Review

Non-alcoholic fatty liver: a common manifestation of a metabolic disorder

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Introduction

Non-alcoholic fatty liver (NAFL) is one of the most common liver diseases encountered in the United States and Europe. This term refers to a spectrum of hepatic pathology that resembles alcoholic liver disease, but appears in individuals who have low or negligible alcohol consumption.

Initially the term non-alcoholic steatohepatitis (NASH) was employed by Ludwig et al. in 1980 to describe a syndrome in morbidly obese females with type 2 diabetes mellitus (DM), in whom the hepatic histology was consistent with alcoholic hepatitis, but there was no history of alcohol use.¹ More recently it has become apparent that NAFL is a spectrum of disease (Table 1).

It has been suggested that the term NASH should be used only for the more severe forms of NAFL that correspond to types 3 and 4 with alcoholic-like histological findings.² As in alcoholic liver disease, steatosis in NAFL is predominantly macrovesicular and generally distributed diffusely throughout the liver lobule, although prominent microvesicular steatosis or zone 3 (perivenular) steatosis is occasionally found. NAFL is now thought to be the commonest cause of abnormal liver enzymes encountered in general practice, and to result in cirrhosis in a significant proportion of the patients.

We review the current evidence on the prevalence, natural history and treatment of NAFL, limiting the discussion to primary NAFL. Many medications, acute and chronic illnesses can produce steatosis and steatohepatitis, but these are beyond the scope of this review.

Prevalence

The prevalence of NAFL is unclear. There are problems relating to referral bias, population heterogeneity, design studies, the imaging modality employed and the use of liver biopsy. NAFL has been reported worldwide.³⁻¹² In general population studies, screening with ultrasound⁷⁻¹¹,¹² or CT¹³ has shown a prevalence ranging from 16–23%. In liver biopsy studies, the prevalence ranges from 15–39%.⁸⁻¹⁰,¹⁴ Other data on the prevalence of fatty infiltration and NASH come from studies performed on subjects who died in automobile or plane crashes, the latter study having the advantage of evaluating only crew members, where the consumption of alcohol might be expected to be very low.¹⁵⁻¹⁶ These studies reported a prevalence of NAFLD of 24% and 15.6%, and NASH of 2.4 and 2.1%, respectively.

Alcohol consumption is a potential confounding feature. The exclusion limit for defining non-alcoholic liver disease has varied from 0 g to 210 g per week.¹,⁶ However, as little as 20 g alcohol consumption daily can cause steatosis,¹⁷ and a hepatotoxic dose may be as low as 20–30 g daily in females and 40 g daily in males.¹⁸,¹⁹ Hepatic

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steatosis itself is a risk-factor for alcohol-induced liver injury,\textsuperscript{20,21} and it is unclear what is a hepatotoxic dosage of alcohol with pre-existing hepatic steatosis.\textsuperscript{22} Thus, much of the variation in the prevalence data may be related to concomitant alcohol consumption.

### Risk factors

Obesity, type 2 diabetes mellitus (DM), female gender and hyperlipidaemia are frequently associated with NAFL (Table 2). Most cases of NAFL occur in the fifth and sixth decades of life, although there has been a disturbing increase in the prevalence in children.\textsuperscript{23} The typical patient profile may need to be adjusted, since NAFL has also been found in males without weight excess or diabetes.\textsuperscript{5} In a review of the National Health and Nutrition Examination Survey (NHANES III) data, including 12,241 adults, NAFL was more prevalent in men than in women in every age group, was more common in post-menopausal than pre-menopausal women, and was more common in African-Americans and Mexicans than in non-Hispanic whites.\textsuperscript{24} Thus it seems that the ‘classic’ profile of NAFL needs to be widened.

#### Obesity

There is a strong link between NAFL and obesity, and more so with visceral fat accumulation.\textsuperscript{25} However, not all obese people develop NAFL. In the NHANES III study, about 30% of obese men and 40% of obese women had NAFLD.\textsuperscript{24} NAFL can occur in non-obese individuals,\textsuperscript{5,26} and intriguingly is common in patients with lipodystrophy, a condition where there is a relative lack of adipose tissue, associated with insulin resistance.\textsuperscript{27} Recent data show that obesity may increase the likelihood of developing liver damage following exposure to other offending factors, for example alcohol. Ultrasound evidence of fatty liver was present in 95% of obese people with high alcohol consumption, compared with 46% in non-obese.\textsuperscript{12} Interestingly, obesity was also found to have a deleterious effect on hepatic damage related to hepatitis C virus (HCV), and weight reduction resulted in decreased steatosis and fibrosis.\textsuperscript{28}

#### Dyslipidaemia

Dyslipidaemia characterized by hypertriglyceridaemia, often accompanied by low high-density lipoprotein cholesterol (HDL-C), is commonly found in patients with NAFL. In a recent report from a lipid clinic, two of every three patients had elevated liver enzymes, and half of the patients had ultrasound evidence of fatty liver.\textsuperscript{29} Most of the patients with hypercholesterolemia had normal ultrasounds, whereas severe hypertriglyceridaemia and mixed hyperlipidaemia increased the risk of

### Table 1  Histological classification of non-alcoholic fatty liver (adapted from reference 6)

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fatty liver alone</td>
</tr>
<tr>
<td>2</td>
<td>Fat accumulation and lobular inflammation</td>
</tr>
<tr>
<td>3</td>
<td>Fat accumulation and ballooning degeneration</td>
</tr>
<tr>
<td>4</td>
<td>Fat accumulation, ballooning degeneration, and either Mallory hyaline or fibrosis</td>
</tr>
</tbody>
</table>

### Table 2  Patient characteristics in published series

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Age (years)</th>
<th>Female (%)</th>
<th>Diabetes (%)</th>
<th>Obesity (%)</th>
<th>Hyperlipidaemia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ludwig\textsuperscript{1}</td>
<td>20</td>
<td>54</td>
<td>65</td>
<td>25</td>
<td>90</td>
<td>67</td>
</tr>
<tr>
<td>Diehl\textsuperscript{7,6}</td>
<td>39</td>
<td>52</td>
<td>81</td>
<td>55</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>Lee\textsuperscript{3}</td>
<td>49</td>
<td>53</td>
<td>78</td>
<td>51</td>
<td>69</td>
<td>4</td>
</tr>
<tr>
<td>Powell\textsuperscript{4}</td>
<td>42</td>
<td>49</td>
<td>83</td>
<td>36</td>
<td>93</td>
<td>81</td>
</tr>
<tr>
<td>Bacon\textsuperscript{5}</td>
<td>33</td>
<td>47</td>
<td>42</td>
<td>21</td>
<td>39</td>
<td>21</td>
</tr>
<tr>
<td>Matteoni\textsuperscript{6}</td>
<td>132</td>
<td>53</td>
<td>53</td>
<td>33</td>
<td>70</td>
<td>92</td>
</tr>
<tr>
<td>Angulo\textsuperscript{6,5}</td>
<td>144</td>
<td>51</td>
<td>67</td>
<td>28</td>
<td>60</td>
<td>27</td>
</tr>
<tr>
<td>Baldridge\textsuperscript{11,7}</td>
<td>12</td>
<td>14</td>
<td>33</td>
<td>0</td>
<td>100</td>
<td>83</td>
</tr>
<tr>
<td>Rashid\textsuperscript{23}</td>
<td>36</td>
<td>12</td>
<td>42</td>
<td>11</td>
<td>83</td>
<td>31</td>
</tr>
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<td>Loguercio\textsuperscript{11,8}</td>
<td>84</td>
<td>36</td>
<td>21</td>
<td>40</td>
<td>5</td>
<td>35</td>
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<td>Knobler\textsuperscript{30}</td>
<td>48</td>
<td>52</td>
<td>44</td>
<td>44</td>
<td>64</td>
<td>90</td>
</tr>
</tbody>
</table>
fatty infiltration by 5–6 times. In our study of patients with NAFL, 90% of the cases had some kind of dyslipidaemia and hypertriglyceridaemia and/or low HDL-C was found in 86%. In the NHANES III study, patients of both sexes who had triglycerides > 200 mg/dl, had a three times greater prevalence of fatty liver on ultrasound, after adjusting for age, ethnic origin, body-mass index (BMI), type 2 DM. The typical dyslipidaemia of NAFL is also characteristic of the commonly occurring insulin resistance syndrome, also referred to as the metabolic syndrome or syndrome X.

**Insulin resistance and type 2 DM**

Since insulin resistance is very common in both obesity and dyslipidaemia, it is likely that this metabolic abnormality is related to NAFL. Insulin resistance plays a pivotal role in Type 2 DM and glucose intolerance and indeed there is strong association between these disorders and liver disease, and up to 75% of diabetic patients have NAFL. Interestingly, recent studies show that even in non-diabetic or normal weight patients with NAFL, a comprehensive evaluation of the insulin response by methods such as hyperinsulinaemic euglycaemic insulin clamp, reveal significant insulin resistance, manifesting as lower glucose utilization and increased lipolysis. Therefore NAFL can be regarded as an additional feature of the insulin resistance syndrome. Furthermore, insulin resistance and hypertension (another component of the insulin resistance syndrome) are both independently associated with advanced forms of NAFL.

**Pathophysiology**

Fat accumulates in the liver when the rate of delivery of fatty acids to hepatocytes exceeds the metabolic capacity to process them. Fatty acids are delivered to the liver bound to albumin from peripheral adipose tissue, and also from local synthesis in the liver as a result of either protein or carbohydrate excess. There are also two major pathways of fatty acid disposal: mitochondrial β-oxidation to ATP and ketone bodies, and secretion into the blood as triglycerides in very low-density lipoprotein (VLDL). Disturbances in these processes can be inherited or acquired, resulting in the accumulation of triglycerides in the liver. Liver accumulation of fat in patients with DM or with the insulin resistance syndrome is mainly related to increased lipolysis of adipose tissue, with increased flux of free fatty acids to the liver that exceeds the liver’s capacity to export VLDL. Another metabolic disorder associated with fatty liver is hypobetalipoproteinaemia. In this condition, truncation of apolipoprotein B leads to impaired capacity of the liver to secrete VLDL, resulting in fatty liver. A role for microsomal triglyceride transfer protein (MTP) in the development of steatosis and even fibrosis has recently been suggested: MTP is crucial for the assembly and secretion of hepatic triglycerides as VLDL, and MTP promoter polymorphisms were related to both steatosis and the degree of fibrosis in a series of 65 patients with NAFL.

Steatosis can be induced by alcohol and drugs, which can inhibit mitochondrial β-oxidation of fatty acids by different mechanisms. Steatosis can also occur in other conditions such as protein-energy malnutrition, carbohydrate overload and endotoxaemia (caused by sepsis or starvation-associated bacterial translocation).

A ‘two-hit’ concept of disease pathogenesis has been proposed. The first hit is steatosis, and this is postulated to sensitize the liver to the second hit, which may be oxidative stress or abnormal cytokine production. Oxidative stress and lipid peroxidation are candidates for the second hit in the pathogenesis of NASH. Both animal data and human studies have shown a link between NASH and oxidative stress and lipid peroxidation. Liver biopsies from patients with NAFL and the advanced form of NASH, stained for 3-nitrotyrosine (a marker of lipid peroxidation) showed a higher level of staining in NASH biopsies compared to biopsies with NAFL.

Mitochondria are thought to be the source of the reactive oxygen species (ROS) leading to lipid peroxidation. The increased hepatic influx of free fatty acids that results from the reduced ability of insulin to suppress lipolysis, is thought to increase the rate of mitochondrial β oxidation, producing the ROS. There are other potential sources of oxidative stress, including the cytochrome P450 enzymes CYP2E1 and CYP3A4 and increased hepatic iron content. Chronic alcohol exposure may also result in oxidant production. Interestingly, ob/ob mice with obesity-related fatty livers have increased endogenous ethanol production, and higher breath ethanol concentrations have been found in obese subjects compared to thin people.

Cytokines, especially tumour necrosis factor-α (TNF-α) are important in the pathogenesis of alcohol-induced liver disease. In mice, alcoholic liver damage is prevented by disruption of the gene that encodes type 1 TNF receptors. Interestingly, treatment with anti-TNF antibodies to ob/ob mice fed a high-fat diet, has recently been shown to result...
in an improvement of the histological changes of NAFL.\textsuperscript{59}

Inflammatory cytokines, especially TNF-\(\alpha\), may also play an important role in the pathogenesis of NASH associated with several conditions: administration of endotoxin, jejunoileal bypass and the insulin resistance syndrome.\textsuperscript{60} Increased gene expressions of TNF-\(\alpha\) and TNF-receptors were found in patients with NASH in the liver and adipose tissues. Furthermore, the levels of mRNA for the TNF-receptor p55 were higher in the more advanced cases of NASH.\textsuperscript{61} This association may be of special importance in linking the characteristic metabolic changes occurring in NASH patients to their liver disease, as recent data have shown increased activity of the TNF-\(\alpha\) system in obesity and insulin resistance states.\textsuperscript{62} Abnormal cytokine production in NASH patients may also be due to abnormal macrophage function, oxidative stress resulting in nuclear translocation of the transcription factor k\(\beta\), or bacterial overgrowth.\textsuperscript{63} There is also evidence that other cytokines such as leptin may be associated with development of the fibrosis associated with NASH.\textsuperscript{60}

In summary, NAFL is considered to result from two hits. The initial hit is the accumulation of lipids in the hepatocytes resulting in steatosis, followed by a second hit which is multifactorial, resulting in steatohepatitis and fibrosis. An understanding of the pathogenesis of NAFL and NASH is central to the development of an effective treatment for this condition.

Natural history of NAFL

The natural history of NAFL is not well defined, partly because of differences in the exclusion limit of alcohol and the required histological criteria between studies. NAFL was previously believed to be a benign non-progressive condition, but it is now appreciated that a subset of patients can develop advanced fibrosis, cirrhosis and hepatocellular carcinoma.

In a review of histological studies of NASH up to 1998, fibrosis or cirrhosis was present in 15–50\% of patients in the index biopsy.\textsuperscript{54} The presence of obesity and/or type 2 diabetes mellitus are the strongest predictors of fibrosis.\textsuperscript{6,65} These same risk factors are also more common in patients with cryptogenic cirrhosis than in patients with cirrhosis of known aetiology.\textsuperscript{66,67} Further evidence for the link between diabetes, obesity and NAFL has come from the field of liver transplantation. In patients who underwent liver transplantation for cryptogenic cirrhosis, NAFL recurred in up to a quarter of the hepatic allografts.\textsuperscript{68} The patients with recurrent NAFL were more likely to be diabetic and had a higher BMI at the time the recurrent disease was diagnosed. These data suggest that NAFL and the more severe form of NASH may have a significant role in the pathogenesis of ‘cryptogenic cirrhosis’.

A recent retrospective study of 132 patients with NAFL of varying severity with up to 18 years of follow-up, provides the most accurate data available on disease progression.\textsuperscript{6} Of the patients with types 2–4 on the index biopsy, 22\% developed cirrhosis, but of 49 patients with steatosis alone, only two progressed to cirrhosis. In addition 8/73 (11\%) of patients with types 3 or 4 died from a liver-related cause, compared with 1/59 with types 1 or 2. Thus simple non-alcoholic fatty liver has a relatively benign prognosis, whereas hepatocyte necrosis and fibrosis implies a much more serious form of the disease.

It has been assumed that NASH is a slowly progressive disease, but there are a few studies which show that it may progress rapidly.\textsuperscript{69–72} Liver failure was described in patients with NASH after bariatric surgery,\textsuperscript{69–71} and a recent report described five cases of subacute liver failure in obese middle-aged females with NASH-related cirrhosis, of whom three had no obvious confounding factors.\textsuperscript{72} The seriousness of NAFL is underlined by a recent case-control study of patients with cryptogenic cirrhosis, in which type 2 DM and hypertriglyceridaemia were independently associated with hepatocellular carcinoma.\textsuperscript{73}

NAFL effects the progression of other diseases as well. Hepatic steatosis related to visceral obesity is a major independent risk factor for fibrogenesis related to chronic HCV hepatitis.\textsuperscript{74} In addition, the NHANES III data showed that patients with NAFL without liver-specific complications, were more likely to visit doctors and take medications than other individuals.\textsuperscript{24} NAFL may thus serve as a marker of ill-health that relates to the frequent co-existence of metabolic abnormalities such as obesity, diabetes and dyslipidaemia.

Clinical features and diagnosis

Clinical features

As with many chronic liver diseases, many patients with NAFL are mildly symptomatic. A common presentation of NAFL is the finding of abnormal liver enzymes on routine blood testing.\textsuperscript{8,46} Symptoms, when present, are also similar to other chronic liver diseases and include fatigue, malaise, and vague right upper quadrant abdominal pain. By one
estimate, these symptoms are present prior to the diagnosis in approximately a third of the patients. On physical examination, hepatomegaly is often present in up to 75% of the patients in some series.1,3,4,76,77 Signs of portal hypertension are much less frequent, although in one series splenomegaly was found in 25% of the patients at the time of diagnosis.5 It is likely that with an increased index of suspicion, the diagnosis of NAFL can be made prior to the appearance of pathological signs on physical examination.

**Laboratory features**

Mild increases of both alanine and aspartate aminotransferase are the most common laboratory findings in NAFL,4–6,77 although occasionally the elevation can be up to 15 times the upper limit of normal.78 The AST/ALT ratio is usually < 1, which is distinct from the classic picture in alcoholic liver disease.78 The AST/ALT ratio tends to increase as cirrhosis develops.65 In addition, there is commonly an increase in both the alkaline phosphatase and γ-glutamyl transferase (GGT). In fact, GGT has been suggested to be a sensitive marker for insulin resistance.41 Serum bilirubin and albumin are usually within normal limits unless the disease has progressed to cirrhosis.78 Abnormal serum lipid profiles and elevated serum glucose are often found and are related to the pathophysiology described above.75

A high serum ferritin and transferrin saturation has been described in patients with NAFL,54 although many other studies have found no evidence of an increase in hepatic iron.1,5,6,78 In cases of doubt, there may be a role for testing for the haemochromatosis mutations.79

**Diagnosis**

In order to make a diagnosis of NAFL, other aetiologies have to be excluded, especially diseases that can cause an increase in hepatic fat.75 These include hepatitis C infection, Wilson’s disease, autoimmune liver disease, galactosaemia, alcoholic liver disease and secondary causes of NAFL. As mentioned above, there is difficulty in assessing the possible pathogenic role of ‘moderate’ alcohol consumption.

Several non-invasive techniques have been used to diagnose fatty accumulation (steatosis) in the hepatic parenchyma.80–82 Two recent studies compared histological and ultrasonographic findings in patients with NAFL and NASH.83,84 The first study found that diagnosing fatty infiltration by ultrasound (US) gave a specificity of 77%, a positive predictive value of 77% and a negative predictive value of 67%.83 The second study, which additionally evaluated computerized tomography (CT) and magnetic resonance imaging (MRI),84 read independently by two radiologists, showed that only the severity of steatosis was reflected by these imaging modalities. The presence of >35% fat in the liver was the optimal amount for detection, with a sensitivity of 100% for US. However, none of the radiological tests could detect the features of hepatocyte ballooning, Mallory body or fibrosis, which are associated with NASH.

Usually the findings on imaging are diffuse, but there may be focal changes in up to a third of cases. Focal fatty liver has characteristic features on CT scan—usually a non-spherical shape, absence of mass effect, and CT attenuation values similar to soft tissue.85 In some cases, however, CT-guided biopsy may be required in order to differentiate focal fatty liver from a malignant process.

Proton nuclear magnetic resonance (NMR) spectroscopy may be a reliable method for measuring quantitative fat in the liver. The hepatic triglyceride content as determined by NMR spectroscopy correlates well with the value obtained at liver biopsy.86 This test is however expensive and not readily available.

Liver biopsy is the preferred method for establishing the diagnosis of NAFL and determining the histological stage, chiefly the existence of NASH. The most common diagnosis in patients biopsied for investigation of raised transaminases is NAFL.87,88 The rationale for biopsying patients with suspected NAFL is based on the knowledge that the existence, or absence, of histological criteria for NASH provide the most important marker for disease progression.6 However, due to the high prevalence of NAFL in the general population, and the associated low but real complication rate of this procedure,89 it appears to us to be unreasonable to refer every patient with mild elevation of liver transaminases for a liver biopsy. Physicians caring for patients with asymptomatic abnormal liver function tests face a difficult decision of whom to biopsy, and should base their decision on an estimation of the individual risk for developing NASH and fibrosis.

There are several clinical and laboratory findings that enable a prediction of the presence of NASH, with or without fibrosis. In a study of 93 mildly obese patients (BMI > 25 kg/m²), age > 50 years, BMI > 28 kg/m², alanine aminotransferase more than twice the upper limit of normal, and serum triglycerides > 1.7 mmol/l were all independent predictors of septal fibrosis,90 and septal fibrosis was strongly associated with necroinflammatory activity. Another report of obese patients undergoing bariatric surgery found that independent
predictors of NASH and fibrosis were an increased ALT, hypertension, an increased insulin resistance index, type 2 DM and an elevated waist–hip ratio. Another report on 144 patients with biopsy-proven NASH, found that age > 45 years, BMI > 31.1 kg/m² in males or > 32.3 kg/m² in females, type 2 DM and an ALT/AST ratio > 1 were all independent predictors of fibrosis. It is uncertain whether one can generalize from studies on selected groups of patients to the ‘real world’ population of patients presenting to medical out-patient clinics. However, based on the evidence currently available, we suggest that liver biopsy be performed in the following cases: (a) ALT greater than twice the upper limit of normal; (b) AST > ALT; (c) failure of the liver enzymes to improve following initial dietary and lifestyle modifications. In addition, liver biopsy may be required in cases of focal fatty liver. Further, larger studies comparing clinical data and a standardized histological scoring system of NAFL will hopefully lead to consensus guidelines.

Treatment

At present there is no treatment for NAFL that is proven to be effective on the basis of randomized controlled trials including liver biopsy, however several therapeutic modalities have been tried with some successes (Table 3).

Dietary intervention

In several small studies in patients with NAFL, weight loss has improved liver enzymes. In children with NASH, weight loss has resulted in normalization of both biochemical and ultrasonographic abnormalities. In our study of 48 middle-aged patients with clinical, ultrasound and histological findings consistent with NAFL or NASH, the patients were treated with dietary intervention, and additionally in some cases with lipid-lowering and oral hypoglycaemic medications as needed. The treatment was associated with significant weight loss and metabolic improvement, and liver enzymes were reduced in 96% of the patients—in half of them, down to the normal range.

The essential elements of a treatment program aimed at improving the associated metabolic abnormalities include weight loss and increased physical exercise, and therefore dietary modifications are usually recommended for patients with NAFL. However, it is unclear how much benefit will be derived from such dietary and lifestyle modifications in patients who have already long-standing DM or who have histologically more severe forms of NASH. Furthermore, rapid weight loss after bariatric surgery has been shown to result in hepatic decompensation in some patients with NAFL and exacerbation of steatohepatitis in others. Thus weight loss should be carried out slowly and under medical supervision. As an adjunct to an overall treatment plan, there may be a role for weight reduction medication.

Treatment of associated insulin resistance

As described above, there is a clear association between insulin resistance and NAFL. Thus it is not surprising that efforts have been made to determine whether treatment of the associated insulin resistance will have an effect on the outcome of NAFL. In mouse models, both metformin and thiazolidinediones have resulted in an improvement of both the insulin resistance and the NAFL. The study by Lin et al. showed that metformin but not caloric restriction reduced hepatomegaly and steatosis in ob/ob mice with associated insulin resistance, without a significant reduction in fasting serum glucose levels. They suggested that metformin improves hepatic insulin resistance by decreasing the hepatic expression of TNF-α. Metformin treatment of 14 patients with NASH for 4 months has been found to be safe and associated with increased insulin sensitivity, decreased mean serum transaminase concentrations (returning to normal in 50%), and decreased liver volume of 20%.

Troglitazone, an insulin-sensitizing thiazolidinedione, introduced as therapy for type 2 DM, was investigated in a small series of with biopsy-proven NASH. There was a significant improvement in liver enzyme abnormalities, and also an improvement in hepatic histology. Troglitazone was subsequently withdrawn as a first-line therapy for type 2
diabetes mellitus due to a rare, but potentially fatal, hepatotoxicity. A large controlled study sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases is underway to test the effectiveness of pioglitazone, another thiazolidinedione drug with a better safety profile. Recently, pioglitazone in combination with vitamin E resulted in an improvement in the histological features of steatosis, but not fibrosis, in a 6-month report on 10 patients, and to decrease transaminases in a short-term study of 12 patients. In addition, rosiglitazone for 48 weeks improved the stage and grade of NASH in 30 subjects. Despite these encouraging results, until there are more data on the use of thiazolidinediones, these potentially hepatotoxic drugs should only be administered in the context of clinical trials.

Lipid-lowering medications

Given the evidence implicating disturbed lipid homeostasis in the pathogenesis of NAFL described above, attempts have been made to check the effect of lipid-lowering medication on patients with NAFL. Two small studies evaluated the effect of fibrates in NAFL. In the first, gemfibrozil treatment resulted in a significant decrease in ALT, AST and GGT levels, but repeat liver biopsies were not performed. In the second, clofibrate treatment for 12 months only resulted in decreased serum alkaline phosphatase but did not show any improvement in mean levels of AST, ALT, GGT, nor in the histological grade of steatosis. Although statins (HMG CoA-reductase inhibitors) have been associated with some reports of liver injuries, there may be some beneficial effect in patients with NAFL. We have reported an improvement in aminotransferase levels with a treatment program including statins, and there is also a preliminary report of the effects of atorvastatin in seven patients, showing lipid-lowering together with a reduced inflammatory score on repeated biopsy.

Antioxidants

The two-hit hypothesis for the pathogenesis of NAFL invokes a role for oxidative stress as the second hit, and antioxidant medications are being examined as possible therapy. Vitamin E is an antioxidant, and has been examined in a small open-label study of 11 paediatric patients diagnosed with NAFL. There was a normalization of liver enzymes during treatment and relapse upon cessation; however, there was no change in the ultrasonographic appearance of the liver and no histological follow-up. Another antioxidant that has been examined in a small study is betaine, a metabolite of choline. Betaine was given for a period of 12 months; three of the seven patients who completed the trial had normal serum aminotransferases, and three others has a 50% decrease in the enzyme levels. In addition, there was a histological improvement in half of the group.

Ursodeoxycholic acid

Ursodeoxycholic acid (USDA) has become a popular treatment for NAFL, although there are only limited data to support its use. USDA is commonly used to treat cholestatic liver diseases and has a good safety profile, but the mechanism for any postulated beneficial effect is unclear. A small study in patients with NAFL treated with USDA, showed an improvement in liver enzymes but not in the histological grade of inflammation or fibrosis. USDA has recently been shown to prevent the development of hepatic steatosis in rats fed a choline-deficient diet.

Liver transplantation

NASH patients who develop end-stage liver disease should be assessed for liver transplantation in a similar manner to other patients with advanced liver disease. The results of liver transplantation in such cases appears to be good, although there are reports of recurrence of the NASH in the transplanted liver.

Conclusion

NAFL is a common disease associated in most cases with insulin resistance and the metabolic syndrome. The spectrum of pathology is wide, ranging from benign steatosis to cirrhosis, hepatocellular carcinoma and (rarely) hepatic failure. The challenge facing physicians is to make the diagnosis, to differentiate benign steatosis from the more serious steatohepatitis and fibrosis, and to develop effective therapies. Patients with histological findings of NASH have both a significantly higher risk of developing cirrhosis (compared with patients with only steatosis and non-specific inflammation) and (compared with others who develop cirrhosis) of dying from liver-related causes. Therefore patients found to have NASH on liver biopsy should be followed more closely, with repeated liver biopsies. In these cases, adding other pharmacological interventions such as ursodeoxycholic acid,
antioxidants, and even liver transplantation in cases with advanced cirrhosis, is to be considered. Our current practice for a diagnostic and therapeutic approach is shown in Figure 1.

Acknowledgements

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