NASH/NAFLD management

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Management of a disease must be informed by understanding of its natural history and prognosis, diagnostic criteria and methods, and by our knowledge of treatments available and their efficacy. It is the purpose of this contribution to draw aspects of all three areas together so that we propose the best management guidelines and strategy in the light of present knowledge towards the end of 2002.

Non-alcoholic fatty liver disease (NAFLD) is largely encountered in office and outpatient practice (1) most patients have either no relevant symptoms or these are ill defined at presentation – these facts inform our management decisions.

Natural history

We believe that almost all individuals who have simple fat alone on liver biopsy – no steatohepatitis or necrosis, no fibrosis, have an excellent prognosis with only 2 out of 99 reported cases developing significant liver disease over about 10 years of follow up (2,3). There is a consensus emerging from the increasing number of studies of natural history that increasing age over perhaps 45 years, presence of overt Type 2 diabetes, and greater degrees of obesity are all associated with increased likelihood of development of significant fibrosis and ultimately cirrhosis. The most important distinction to be made is between individuals with fatty liver alone (FL) and those with nonalcoholic steatohepatitis (NASH) – features of steatohepatitis and, particularly, fibrosis. Our own group has sought to determine whether any clinical or laboratory features could distinguish between simple FL and NASH in an unselected consecutive group of patients presenting with NAFLD. Complete data (including liver biopsy) was available in 112 patients, 63 with simple FL and 49 with NASH on biopsy. The only clinical feature that differed between these groups was in respect of Type 2 diabetes – 37% in NASH, 16% in FL (OR 2.8 CI 1.2-6.7, $p < 0.01$). The only laboratory distinction was a higher percentage of NASH patients with ALT > $\times$ 2 upper limit of normal – 41% NASH vs 16% FL (OR 3.7, CI 1.5-8.8, $p < 0.005$). A combination of Type 2 diabetes (T2DM) and ALT > $\times$ 2 upper limit of normal was seen in 18% patients with NASH and 0% of those with FL (OR 29.8 CI 1.7-526, $p < 0.001$). Positive predictive value was 100% and negative predictive value was 69% for NASH. If these preliminary results are confirmed they will be of considerable use in clinical practice (Saksena *et al*. *Hepatology*, 2002, **36** : 222A).

We can postulate that genetic and environmental factors may determine who goes on to develop serious liver disease, certainly this is also a function of time. Summarising information from the major clinical studies the median age of patients with NASH but without cirrhosis is 45-50 years. There is a gap in our knowledge but it is increasingly clear that in a substantial proportion of patients with "cryptogenic" cirrhosis – perhaps 60% – the underlying cause is NASH. One is now beginning to realise that most of the patients whom we see age 60 with "cryptogenic" cirrhosis were obese 10 or 20 years ago and may have developed T2DM(4,5). The gap in our knowledge is that we still don't understand how an obese 50 year old with liver inflammation and possibly fibrosis together with a lot of fat in their liver ends up as a less obese but probably diabetic 60 year old with a histologically well developed cirrhosis and little fat. Recent studies from France, Japan and Italy have now extended our knowledge to suggest that patients with (previous) NASH related "cryptogenic" cirrhosis are at similar risk of developing hepatocellular cancer (HCC) as individuals with other forms of cirrhosis – that due to HCV for example (6,7). There is also some suggestion that once NASH related "cryptogenic" cirrhosis presents its clinical course is at least as severe as that in other forms of cirrhosis (6). All of this information needs considerable confirmation.

Diagnosis

History

In patients presenting with cryptogenic abnormal liver blood tests – particularly elevated ALT ± AST – in middle age there are seldom any relevant points in the clinical history but a careful history related to medications should be taken – particularly in non-obese individuals. Family history of NAFLD or cryptogenic

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cirrhosis, and also T2DM are of possible relevance (8). It is important to emphasise that in patients presenting with "cryptogenic" cirrhosis a careful history of previous obesity going back up to 20 years should be obtained.

Careful alcohol history is obviously highly relevant. It is interesting to note cultural differences here between some European centres which regard up to 28 units alcohol/week as being compatible with a diagnosis of "non-alcoholic" steatohepatitis and the more rigid North American approach which suggests that over 7 units/week should exclude this diagnosis. My own view is that 14 units per week in men or women is a reasonable cut off. It is important to add that diagnostic "purity" whilst of interest, particularly from the point of research, is not absolutely necessary. In an individual patient in whom a careful alcohol history has suggested consumption around 30 units per week who is also significantly obese and may have Type 2 diabetes the question of whether the liver inflammation, fibrosis, and marked fatty deposition found on liver biopsy is due to "alcoholic" or "non-alcoholic" causation is academic, almost certainly both should be addressed in management. It is also interesting to note that there are intercontinental differences in respect of the definition of obesity. In France obesity is defined as BMI > 29, in the UK usually obesity is defined as BMI > 30, in the American mid west (the home of the double bar stool) obesity among women is defined as BMI > 32.3. A personal definition would be that an individual with BMI > 26 is "overweight", BMI > 30 is "obese" – again except in strict research terms precise numbers are probably not of extreme importance. In research studies waist-hip ratio is probably a more relevant anthropometric measurement.

Laboratory

The laboratory investigation and definition of NASH/NAFLD may be considered in two parts. Investigations of exclusion, and investigations of assessment. These are listed in Table 1A and 1B. Help in distinction between ALD and NASH/NAFLD is described in Table 2.

Table 1. — **NAFLD/NASH Investigations of Exclusions**

Exclusion	Assessment
HBV markers Anti HCV HFE genotype Autoantibodies*	ALT AST Gamma GT Albumin Globulins Bilirubin Prothrombin time Alkaline phosphatase

*Low titre anti smooth muscle antibodies (ASM) may be seen in NASH in the complete absence of any other clinical, lab based or histological features to suggest autoimmune disease.

Table 2. — **Laboratory Investigation - Distinction between alcoholic liver disease and NAFLD/NASH**

Test	Alcoholic	Non-alcoholic
AST/ALT	Often > 1	Often < 1 (if mild)
Bilirubin	↑ or ↑↑	Normal
Alkaline phosphatase	Normal or ↑	Normal
Albumin	Normal or ↓	Normal (until late cirrhosis)
Prothrombin time	↑	Normal
Gamma glutamyl Transpeptidase	↑	↑
Mean corpuscular volume	↑	Normal
Cholesterol	often ↑	often ↑
Bl ethanol	Present	Absent

Imaging

Despite advances in the sophistication (and cost) of liver imaging the most reliable method of assessment of fatty liver is with ultrasound (9). Unenhanced CT, examining the difference between liver and spleen attenuation values, is also acceptable (10). There are three important caveats to reliance upon ultrasound or CT interpretation in evaluation of fatty liver. First, it is impossible to say anything about presence or absence of mild to moderate degrees of fibrosis in the presence of marked fatty infiltration of the liver. Still less is it possible to comment upon inflammatory changes in the liver. Ultrasound or CT can reliably distinguish advanced cirrhosis on the basis of liver outline and the abdominal signs of portal hypertension – otherwise an imaging report should merely comment on the extent and severity of fatty change.

Second, it is occasionally difficult to distinguish between diffuse hepatic steatosis and widespread liver fibrosis – so called "fatty-fibrotic" pattern (11). Third, sometimes misinterpretation of an area of focal fatty sparing in the liver may occur as this is interpreted as an hypoechoic mass lesion (where the rest of the liver is fatty but interpreted as "normal" rather than abnormally increased in echogenicity (12).

Liver biopsy

Liver biopsy should be considered in respect of making a diagnosis, staging the disease, and in the assessment of treatment. Of course, it is vital in aspects of clinical research – particularly in relation to clinical trials. The position of liver biopsy in management of NAFLD/NASH may in some ways be analogous to its position in HCV (13).

Provided history, relevant laboratory investigations, and ultrasound are all suggestive of NAFLD/NASH, particularly in an overweight/obese individual, the overall diagnosis is not really in doubt. Far more important is the question of staging the disease. Histology, particularly the distinction between NAFLD and NASH – is very important in terms of determining the likely natural history and prognosis in an individual patient. The

study from our own group mentioned above may offer some non-invasive guidelines, if confirmed, in this respect. However, distinction between simple FL and NASH cannot be reliably made without liver biopsy at present nor can we confidently distinguish between mild steatohepatitis/necrosis ± a little fibrosis against more advanced fibrosis/early cirrhosis without biopsy in an individual patient.

As with evaluations of treatment for most parenchymal liver disease, both for an individual patient, and in the context of control trials, liver biopsy remains a gold standard. In the context of their individual patients physicians may decide that the risk/benefit ratio of a second liver biopsy following treatment dictates that this second biopsy is foregone. In the context of well conducted trials I suggest that liver biopsies before and after treatment with relevant assessment of grade and stage are imperative (14,15).

Associated features

NAFLD/NASH is almost always part of the metabolic syndrome (16). Rarities – post jejunoileal bypass, associated with bacterial contamination of the small bowel, as a very rare adverse effect of a few drugs, or as a feature of a rare lipodystrophy – must, of course, be considered but in general in evaluation and management of a patient with NAFLD/NASH it is the features of the metabolic syndrome and some possibly related conditions which should be considered.

(i) *Obesity*

Patients should be weighed and their height measured – hence their body mass index (BMI) calculated. Since central obesity is more relevant to NAAFLD/NASH than overall obesity waist/hip ratio may be measured but this is more "operator dependent" and probably should only be carried out in an experienced centre. Measure waist circumference as an overall indicator of central obesity (in men ideal waist circumference is < 94 cm, 37" - in women < 80 cm, 32"). I have already suggested pragmatic definitions based on BMI for overweight and obesity.

(ii) *Type 2 diabetes/insulin resistance*

The possible presence of previously undiagnosed T2DM should be assessed accordingly to WHO criteria (17). Diabetic control should also be assessed in conventional fashion using random blood glucose and HbA1c. In any research setting a measure of insulin resistance – most easily the homeostasis model assessment (HOMA) should be carried out. If patients are overtly diabetic then regular standard good quality diabetic care and surveillance should be instituted. (Also see below under treatment). In addition dietary assessment bearing in mind WHO recommendations should be made.

(iii) *Other manifestations of the metabolic syndrome*

Patients blood pressure (BP) should be checked and appropriate treatment instituted if BP is elevated. It is outside the scope of this contribution to discuss management of hypertension. This is well described in guidelines of the International Society of Hypertension and elsewhere (18).

Fasting plasma lipids – cholesterol and triglycerides should be measured, hence any hyperlipidaemia may be characterised.

(iv) *Less well recognised possibly associations*

It has been suggested that both coeliac disease and possibly the sleep apnoea syndrome (19) may have an association with NAFLD/NASH. It may, therefore, be worth checking for the presence of anti endomyceal antibodies (reasonably sensitive and specific for coeliac disease) and to ask for a corroborative history of possibly sleep apnoea – in particular day time sleepiness. It has also been suggested that non-specific antoantibodies – noticeably antinuclear antibodies (ANA) and anti smooth muscle antibodies may occur in NAFLD. At present no significance has been attached to this observation (20).

The association between iron overload and NASH is controversial. If patients have liver biopsy stainable iron should sought although it is rarely found (21). The C282Y mutation of the HFE gene should be sought during standard blood tests in evaluation of possible NAFLD/NASH (Table 1B) to exclude possible hemochromatosis. Some authors suggest that heterozygotes for this HFE gene are more commonly seen in NASH (22).

Treatment

It is not the purpose of this review of practical clinical management to rehearse the wide variety of medical treatments currently under consideration in clinical trials. Practical clinical management must make a clear distinction between clinical trials in which usually 1 or at most 2 treatments are offered and pragmatic management by physicians of their individual patients. Hence, outside the setting of clinical trials I would suggest that, at present, the pragmatic approach to treatment shown in Table 3 be adopted.

In any patient with steatohepatitis alcohol consumption should be minimal. I recommend less than 7 units alcohol/week. This has the added advantage of reducing caloric intake.

If patients either have evidence of iron overload on liver biopsy or are heterozygous for the C282Y mutation of the HFE gene then some authorities recommend venesection to reduce iron stores and hence theoretically the risk of oxidative stress in the liver leading to worse disease.

Table 3.

Feature	Management
Obesity	Weight reducing diet. Aim at American Heart Association dietary balance. ± Orlistat
Type 2 diabetes Insulin resistance (without diabetes)	1. Metformin or thiazolidinedione 2. Exercise 3. In overt T2DM manage/screen for complications of diabetes
Hyperlipidaemia	Diet ± statin

Transplantation

At present transplantation for overt NASH is rare – certainly accounting for less than one percent of liver transplantations in the United States. Formerly when jejunoileal bypass surgery for weight reduction was widely carried out (it is now almost completely abandoned) liver failure associated with very aggressive steatohepatitis was encountered rather more frequently. Transplantation for cryptogenic cirrhosis probably arising from former metabolic syndrome is also a relatively uncommon indication for transplantation (23). However, the suggestion that this means that this form of cryptogenic cirrhosis is correspondingly rare, and, by implication, unimportant, is erroneous, since the best evidence suggests that the median age for such patients is in the mid-60s, an age at which, often by virtue of co-morbidity, patients become substantially less likely to be submitted for liver transplantation. Thus, the eligibility criteria for consideration of transplantation in a NASH/metabolic syndrome related cryptogenic cirrhosis patient should be the same as they are for other forms of chronic liver disease. Following transplantation particular attention should be paid to weight, insulin resistance/T2DM and hyperlipidaemia since NASH recurrence is becoming well recognised as probably one of the commonest forms of disease recurrence following liver transplantation. Indeed the occurrence of NASH following transplantation for cryptogenic cirrhosis is now one of the clues which point to this association (24). Finally, in addition to appropriate consideration for transplantation of patients with metabolic syndrome associated cirrhosis good practice suggests that these patients should be checked for the presence of oesophageal varices (as with other cirrhotic patients), and consideration should be given to regular screening for the development of hepatocellular cancer (aFP, ultrasound). It is too early yet to offer really firm advice in respect of screening for HCC in such patients however.

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