improvement in liver biochemistry. B4 However, in this study there was no pre or post-treatment histological assessment.[76] In adults, two small pilot studies of oral vitamin E have reported non-significant improvements in histology after 6[66] and 12[77] months. B4 However, a recent small RCT of vitamin E combined with vitamin C found no difference in the proportion of patients with improvement in their fibrosis score between the drug and placebo groups, although this study may have lacked power to show a benefit from this intervention, should it exist.[78] Finally, the recently reported improvement in liver biochemistry in non-iron overloaded patients with clinical evidence of NASH following phlebotomy to near iron depletion has been attributed to a reduction in iron-mediated oxidative stress as well as to improved insulin sensitivity.[79]

Anti-endotoxin/cytokine therapy

At present, studies examining therapies for NASH based on reducing levels of gut-derived endotoxin or on the resulting release of TNF-α from Kupffer cells have been restricted to the *ob/ob* leptin-deficient, murine model of NASH.[80] Studies with probiotics and anti-TNF antibodies have, however, been encouraging and pilot studies with the anti-TNF-α agent pentoxifylline are ongoing.

Ursodeoxycholic acid

Ursodeoxycholic acid (UCDA) is the epimer of chenodeoxycholic acid and appears to replace endogenous, hepatotoxic bile acids. UDCA has membrane stabilizing or cytoprotective, immunological and anti-apoptotic effects. Initial observational studies evaluating the therapeutic benefit of UDCA (10–15 mg/kg per day) in patients with NASH reported a significant improvement or normalization of liver test results and a reduction in the degree of steatosis in the only study with post-treatment histology.[71,81] However, a recent large placebo-controlled randomized trial in 166 patients with NASH has shown no benefit of 2 year long therapy with UDCA (13–15 mg/kg per day). [82] Weight was stable in both groups. In 107 paired biopsies, changes in the degree of steatosis, necroinflammation and fibrosis were not different between UDCA and placebo. Ala

Liver transplantation for patients with non-alcoholic fatty liver disease

Patients with NAFLD that progress to decompensated cirrhosis or who develop HCC are candidates for liver transplantation. Unsurprisingly, steatosis recurs in the majority of patients by 4 years, with 50% developing recurrent NASH and fibrosis, and cases of recurrent cirrhosis are also reported.[83,84] Risk factors for recurrence are the presence of insulin resistance/type 2 DM pre and post-transplantation, weight gain post-transplantation and cumulative steroid

Table 26.4 Minimum requirements for clinical trials of NASH therapy

Study parameter	Requirement
Basic design	Double-blind, randomized, controlled
Entry criteria	Recent biopsy evidence of NASH Drinking within "sensible" alcohol limits Secondary causes of NASH and other primary liver diseases excluded
Patient numbers	Sufficient for adequate statistical power
Study duration	At least a year, preferably 2 years
Stratification	For presence of type 2 diabetes mellitus
Primary study endpoints	Improvement in fibrosis stage Improvement in necroinflammation grade
Secondary endpoints	Quality of life Cost benefit

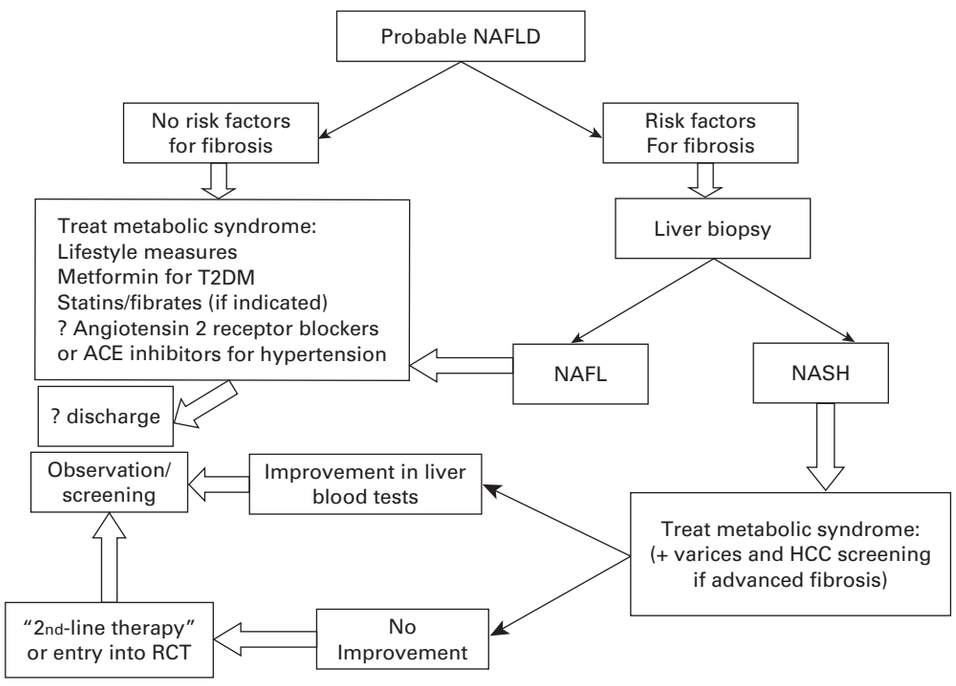

Figure 26.2 Management strategy for patient presenting with suspected non-alcoholic fatty liver disease. It is assumed that these patients have had other causes of abnormal liver blood tests excluded by history (for alcohol excess and hepatotoxic drugs) and serology (for autoimmune disease and viral hepatitis) and have steatosis detected on abdominal ultrasound. ACE, angiotensin converting enzyme; HCC, hepatocellular carcinoma; RCT, randomized controlled trials; T2DM, type 2 diabetes mellitus; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; HCC, hepatocellular carcinoma

dose.[84] These factors clearly suggest several strategies aimed at reducing the frequency of disease recurrence in a group of patients that seem likely to contribute increasing numbers to transplant programs in the future.

Conclusions

At present there is no established therapy for NAFLD based on evidence from large, RCTs. Treatment for all patients, whatever the severity of their disease, should therefore be directed at the associated risk factors: obesity, type 2 DM, hyperlipidemia and hypertension. This strategy will reduce morbidity and mortality and may also be beneficial to the liver. Patients with one or more risk factors for advanced NAFLD should probably undergo liver biopsy to determine their disease stage. Patients with advanced fibrotic disease should be followed up and enter surveillance programs for varices and HCC. For the future, studies in animal models of NAFLD and pilot studies in humans have reported encouraging data for a variety of novel treatment strategies based on our increasing understanding of disease pathogenesis. It is hoped that within the next few years results from currently ongoing large clinical trials of these strategies (Table 26.4) will provide a firm evidence base for the use of safe, well-tolerated lifestyle modifications and/or pharmaceutical agents with beneficial effects on liver histology, currently the best available surrogate marker for long-term prognosis.[77] An overall management strategy for patients presenting with suspected NAFLD is suggested in Figure 26.2.

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