Chapter 25: NAFLD and NASH

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Introduction

Both non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steato-hepatitis (NASH) are often associated with obesity, diabetes mellitus and asymptomatic elevations of serum ALT and gamma-GT. Ultrasound monitoring can suggest the presence of a fatty infiltration of the liver; differentiation between NAFLD and NASH, however, requires a liver biopsy. Such differentiation may be important because NASH is associated with a much higher risk of liver fibrosis and cirrhosis than NAFLD. Moderate loss of weight due to dietary and life-style modifications is the only therapy proven to be effective in NASH. Complete alcohol abstinence and good control of diabetes mellitus are probably also important to reduce the risk of severe liver disease in NASH.

Prevalence

NAFLD is present in the general population of industrialized countries in 20 to 40% and is the most prevalent chronic liver disease (Browning 2004; Chitturi 2004; McCullough 2005). It is more prevalent in obese and diabetic subjects (Bellentani 1994; Wanless 1990; Clark 2002; Chitturi 2004). Among all subjects with NAFLD, features of non-alcoholic steato-hepatitis (NASH) can be seen in 10-20%. The prevalence of NASH in western countries is approximately 2-6%. In the US, NASH was estimated to affect 5-6% of the general population (McCullough 2005). It has been suggested that NASH accounts for more than 50% of cryptogenic cirrhosis (Ratziu 2002). NAFLD may progress to NASH with fibrosis, cirrhosis, and hepatocellular carcinoma (Marchesini 2003; Caldwell 2004). The term NASH was introduced by Ludwig (Ludwig 1980) who described 20 Mayo Clinic patients with a hitherto unnamed disease associated with hepatomegaly, abnormal ALT, a fatty liver histology, lobular hepatitis, and fibrosis mimicking alcoholic hepatitis in the absence of alcohol intake; most patients had obesity and diabetes mellitus.

Demographics and risk factors

In the US, NAFLD is 3-5 times more prevalent in men than in women; such differences in gender might partly be explained by the fact that men have a higher BMI and that some male patients with NAFLD drink more alcohol than they report drinking (Schwimmer 2005; Bahcecioglu 2006; Loguercio 2001). The NAFLD prevalence in the US is particularly high in people of Hispanic (28%) or Asian origin (20-30%) (Schwimmer 2005; Weston 2005). Due to the dramatic increase in obesity in the US and many other industrialized countries, there is also a dramatic increase in the prevalence of NAFLD and NASH. In the US almost 50% of obese boys have NAFLD (Schwimmer 2005). In many countries more than 80% of NAFLD patients have an increased BMI and 30-40% are obese; approximately 50% show signs of insulin resistance, 20-30% have type 2 diabetes, 80% show hyperlipidemia, and 30-60% have arterial hypertension. Correspondingly there is a strong association between NAFLD

and NASH and the metabolic syndrome throughout the world (Marchesini 1999; Bedogni 2005). In comparison with NAFLD patients, NASH patients are older, more obese and more often have high serum liver enzymes, diabetes mellitus and metabolic syndrome (Ratziu 2002; Adams 2005; Hamaguchi 2005; Fassio 2004).

Pathogenesis

The degree of fatty infiltration in NAFLD is graded according to the percentage of hepatocytes with fat deposits: mild NAFLD involves less than 30% hepatocytes, moderate NAFLD up to 60%, and severe NAFLD more than 60% (Ploeg 1993). NAFLD may regress if the cause is eliminated. NASH is associated with insulin resistance, increased circulating levels of leptin, adiponectin, tumour necrosis factor and some interleukins (Friedman 1998; Marra 2004). It is thought that there is an increased flow of free fatty acids from visceral fat to the liver contributing to abnormalities in intracellular lipid metabolism (Hashimoto 1999; Vendemiale 2001). Insulin resistance and increased free fatty acids may both affect mitochondrial oxidation of fatty acids causing free radical generation in hepatocytes (Grattagliano 2003). Thus, NASH is caused by two mechanisms or toxic "hits"; the first mechanism is the hepatic accumulation of triglycerides (NAFLD) due to insulin resistance and the second is thought to be the generation of free radicals with subsequent release of mediators and cytokines (McCullough 2006). Insulin resistance has been closely linked to non-alcoholic fatty liver disease in both clinical trials and laboratory-based studies (McCullough 2006; Marchesini 2001; Sanyal 2001). The actual process by which NAFLD turns into NASH however remains ill defined despite this double-hit theory. Likely, genetic factors (similar to those responsible for the metabolic syndrome) as well as exogenic factors (like drugs, moderate amounts of alcohol, and other toxins) may contribute to the evolution of NAFLD into NASH. The role of hepatic iron in the progression of NASH remains controversial, but in some patients, iron may have a role in the pathogenesis of NASH by promoting oxidative stress. Iron overload has been shown to cause lipid peroxidation and to activate hepatic stellate cells (Lee 1995). In some reports, an increased prevalence of the Cys282Tyr HFE gene mutation in patients with NASH has been reported (George 1998). The presence of the Cys282Tyr mutation was associated with increased hepatic iron concentration that in turn is associated with the severity of the fibrosis. Other studies have shown that other heterozygote HFE gene mutations are more prevalent in NASH patients when compared with controls (Bonkowsky 1999). In another clinical cohort, there was no association between hepatic iron and histological or clinical outcome (Younoussi 1999).

Natural history

The natural history of NAFLD in the general population is not well-defined since most data come from selected patients and tertiary centres (Dam-Larsen 1996; Lee 1989; Teli 1995). Correspondingly, published mortality and morbidity in hospitalized NAFLD are approximately 5 times higher than what is seen in the general population (Matteoni 1999). In the general population the risk for liver-related death in NAFLD appears to be associated mainly with age, insulin resistance, and histological evidence of hepatic inflammation and fibrosis (Adams 2005). Probably around 10% of NAFLD patients will progress to NASH over a period of 10 years (Figure 1). Cirrhosis later develops in 5-25% of patients

with NASH and 30-50% of these patients die from liver-related causes over a 10-year period (McCollough 2005; Matteoni 1999). Cirrhosis in patients with NASH can also decompensate into subacute liver failure, progress to hepatocellular cancer (HCC), and recur after liver transplantation (McCollough 2005). Steatosis alone is reported to have a more benign clinical course, with cirrhosis developing in only 1-3% of patients (Day 2004; Day 2005; McCollough 2005; Matteoni 1999). Patients with NASH and fibrosis also have a significant risk for hepatocellular carcinoma (El-Serag 2004) (Figure 1).

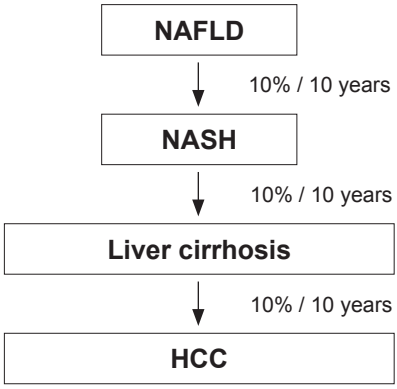

Figure 1. Natural history of NASH.

HAIR index (hypertension; ALT >40 U/l; insulin resistance) ≥2 are 80% sensitive, 89% specific for NASH (Dixon 2001)
BAAT index (BMI >28; Age >50 years; ALT >2x UNL; increased triglycerides) ≤1 has 100% negative predictive value for NASH (Ratziu 2000)

Table 1. Non-invasive predictors of NASH.

Diagnosis

NAFLD and NASH require valid reporting about alcohol consumption. Since only approximately 10% of western populations are completely abstinent from alcohol, one needs to set a threshold above which one assumes that alcohol at least contributes to the pathogenic process of NAFLD and NASH. Most authors use a daily alcohol ingestion of 20 g as such a threshold (Figure 2); others use lower values such as 10 g/day or as high as 40 g/day for men. The workup of NAFLD and NASH also includes checking into drug abuse, HBV and HCV infections, haemochromatosis, autoimmune liver disease and, in younger patients, Wilson's Disease. In special groups of

patients NASH may be accompanied by drug- and alcohol-induced liver disease and by HCV and HBV infections. The combination of NAFLD/NASH and HCV infection plays a particularly important clinical role because in this situation the rate of liver fibrosis is increased and the success of antiviral therapy is diminished (Ramesh 2004). NASH can be induced by various drugs and toxins including corticosteroids, amiodarone, methotrexate, tetracycline, tamoxifen, and valproate (Pessayre 2002). Thus, one needs to carefully assess the full clinical history of patients. In practice NAFLD is often diagnosed by combining elevated levels of ALT and gamma-GT with the sonographic appearance of an increase in the echodensity of the liver. However, a considerable number of patients with NAFLD and even with NASH and fibrosis have normal serum liver enzymes (Abrams 2004). Usually ALT is higher that AST unless there is already severe fibrosis or cirrhosis. Fasting serum glucose should be checked in all patients with NAFLD and NASH; one will also often find elevated serum insulin, insulin resistance, and/or diabetes (Table 2).

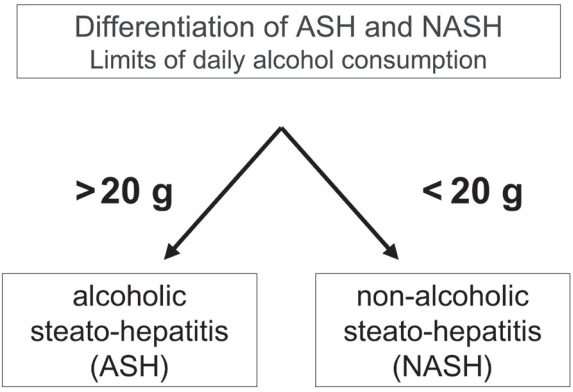

Figure 2. Differentiation of alcoholic liver disease (ASH) and NASH.

Moderate weight loss
Drugs for treatment of obesity (e.g., orlistat or sibutramine)
Complete abstinence from alcohol
Good control of diabetes mellitus
Insulin sensitizers (e.g., glitazones)
Surgery for massive obesity (e.g., gastric bypass surgery)
Liver transplant (LTX)

Table 2. Treatment options for NASH.

Many authors also recommend to routinely look for metabolic syndrome, which is diagnosed when three of the following features are seen (Greenland 2003):

- waist circumference ≥102 cm for men and ≥88 cm for women,
- fasting glucose level ≥6.1 mmol/l,
- triglyceridemia ≥1.7 mmol/l,
- increase in high-density lipoprotein cholesterol (>1.3 mmol/l in women; >1.03 mmol/l in men)
- hypertension ≥135/80 mm Hg.

Ultrasound of the liver has a high sensitivity and specificity (both approaching 90%) for detection of fatty infiltration but does not allow assessment of the presence or degree of inflammation and fibrosis (Davies 1991). Therefore, diagnosis of fat in the liver is easily made by ultrasound but diagnosis of NAFLD or NASH can not be made without a liver histology. In addition liver biopsy is still the only way to reliably differentiate NASH from NAFLD (Harrison 2003). Today most pathologists use the Brunt description to score the histological degree of NASH (Brunt 1999) (Figure 3). Since NAFLD is a very frequent but also relatively benign disease, one aims to identify some risks factors for NASH in order to avoid doing liver biopsies in all NAFLD patients. Risk factors for NASH include older age, excessive obesity, diabetes mellitus, other hepatotoxins, and clinical, laboratory or sonographic signs suggesting severe liver disease; two non-invasive scores have been used to predict NASH and might be used to identify patients who should have a liver biopsy (Dixon 2001; Ratziu 2000). Combinations of various serum markers of liver fibrosis and the results from liver stiffness measured by the fibroscan have been suggested to predict the presence of NASH and fibrosis (Rosenberg 2004; Suzuki 2005). These tests have not yet replaced the liver biopsy.

Grade	Steatosis	Ballooning of hepatocytes	Degree of inflammation
1	<33%	Minimal	Mild
2	34-66%	Present	Moderate
3	>66%	Marked	Portal moderate, lobular moderate

Stage	Fibrosis
1	Perisinusoidal
2	Perisinusoidal and portal/periportal
3	Bridging septa
4	Extensive bridging fibrosis, cirrhosis

Figure 3. Histological Brunt score (Brunt 1999).

Diet and lifestyle recommendations

Today, the only effective treatment for NAFLD and NASH is a slow and moderate weight loss, usually associated with other lifestyle modifications. Several studies have shown that rapid weight loss (very low calorie diet or starving) increases the risk of progression of liver disease and even liver failure (Grattagliano 2000; James 1998; Neuschwander-Tetri 2003). Patients should therefore be educated not to induce rapid weight loss, but to aim at a weight loss of less than 10% of their body weight over 6-12 months (Okita 2001). It is unclear whether special diets are helpful; probably it is more important that the patients simply eat healthy foods like vegetables and fruits, rich in fibre and complex carbohydrates with a low glycemic index; they should avoid meat, saturated fat and products with less complex carbohydrates. Lifestyle modifications should include an increase in physical activity and sports as well as abstinence from alcohol. With the results of recent studies, coffee consumption does not need to be limited.

Pharmacological treatment

There is no drug proven to be beneficial in NAFLD and NASH; therefore no drug has been approved by FDA or EMEA. In general, drugs that might reverse insulin resistance such as metformin and thiazolidinediones (rosiglitazone, pioglitazone) are the most promising (Angelico 2007); in smaller studies these drugs have shown some histologic improvement of NASH (Bugianesi 2004; Belfort 2006).

In general all drugs that induce weight loss might be beneficial in NAFLD and NASH, in particular when diet and life-style modification do not work. Both sibutramine and orlistat have shown to improve some characteristics of NAFLD and NASH such as the sonographic degree of liver steatosis as well as the histological degree of steatosis and fibrosis (Sabuncu 2003; Derosa 2004, Hussein 2007; Harrison 2007).

Antioxidants and cytoprotective substances have also been proposed to treat NAFLD and NASH including vitamin E, vitamin C, glutathione, betaine, acetylcysteine, S-adenosyl-L-methionine and ursodesoxycholic acid. After a recent Cochrane analysis, none of these substances has shown significant benefit in validated randomized studies (Lirussi 2007).

Surgery for obesity

Gastric bypass has also recently been shown to improve NASH (Liu 2007; de Almeida 2006; Furuya 2007); however, surgery is usually restricted to patients with massive obesity.

Liver transplantation (LTX) for NASH

LTX is the final option for patients with end-stage liver disease due to cirrhosis and complications of portal hypertension with NASH. Due to the increase in the prevalence of NASH, there is also an increase in LTX done for end-stage liver disease caused by NASH (Burke 2004). However, NASH can recur after LTX, particularly if patients have previously undergone jejunoileal bypass surgery (Kim 1996; Requart 1995; Weston 1998; Contos 2001; Burke 2004). LTX does not cure the metabolic defect that causes NASH.

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