1 Overview: an introduction to NASH and related fatty liver disorders

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Key learning points

1 Non-alcoholic steatohepatitis (NASH) is a form of metabolic liver disease in which fatty change (steatosis) is associated with lobular inflammation, hepatocyte injury, polymorphs and/or hepatic fibrosis.
2 NASH comprises a pathogenic link in the chain of non-alcoholic fatty liver diseases (NAFLD) that extends from bland steatosis to some cases of 'cryptogenic cirrhosis'.
3 NAFLD and NASH are usually hepatic manifestations of the insulin resistance syndrome, but the factors that transform steatosis to NASH remain unclear.
4 In 20–25% of cases, NASH may progress to advanced stages of hepatic fibrosis and cirrhosis; liver failure then becomes the most common cause of death.
5 Clinicians should consider NAFLD/NASH as a primary diagnosis by its metabolic associations with obesity, insulin resistance and type 2 diabetes, rather than simply as a disease of exclusion.
6 Correction of insulin resistance by lifestyle modification (dietary measures and increased physical activity) is a logical approach to prevent or reverse NAFLD/NASH.

Abstract

This chapter introduces the history, definitional and semantic issues, spectrum and general importance of non-alcoholic fatty liver diseases (NAFLD). Non-alcoholic steatohepatitis (NASH) is a form of metabolic liver disease in which fatty change (steatosis) is associated with lobular inflammation, hepatocyte injury and/or hepatic fibrosis. It comprises a pathogenic link in the chain of NAFLD that extends from bland steatosis to some cases of 'cryptogenic cirrhosis'. NAFLD and NASH are usually hepatic manifestations of the insulin resistance (or metabolic) syndrome (syndrome X), but the factors that transform steatosis to NASH remain unclear. NAFLD/NASH is the most common type of liver disease in affluent societies, affecting between 2 and 8% of the population. NASH typically causes no symptoms. When present, clinical features such as fatigue, hepatomegaly and aching hepatic discomfort are non-specific. In 20–25% of cases, NASH may progress to advanced stages of hepatic fibrosis and cirrhosis; liver failure then becomes the most common cause of death, and hepatocellular carcinoma (HCC) may occasionally occur. Correction of insulin resistance by dietary measures and increased physical activity (lifestyle intervention) is a logical approach to prevent or reverse early NASH, and modest weight reduction can normalize liver test abnormalities. Drug therapy aimed at reversing insulin resistance, correcting diabetes and lipid disorders, or

providing ‘hepatocellular protection’ has been shown to improve liver tests in short-term small studies, but larger randomized controlled trials are needed to establish whether any of these approaches arrest progression of hepatic fibrosis and prevent liver complications, and at what stage interventions are cost-effective.

History of NASH

In 1980, Ludwig *et al*. [1] described a series of patients who lacked a history of ‘significant’ alcohol intake but in whom the liver histology resembled that of alcoholic liver disease. They were the first to use the term ‘non-alcoholic steatohepatitis’ for this condition, the principal features of which were hepatic steatosis (fatty change), inflammation and exclusion of alcohol as an aetiological factor. Further small case series were published during the next 15 years [2–10]. After much debate, the entity of NASH became accepted, but it is only in the last 10 years that NASH and other forms of metabolic (non-alcoholic) fatty liver diseases (NAFLD) have been widely recognized and diagnosed in clinical practice. The pace of research into the pathogenesis, natural history and treatment of NAFLD/NASH has acclerated in the last 5 years (Fig. 1.1). Thus, Marchesini and Forlani [11] were able to locate only 161 articles which addressed this topic between 1980 and 1999 (approximately 8/year) but 122 in 2000–01 (approximately 60/year). These advances have been reviewed elsewhere [11–19].

What is NASH?

Terminology and definitions

The spectrum of fatty liver disease associated with metabolic determinants and not resulting from alcohol (NAFLD) extends from hepatic steatosis through steatohepatitis to cirrhosis (Table 1.1). As described in Chapter 2, NASH can be defined pathologically as significant steatohepatitis not resulting from alcohol, drugs, toxins, infectious agents or other identifiable exogenous causes (Table 1.2). However, standardized definitions are lacking, particularly of what pathology is encompassed by ‘significant steatohepatitis’ (such as types 3 or 4 NAFLD; see Table 1.1). Outstanding challenges confronting pathological definition include the following.

1 Agreement on the importance, validity and concordance between observers of histological features of hepatocellular injury, especially ballooning degeneration.

2 Categorizing the grade and diagnostic reliability of patterns of hepatic fibrosis.

3 Interpretation of what cases of ‘cryptogenic cirrhosis’ can be attributed to NASH.

This book adopts general recommendations on nomenclature for what comprises NASH that are similar to those suggested by Brunt *et al*. [20] and

1950	• Cirrhosis noted in diabetics
1970s	• Jejuno-ileal bypass liver disease resembles alcoholic hepatitis
1979/80	• Ludwig *et al*. [1] Coined term NASH for steatohepatitis in non-drinkers
	• ~8 papers/year
	• Small series
	• NASH is benign (Powell *et al*. 1990 [8])
1994	• Expanded scope of NASH (Bacon *et al*. 1994 [10])
1996	• CYP2E1 induced in rodent dietary model
	• Endotoxin induces inflammation in steatotic liver
1998	• CYP2E1 induced in human NASH
	• First NIH conference on NASH
	• Pivotal importance of insulin resistance
1999	• Several animal models
	• First clinical trials
2002	• ~60 papers/year
	• AASLD single topic conference
	• First European and Japanese single topic conferences
	• NASH established as part of insulin resistance syndrome
2004	• Release of first book on NAFLD/NASH

Fig. 1.1 Chronology of the pace of research into pathogenesis, natural history and treatment of NAFLD/NASH.

Table 1.1 Categories of non-alcoholic fatty liver diseases (NAFLD): relationship to NASH. (After Matteoni *et al.* [15].)

Category	Pathology	Clinicopathological correlation
Type 1	Simple steatosis	Known to be non-progressive
Type 2	Steatosis plus lobular inflammation	Probably benign (not regarded as NASH)
Type 3	Steatosis, lobular inflammation and ballooning degeneration	NASH without fibrosis—may progress to cirrhosis
Type 4	Steatosis, ballooning degeneration and Mallory bodies, and/or fibrosis	NASH with fibrosis—may progress to cirrhosis and liver failure

Table 1.2 Causes of secondary steatohepatitis.

Alcohol (alcoholic hepatitis)
Drugs (tamoxifen, amiodarone, methotrexate)
Copper toxicity (Wilson's disease, Indian childhood cirrhosis)
Jejuno-ileal bypass (see Chapter 20)
Other causes of rapid profound weight loss (massive intestinal resection, cachexia, bulimia, starvation)
Hypernutrition in adults (parenteral nutrition, intravenous glucose)
A-betalipoproteinaemia
Jejunal diverticulosis (contaminated bowel syndrome)
Insulin resistance syndromes (familial and acquired lipodystrophies, polycystic ovary syndrome)

discussed at a single topic conference of the American Association for Study of Liver Diseases (AASLD), September 2002, Atlanta, Georgia (see Chapter 2) [19,20].

When one particular cause of steatohepatitis is evident, the term steatohepatitis is qualified (e.g. alcoholic steatohepatitis, drug-induced steatohepatitis, experimental [dietary] steatohepatitis). Such cases are often referred to as 'secondary NASH' (Table 2.2; see Chapters 13, 20 and 21). Because of its strong association with 'metabolic' determinants (obesity, insulin resistance, type 2 diabetes, hyperlipidaemia), the acronym 'MeSH' has been been suggested as an alternative for 'idiopathic' (or 'primary') NASH, but seems unlikely to gain widespread acceptance.

Non-alcoholic fatty liver diseases

The term NAFLD is gaining acceptance and is useful because it is more comprehensive than NASH (Table 1.1) [15–17]. NAFLD includes less significant forms of steatosis either alone (type 1 NAFLD) or with inflammation but no hepatocyte ballooning or fibrosis (type 2). The term NAFLD will be used here when the pathology of metabolic liver disease is not known, or when specifically referring to the fuller spectrum. This now includes some cases of cryptogenic cirrhosis in which steatohepatitis and steatosis are no longer conspicuous.

Primary and secondary steatohepatitis: the importance of alcohol

A key definitional issue is potential overlap between 'primary' (metabolic) NAFLD/NASH and pathologically similar fatty liver diseases associated with a single causative factor (Table 1.2). The most important consideration is the level of alcohol consumption considered unlikely to have any causal role in liver disease. Early publications describing 'alcoholic hepatitis-like lesions' were in non-drinkers or those with minimal intake (less than one drink a week in the Ludwig series). Since then, reports of NAFLD/NASH have used a variety of thresholds for alcohol intake. Some have required rigorous alcohol restriction, particularly for cases of 'cryptogenic cirrhosis' attributable to

NASH (e.g. none, or less than 40 g/week) [21,22]. Conversely, other authors have allowed alcohol intake to be as high as 210 g/week [23].

It is noted that 30 g/day is close to the level of 40 g/day associated with an increased risk of cirrhosis in women [24]. Safe levels of alcohol intake have also been difficult to define for other liver diseases, such as hepatitis C for which less than 10 g/day was recommended by the first National Institutes of Health (NIH) Consensus Conference in 1997 [25], but up to 30 g/day for men and 20 g/day for women by the second NIH Consensus Conference [26]. In this book, the definition of NASH requires alcohol intake to have never been greater than 140 g/week (ideally, ≤ 20 g/day for men and ≤ 10 g/day for women). However, it is acknowledged that there may be potential for even these low levels of alcohol intake levels to contribute to cell injury, fibrogenesis and hepatocarcinogenesis in steatohepatitis. Conversely, it remains possible that low levels of alcohol intake confer health benefits in obese persons with liver disease [27]. The implications for recommending optimal levels of alcohol intake for people with NAFLD/NASH are considered in Chapter 15.

Interaction between steatohepatitis and other liver disorders

Another challenge is when the metabolic determinants of NASH (Table 1.3) coexist with known causes of liver disease. The latter include 'moderate' levels of alcohol intake (30–60 g/day in men, 20–40 g/day in women), hepatitis C and potentially hepatotoxic drugs (methotrexate, tamoxifen, calcium-channel blockers, highly active antiretroviral therapy) [28]. The likelihood that steatosis or the metabolic determinants that result in NASH contribute to liver injury and fibrotic severity of other liver diseases is canvassed in Chapter 23.

Importance of NASH

Reasons why NASH is an important form of liver disease are summarized in Table 1.4.

Table 1.3 Metabolic associations of NASH.

Type 2 diabetes mellitus
Family history of type 2 diabetes
Insulin resistance, with or without glucose intolerance
Central obesity (waist : hip ≥ 0.85 in women, ≥ 0.90 in men; waist > 85 cm in women, > 97 cm in men*)
Obesity (BMI ≥ 30 kg/m^2 in white people, ≥ 27 kg/m^2 in Asians)
Hypertriglyceridaemia
Rapid and massive weight loss in overweight subjects

* Values vary between countries; 90 cm for women and 102 cm for men often used in USA.

Table 1.4 Reasons why NAFLD/NASH is important.

High prevalence of fatty liver disorders in urbanized communities with affluent ('Western') economies throughout the world
Most common cause of abnormal liver tests in community—?2–8% of population have NAFLD
NASH now rivals alcoholic liver disease and chronic hepatitis C as reason for referral to gastroenterologist or liver clinic
NASH is a potential cause of cirrhosis, which may be 'cryptogenic', and lead to end-stage liver disease
Liver failure is most common cause of death in patients with cirrhosis resulting from NASH
Standardized mortality of liver disease in type 2 diabetes greatly exceeds vascular disease
NASH recurs after liver transplantation
Hepatic steatosis as a cause of primary graft non-function after liver transplantation
Role of metabolic determinants of NASH in pathogenesis of other liver diseases, particularly hepatitis C and alcoholic cirrhosis
Possible role of NASH/hepatic steatosis in hepatocarcinogenesis

The NASH epidemic

In much of the world, abnormal liver tests attributable to hepatic steatosis or NASH have become the most common liver disease in the community. Depending on how an abnormal value for aminotransferase is defined in studies, such as the Third National Health and Nutritional Examination Survey (NHANES III), between 3 and 23% of the adult population may have NAFLD/NASH [29–31]. In studies that have employed hepatic imaging, autopsy or biopsy approaches, approximately 70% of obese people have hepatic steatosis and/or raised alanine aminotransferase (ALT) [12,21, 27,31–37]; NASH is present in approximately 20% of these [7,27]. In old autopsy studies, ~ 10% of diabetics had cirrhosis, but other factors (hepatitis B and C) were possible confounding variables. In more recent studies, both the prevalence and severity of NASH appear to be increased considerably in patients with type 2 diabetes [11,21,36,38–40].

The epidemiology of NAFLD/NASH is discussed in Chapter 3. Based on the continuing epidemic of obesity and type 2 diabetes through much of the world, it is likely that the prevalence of NASH will increase further during the next decade. In the USA and Australia, up to 60% of men and 45% of women are now overweight, and about one-third of these are obese [41, 42]. Similar increases have been noted in societies that until the last one or two generations were participating in physically active ('hunter gatherer') lifestyles (see Chapter 18). The prevalence of type 2 diabetes has doubled, trebled or increased 10- to 20-fold (as in Japanese youth) during the last decade, rates reaching 40% or more of the adult population in some communities [43–45]. Childhood cases of NASH are also clearly related to obesity and type 2 diabetes (see Chapter 19) [46,47]. Some possible reasons for high rates of obesity and type 2 diabetes in contemporary affluent societies ('east' and 'west', 'north' and 'south'), and the implications for prevention and interruption of NASH are discussed in Chapters 3–5 and 18.

NAFLD/NASH varies in severity and clinical outcome

Steatosis alone has an excellent prognosis. It seems probable that most cases of steatosis with lobular inflammation but without conspicuous hepatocyte injury or fibrosis (NAFLD type 2) behaves in the same way, with very low rates of fibrotic progression (see Chapter 3). However, 20–25% of cases with NASH have or will progress to cirrhosis [15,16,19,21,22,39]. There is mounting evidence that a proportion of cases of 'cryptogenic cirrrhosis' may be attributable to NASH, in which the histological features of steatohepatitis have resolved (see Chapter 14) [15,21,31,35,48]. Rare cases of subacute hepatic failure have also been attributed to possible NASH [49].

Earlier studies of NAFLD/NASH emphasized the good overall prognosis [8,10]. More recent studies that have defined cases according to fibrotic severity indicate that those with significant fibrosis may progress to liver failure [15,22,50]. Among cases of cirrhosis, the risk of death or liver transplantation may be as high as cirrhosis resulting from hepatitis C (both ~ 30% at 7 years) [15,16,22,50]. If this indolent progressive course is confirmed in larger prospective studies, NASH will cause a formidable disease burden in forthcoming decades.

A few well-documented cases of cirrhosis resulting from NASH have presented with, or less commonly have terminated in HCC [16,51]. HCC was recently noted to be a cause of death among obese patients with cryptogenic cirrhosis [52,53]. However, it is not clear that all such cases were caused by NASH [22], and several were diagnosed within 9 months of presentation. Others have suggested that steatosis could increase the risk of HCC associated with other liver diseases [54,55], but conflicting data have been noted (see Chapter 22).

Metabolic risk factors for NASH may worsen other liver diseases

As well as providing the setting for NASH, insulin resistance, obesity, type 2 diabetes and hepatic steatosis are now recognized as factors that favour fibrotic progression in hepatitis C [56,57]. Obesity is also an independent risk factor for alcoholic cirrhosis [58]. Thus, 'NASH determinants' may contribute to the overall burden of cirrhosis directly as the hepatic complication of obesity, insulin resistance and diabetes, and indirectly as factors that favour cirrhosis among people with chronic viral hepatitis or alcoholism (see Chapter 23).

When should the clinician think of NASH?

Clinicians need to consider that NAFLD/NASH is the most likely cause of liver test abnormalities in the

Table 1.5 Pointers to NAFLD/NASH in clinical practice.

Unexplained elevation of ALT and GGT, typically minor, in a person with metabolic risk factors (Table 1.3)
'Rubbery' hepatomegaly
Recent weight gain and expanding waistline
Lifestyle or medication changes favouring weight gain (marriage, retirement, unemployment, antidepressants)
Family history of type 2 diabetes, NAFLD, vascular disorders or hyperlipidaemia
Raised serum ferritin not attributable to iron storage disorder or alcohol
Abnormalities of hepatic imaging—diffuse echogenicity on ultrasonogram ('bright liver'), radiolucency on CT
Patient with chronic HCV infection and diabetes and/or obesity, 'rubbery' hepatomegaly or steatosis with HCV genotype 1 infections (see Chapter 23)
Patient with chronic HBV infection, raised ALT but non-detectable HBV DNA in presence of metabolic risk factors

ALT, alanine aminotransferase; CT, computerized tomography; GGT, gamma-glutamyl transpeptidase; HBV DNA, hepatitis B virus DNA; HCV, hepatitis C virus.

presence of metabolic risk factors (Table 1.3), and when other causes of liver disease have been excluded (see Chapter 13). The importance of considering NAFLD/NASH as a primary diagnosis, rather than purely as a disease of exclusion, is emphasized in this book (see Chapter 5).

NAFLD/NASH is usually suspected because of abnormal liver biochemical tests in an apparently healthy person with no symptoms (Table 1.5). However, fatigue, or vague discomfort over the liver with 'rubbery' hepatomegaly are common. Significant hepatic pain and tenderness are rare. The presence of a firm liver edge, or more rarely a palpable spleen, muscle wasting, ascites, jaundice or hepatic encephalopathy indicate possible cirrhosis, with or without complications of portal hypertension and hepatic decompensation (see Chapters 13 and 14).

In a person with abnormal liver biochemistry tests, a history of recent weight gain or an expanding waistline are often clues to the diagnosis of NASH. However, rapid and extensive weight loss in an obese person can lead to an initial diagnosis of NASH. Such weight loss may occur through intercurrent illness, older forms of obesity surgery (see Chapter 20) or drastic reductions in energy intake caused by fasting, bulimia or 'crash' dieting (Table 1.2). Cycles of rapid weight gain followed by precipitant *weight loss* have led to cirrhosis or hepatic decompensation [3].

The past medical and family history often provide clues to metabolic disorders that underlie NASH [59], particularly type 2 diabetes, and other features and complications of insulin resistance such as arterial hypertension and coronary heart disease [11]. Similarly, laboratory tests, such as a raised serum urate, triglyceride, low-density lipoprotein (LDL) cholesterol and low levels of high-density lipoprotein (HDL) cholesterol are pointers to insulin resistance. The genetic factors that could predispose to NASH are considered in Chapter 6, and the insulin resistance syndrome is discussed in Chapter 5.

A raised serum ferritin level is a common 'confounder' in cases of NAFLD/NASH [60–62]. As in alcoholic liver disease, this most often reflects increased hepatic release of ferritin as an 'acute phase reactant', reflecting the hepatic inflammatory response and increased permeability of steatotic and injured hepatocytes. If a persistently raised serum transferrin saturation suggests increased body iron stores, haemochromatosis gene testing should be conducted in those with a northern European or Celtic background. The proposed role of hepatic iron in worsening fibrotic severity in NASH is controversial (see Chapter 7) [60–62].

Confirming the diagnosis is NASH

Liver biochemical function tests, serum lipids and other laboratory results

Abnormal biochemical results (liver function tests) typically comprise minor (1.5- to 5-fold) elevations of ALT and gamma-glutamyl transpeptidase (GGT). The following laboratory tests may provide clues to the presence of cirrhosis: low platelet count, raised aspartate aminotransferase (AST) that is higher than ALT, and subtle changes in serum albumin or bilirubin that are not attributable to other causes (see Chapter 14).

Fasting hypertriglyceridaemia is present in 25–40% of patients with NASH [8,9,10,16,39]. It may be associated with hypercholesterolaemia (increased LDL cholesterol, particularly with low levels of HDL and a high LDL : HDL ratio). This pattern of lipid disorders is a feature of the insulin resistance syndrome.

Anthropometric measurements

Because nearly all patients with NASH have central obesity, anthropometric measurements should be routinely recorded at liver clinic visits (see Chapter 15). Height and weight are used to calculate body mass index (BMI), while girth (circumference at umbilicus), or waist : hip ratio form simple pointers to central obesity (see Chapters 5 and 15 for details). Some nutritionists recommend waist circumference as more useful than body weight for monitoring benefits of lifestyle change in overweight people.

Determination of insulin resistance

The near universal association of NASH with insulin resistance means that tests to document this pathophysiological state should form part of the approach to diagnosis. Fasting serum insulin and blood glucose levels can be used to construct the relatively crude (but practically useful) homoeostasis model assessment of insulin resistance (HOMA-IR). Values for HOMA-IR differ between population subgroups. Thus, application of this method requires reference to a local group of normal age-matched controls.

As discussed in Chapter 4, diabetologists prefer an 'active' measure of insulin sensitivity as opposed to a fasting one; the latter will be misleading when there is secondary failure of insulin secretion by pancreatic β cells. A simplified 75-g oral glucose tolerance test with 1 and 2 h blood glucose and serum insulin levels can be very informative. Fasting serum C-peptide level is an excellent measure of insulin production. It therefore appears to be a sensitive indicator of insulin resistance that can be used in hepatological practice.

Hepatic imaging

Hepatic imaging performed as part of investigations into abdominal pain, abnormal liver tests or suspected hepatic malignancy may be the first clue to the presence of steatosis [63]. The sensitivity of hepatic ultrasound for steatosis (increased echogenicity, or 'bright liver') appears fairly high, particularly when extensive steatosis (involving at least 33% hepatocytes) is present [63]. CT also appears to be relatively sensitive for hepatic steatosis, and has the advantage that nodularity resulting from cirrhosis may sometimes be appreciated. Careful attention should be given to features of portal hypertension (portal vein dilatation, splenomegaly, retroperitoneal varices). Otherwise, both ultrasonography and computerized tomography (CT) have low positive predictive value for detecting features of cirrhosis.

Neither ultrasonography nor CT is able to distinguish NASH from other forms of NAFLD (see Chapter 13). Thus, while hepatic imaging is useful for providing supportive evidence in favour of hepatic steatosis, it cannot substitute for liver biopsy for elucidating the fibrotic severity of NASH.

Newer imaging techniques (dual-energy X-ray absorptiometry [DEXA], magnetic resonance imaging [MRI]) are also valuable in determining body composition. Total body fat can be estimated accurately with DEXA, but greater interest will come from studies attempting to discern patterns of adipose tissue distribution (visceral versus subcutaneous or ectopic); these patterns are likely to correlate more closely with insulin resistance (see Chapter 4).

Liver biopsy

Clinical guidelines for when liver biopsy is indicated for suspected NASH are not yet standardized [16,18], with views ranging from the nihilistic to the enthusiastic! In considering whether a liver biopsy is indicated, one approach is to assess risk factors for fibrotic severity (obesity, diabetes, age over 45 years, and AST : ALT > 1) and to seek 'warning signs' of cirrhosis (see Chapter 14) [15,16,18]. One approach is not to recommend biopsy at first referral (see Chapter 15). If lifestyle intervention aimed at correcting insulin resistance and central obesity fails to normalize liver tests, and particularly if there are warning signs for cirrhosis or the patient expresses a strong desire to know the severity of their liver disease, the physician should proceed to liver biopsy (see Chapters 13 and 15). Liver biopsy interpretation is described in Chapter 2.

In following any paradigm for liver biopsy, it should be noted that liver test abnormalities in NASH are poorly related to fibrotic severity. Some patients with NASH cirrhosis may have normal ALT levels. A nihilistic approach to liver biopsy for NASH therefore raises the concern that some patients with advanced hepatic fibrosis and/or cirrhosis would not be counselled and monitored appropriately. Further, liver biopsy can sometimes produce unexpected findings indicative of another liver disease, thereby changing management.

Why does NASH happen?

The recurrence of NASH after orthotopic liver transplantation (see Chapter 17) is a dramatic demonstration of the importance of extrahepatic (metabolic) factors in its pathogenesis. Among these, genetic and acquired abnormalities of fatty acid turnover and oxidation are likely to be crucial in causing steatohepatitis [16,17,19,64]; some facilitate accumulation of free fatty acids (FFA), others favour the operation of oxidative stress. Factors that facilitate recruitment of an hepatic inflammatory (or innate immune) response, or determine the tissue response to liver injury are other potentially relevant variables.

Human and animal studies have started to address key issues in NASH pathogenesis, such as the nature of insulin resistance—why it occurs, whether it is responsible for inflammation and liver cell injury as well as FFA accumulation, the mechanisms for inflammatory recruitment and perpetuation, the biochemical basis and significance of oxidative stress, the cell biological basis of hepatocye injury and the pathogenesis of fibrosis (see Chapters 4, 7, 8 and 10–12). It seems likely that many such factors are genetically determined (see Chapter 6). In this way, NASH, like type 2 diabetes, atherosclerosis and some cancers, is the outcome of an interplay between several genetic and environmental factors.

Lipid accumulation also favours increased concentrations of FFA that may be directly toxic to hepatocytes. It has recently been proposed that such 'lipotoxicity' in NASH results from failure of leptin or other hormones that modulate insulin sensitivity to correct for insulin resistance [65]. The humoral and dietary modulation of insulin receptor signalling that underlies this new concept is discussed in Chapter 4. The fatty liver also provides an excess of unsaturated FFA, oxidation of which results in the autopropagative process of lipid peroxidation. It is now clear that the steatotic liver is more susceptible to oxidative stress, as well as to injury after injection of endotoxin [16,18,64].

The liver normally responds to the chronic presence of oxidants by increasing synthesis of protective antioxidant pathways, such as those based on reduced glutathione (GSH). If GSH levels are depleted (as with fasting, toxins such as alcohol, or consumption by prooxidants), the products of lipid peroxidation create and amplify oxidative stress. In turn, oxidative stress can cause liver injury (e.g. by triggering apoptosis and inciting inflammation). The mechanisms that may trigger and perpetuate inflammatory recruitment in NASH, and the importance of cytokines such as tumour necrosis factor-α (TNF-α) are discussed in Chapter 10.

Evidence has been deduced from human studies as well as in experimental models that cytochrome P450 2E1 (CYP2E1) is overexpressed in steatohepatitis [66–68], most likely because of impaired insulin receptor signalling. CYP2E1 is a potential source of reduced (reactive) oxygen species (ROS). In the absence of CYP2E1, CYP4A takes on the role as an alternative microsomal lipid oxidase, and it too may generate ROS [67]. CYP2E1 and CYP4A catalyze the ω and ω-1 hydroxylation of long-chain fatty acids. The products are dicarboxylic fatty acids, which cannot be subjected to mitochondrial β-oxidation and are so targeted to the peroxisome for further oxidation. In turn, this generates hydrogen peroxide (coupled to catalase) as an essential by-product [69].

The relative importance of metabolic sites of ROS generation in hepatocytes (mitochondria, endoplasmic reticulum, peroxisomes), and products of the inflammatory response in contributing to oxidative stress in steatohepatitis remains unclear; interactive processes are likely to operate [64]. However, mitochondria could be a critical source of ROS in fatty liver disorders (see Chapter 11) [38,70].

Hepatic inflammation and cellular injury to hepatocytes can induce and activate transforming growth factor-β (TGF-β), which has a key role in activating stellate cells to elaborate extracellular matrix as part of the wound healing process. It is now apparent that leptin has a key role in hepatic fibrogenesis, and leptin also appears to be necessary for appropriate liver regeneration as part of the 'wound healing' response to chronic steatohepatitis and other forms of liver injury (see Chapter 12). Thus, leptin, originally characterized as an anti-obesity hormone acting on the central nervous system to regulate appetite, could have multiple roles in the pathogenesis of NASH by modulating fat deposition in hepatocytes (antilipotoxicity), and regulating the hepatic fibrotic and regenerative response to steatohepatitis. A more detailed account of the cell biology of NASH is presented in Chapter 12.

Approaches to management of NASH

Lifestyle adjustments

Attempts to correct steatosis and liver injury in NASH can begin before the diagnostic process is complete (see Chapter 15). The aim is to correct insulin resistance and central obesity. Rapid and profound weight loss is potentially dangerous for the person with fatty liver disease [3]. It is prudent and more realistic to recommend slow reductions in body weight that are achievable and sustainable by permanent changes in lifestyle. It has been shown that such reductions improve liver tests [71], and there is mounting evidence that this is associated with removal of fat from the liver, decreased necroinflammatory change and even resolution of fibrosis [72,73].

In accordance with the results of recent type 2 diabetes intervention studies [74,75], physical activity should include at least 20 min of exercise each day (140 min/week), equivalent to rapid walking. The essentials of dietary modification are the same as for diabetes: reduce total fat to less than 30% of energy intake, decrease saturated fats, replace with complex carbohydrates containing at least 15 g fibre, and rich in fruit and vegetables. Consideration of low versus high glycaemic foods (e.g. brown or basmati rice versus conventional long or short-grain white rice); reduction of simple sugars and alcohol intake is also likely to be beneficial.

Some authors have advocated referral to a dietitian or 'personal case manager' to provide education and closer supervision of dietary regimens and lifestyle interventions [73–75]. Approaches to lifestyle modification and weight reduction are discussed in more detail in Chapter 15. The effectiveness and cost-efficacy of such approaches are important aspects that warrant further study.

Measures to control hyperlipidaemia and hyperglycaemia

Increased physical activity and low-fat diet improve insulin sensitivity and can, in some cases, reverse insulin resistance. The value of exercise in improving glycaemic control in diabetes is now generally accepted. In other respects, treatment of diabetes in patients with NASH should conform to conventional approaches, although this may change in future if drugs that help reverse insulin resistance live up to initial promise against NAFLD/NASH without causing unacceptable weight gain. These agents include metformin and the thiolazinediones (see Chapter 16). Drugs that correct lipid disorders, anti-oxidants (vitamin E, betaine) and other hepatoprotective agents (ursodeoxycholic acid) are also under study in NASH (see Chapter 16).

Concluding remarks: can NAFLD/NASH be prevented or reversed?

Because liver failure does not occur in NAFLD/NASH unless cirrhosis has developed, reducing or reversing fibrotic progression must be the ultimate objective of treatment. While several agents improve liver tests over the short term in patients with NAFLD/NASH (see Chapter 16), none have yet (June 2003) been shown to have long-term efficacy and to impact on fibrotic progression (but see Chapter 24). In the absence of evidence of such efficacy, patients should currently only receive drug therapy directed at NASH within the context of a clinical trial, particularly as some of the compounds presently under study carry toxic potential or other unwanted effects (see Chapters 16 and 24).

There is now compelling evidence that type 2 diabetes can be prevented (or at least delayed in onset) by lifestyle interventions [74,75]. Both the Finnish and US Diabetes Intervention Projects showed a 58% reduction in incidence of type 2 diabetes among those at high risk could be achieved with only modest reductions in body weight [74,75]. NASH, another consequence of insulin resistance (see Chapter 5), should also be preventable by changes in diet and physical activity. There is now evidence that weight reduction and lifestyle changes nearly always improve liver tests in NAFLD, and also have potential to improve liver histology in obese patients with hepatitis C or fatty liver disorders [71–73] (Chapter 24). Whether this approach would be a cost-effective way to reduce the number of patients progressing to cirrhosis and liver failure is clearly worthy of study.

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