Chapter 5
Nonalcoholic Fatty Liver Disease

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5.1 Introduction

Nonalcoholic fatty liver disease (NAFLD) is the main hepatic complication of obesity, insulin resistance, and diabetes and soon to become the leading cause for end-stage liver disease in the United States [1]. NAFLD is characterized by an accumulation of fat (steatosis) within >5 % of hepatocytes in the absence of secondary causes of hepatic steatosis. NAFLD is a spectrum of disease that ranges from steatosis (hepatic fat without significant hepatocellular injury) to nonalcoholic steatohepatitis (NASH; hepatic fat with hepatocellular injury) to advanced fibrosis and cirrhosis.

As a direct consequence of the obesity epidemic, NAFLD is the most common cause of chronic liver disease, while NASH is the second leading indication for liver transplantation [1]. NAFLD prevalence is estimated at 25 % globally [2] and up to 30 % in the United States [3–5]. Roughly 30 % of individuals with NAFLD also have NASH, the progressive subtype of NAFLD. Within the United States, NAFLD

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prevalence varies among racial and ethnic subgroups, with the highest prevalence observed among Hispanic persons (estimated prevalence 27–29 %), followed by non-Hispanic whites (15–18 %) and non-Hispanic blacks (11–16 %) [6, 7]. NAFLD prevalence increases with age, and some studies suggest that NAFLD may be more prevalent among men compared to women [3, 5, 8].

Established risk factors for NAFLD are obesity, particularly central obesity, type 2 diabetes, hypertriglyceridemia, and the metabolic syndrome (Table 5.1) [9]. More recently recognized risk factors include polycystic ovarian syndrome and obstructive sleep apnea; the latter may contribute to NAFLD independent of obesity due to hypoxia perpetuating insulin resistance [10–12]. Patients with diabetes and NAFLD tend to have more aggressive diseases (vis-à-vis progression to cirrhosis and liver-related mortality) compared to those without diabetes [13]. NASH is estimated at 22 % among patients with diabetes, compared to 5 % of the general population [4, 14].

Table 5.1 Features of the metabolic syndrome. Metabolic syndrome is diagnosed in the presence of ≥3 features [52]

Cause	Method of evaluation
Central obesity	Waist circumference >102 cm in men
	Waist circumference >88 cm in women
Impaired fasting glucose	Fasting blood glucose >110 mg/dL
Hypertension	Systolic blood pressure >130 mmHg or diastolic blood pressure >85 mmHg
Hypertriglyceridemia	Triglycerides >150 mg/dL
Low HDL cholesterol	HDL <40 mg/dL in men, HDL <50 mg/dL in women

HDL high-density lipoprotein

5.2 Diagnosis

Current guidelines from the American Association of the Study of Liver Disease and the European Association for the Study of the Liver advise against routinely screening for NAFLD in the general population due to uncertainties surrounding diagnostic tests and treatment options [5, 15]. Thus, NAFLD is typically diagnosed following incidental detection of elevated aminotransferases or steatosis on abdominal imaging. NASH cirrhosis is often diagnosed incidentally after the discovery of cirrhosis.

Making a diagnosis of NAFLD requires demonstration of hepatic steatosis (by imaging or liver biopsy) and exclusion of secondary causes of hepatic steatosis and alternate causes of liver disease (Table 5.2). Clinical history, biochemical testing, and imaging findings are used in combination to diagnose NAFLD.

Patients with NAFLD may present with nonspecific symptoms such as fatigue or right upper quadrant pain but are generally asymptomatic. Physical exam may reveal hepatomegaly or signs of insulin resistance (dorsocervical hump or acanthosis nigricans). Women with NAFLD may have findings that raise suspicion for polycystic ovarian syndrome (i.e., history of irregular menses and/or infertility and hirsutism). Blood work may reveal elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) two to three times the upper limit of normal, with aspartate transaminase (AST)/alanine transaminase (ALT) enzyme ratio <1. An AST/ALT ratio >1 may indicate the presence of cirrhosis. It is important to note that ALT and AST are often normal among patients with NAFLD and are not reliable indicators of the presence or severity of NAFLD [9, 16, 17].

If NAFLD is suspected in a patient with elevated aminotransferases, imaging should be done to evaluate for hepatic steatosis. Abdominal ultrasound, magnetic resonance imaging (MRI), and computed tomography (CT) scanning are the available imaging modalities. Abdominal ultrasound is the

Table 5.2 Secondary causes of hepatic steatosis and liver disease: suggested workup

Cause	Screening method	Abnormal values that should trigger further workup for alternative causes of liver disease
Alcohol	History	Heavy alcohol use defined as > 21 drinks/week for men >14 drinks/week for women for at least 2 years
Medications	Medication review for amiodarone, tamoxifen, corticosteroids, methotrexate, valproate, highly active antiretroviral therapy	Positive medication review
Infections	Hepatitis C antibody Hepatitis B surface antigen Hepatitis B core antibody HIV	Positive serology
Wilson's disease (screen patients < 45 years)	Ceruloplasmin	Ceruloplasmin <20 mg/dL
Autoimmune hepatitis	Antinuclear antibody Smooth muscle antibody	Positive serology
Iron overload	Ferritin Transferrin saturation	Transferrin saturation >45 % and ferritin >200 (premeuopausal woman) OR >300 (postmenopausal woman or man)

first-line imaging test for steatosis. The advantages of ultrasound are that it is widely available, inexpensive, and noninvasive; the disadvantages are that it is operator dependent, limited by central obesity and overlying intestinal gas, and has a very low sensitivity detecting hepatic fat content <30% [18]. MRI is the most sensitive modality for detecting hepatic steatosis and can precisely map and quantify hepatic fat; however, its clinical use is restricted by limited availability, cost, and patient claustrophobia [19]. CT scan is the least favored option because it is the least sensitive for hepatic steatosis and is further limited by expense, radiation, and intravenous iodine contrast exposure [20]. None of these imaging techniques can be used to distinguish between the subtypes of NAFLD (simple steatosis vs. NASH) or to stage liver fibrosis.

A complete workup should be done to exclude alternative causes of hepatic steatosis and chronic liver disease as outlined in Table 5.2. The most frequent secondary causes of hepatic steatosis include hepatitis C infection (see Chap. 7), excessive alcohol intake, and a variety of medications such as amiodarone, tamoxifen, methotrexate, and steroids among others [5]. Autoantibodies (antinuclear antibody and anti-smooth muscle antibody) are positive up to 20 % of patients with NAFLD and are not associated with autoimmune hepatitis [21]. Serum ferritin is frequently elevated in the setting of NAFLD and may reflect inflammatory activity and/or insulin resistance. However, if positive autoantibodies or elevated ferritin are found, further diagnostic testing must be done to evaluate for autoimmune hepatitis and hemochromatosis, respectively, before concluding NAFLD. If there is diagnostic uncertainty, a liver biopsy should be performed.

Unfortunately, NASH may be diagnosed for the first time in a patient who has already developed cirrhosis. These patients are often described as having "cryptogenic cirrhosis." Patients with NASH cirrhosis will have typical physical exam and biochemical findings of cirrhosis. Imaging and liver biopsy are not useful for establishing NASH as the cause of cirrhosis. This is because advanced fibrosis results in permanent change in liver morphology with loss of steatosis and

hepatocyte ballooning. When fatty acids accumulate causing lipotoxicity, the liver's protective mechanisms can become overwhelmed. Consequently, this activates several signaling pathways causing release of profibrotic cytokines and activation of hepatic stellate cells, both of which promote formation of fibrotic tissue [22]. Thus, imaging and liver histology will show findings of cirrhosis but will no longer demonstrate hepatic steatosis [23]. Instead, NASH is diagnosed based on exclusion of alternative causes of liver disease (Table 5.2) and medical history suggestive of a history of central obesity, features of metabolic syndrome, and/or type 2 diabetes.

5.3 NAFLD Subtypes, Natural History, and Prognosis

Compared to the general population, NAFLD is associated with excess mortality from three main causes in the following order: cardiovascular complications, (all-cause) malignancy, and liver disease [24, 25]. The two main subtypes of NAFLD are simple steatosis and NASH. Evaluation of liver histology is the only way to distinguish between NAFLD subtypes and is the basis for therapeutic decisions. Knowledge of the stage of fibrosis has important implications for prognosis. Liver disease-related mortality is primarily associated with NASH and with advanced fibrosis.

Simple steatosis (also known as nonalcoholic fatty liver) is characterized by the presence of steatosis without ballooned hepatocytes (which represents hepatocyte injury) or fibrosis. Mild inflammation may be present. Simple steatosis is associated with a very low risk of progressive liver disease and liver-related mortality. Because of the low risk of liver-related complications, the simple steatosis subtype does not require specific treatments for liver disease. Patients with simple steatosis are at an increased risk of cardiovascular complications compared to patients without NAFLD, particularly if there is concomitant diabetes. Therefore, cardiovascular risk factor reduction should be carefully pursued among patients with simple steatosis [5].

The presence of ballooned hepatocytes in addition to steatosis is the histologic feature diagnostic for NASH. Patients with NASH are at risk for progressive liver fibrosis and liver-related mortality, cardiovascular complications, and hepatocellular carcinoma (HCC) even in the absence of cirrhosis [26]. Liver fibrosis stage progresses at an estimated rate of one stage every 7 years [27]. Twenty percent of patients with NASH will eventually develop liver cirrhosis [9]. Therefore, management of patients with NASH should be geared toward reducing the risk of liver disease progression.

Fibrosis is the only histopathologic feature that predicts mortality [28, 29]. Fibrosis is staged using the Metavir scoring system and ranges from absent (stage 0) to cirrhosis (stage 4). Overall mortality is increased among patients with advanced fibrosis (stage 3–4) compared with no/early fibrosis (stage 0–2) irrespective of the extent of steatosis, ballooning, and inflammation [28]. The increased mortality seen among patients with advanced fibrosis is related to complications of liver disease, hepatocellular carcinoma, and possibly increased cardiovascular disease.

5.4 Indications for Liver Biopsy

Liver biopsy is vital to determining therapy and establishing prognosis of patients with NAFLD. Determination of a diagnosis of nonalcoholic steatohepatitis by liver biopsy is required prior to the initiation of liver specific treatments. In addition, liver biopsy allows for an assessment of hepatic fibrosis and provides important prognostic information regarding mortality. However, the cost, potential for complications, and invasive nature of liver biopsy limit its universal use among patients with NAFLD. Unfortunately, there are no guidelines with firm recommendations to guide the selection of candidates for liver biopsy, and clinicians have to rely on clinical risk factors to identify patients with NAFLD most at risk for progressing to NASH.

Insulin resistance is strongly associated with NASH. Metabolic syndrome, type 2 diabetes, and polycystic

ovarian syndrome are associated with high risk of NASH on index liver biopsy [30]. In addition, risk of NASH increases with age (>45 years), hypertension, central obesity, dyslipidemia, the number of metabolic risk factors present, and those with a family history of diabetes [31].

Based on these observations, patients with NAFLD with features of the metabolic syndrome, insulin resistance, or type 2 diabetes should be considered for liver biopsy. Patients with persistently abnormal aminotransferases (>6 months) or clinical findings concerning for advanced fibrosis/cirrhosis should also be considered for liver biopsy [5, 9].

5.5 Noninvasive Methods for Predicting Fibrosis

Several noninvasive methods have been proposed for prediction of advanced fibrosis. These include clinical prediction models and liver elastography. While none are 100 % accurate, these tools are frequently incorporated into clinical practice to identify patients most at risk for advanced fibrosis and, therefore, targeted for liver biopsy. The best validated and most widely used clinical prediction model for advanced fibrosis is the NAFLD fibrosis score (NFS). The NFS is based on a formula consisting of routinely available clinical data (age, body mass index [BMI], presence of hyperglycemia, AST/ALT ratio, platelet count, and albumin) and is easily determined using an online calculator (http://nafldscore.com/). The formula provides an estimated stage of liver fibrosis for the individual patient, graded as F0–F4:

- F0: indicates the absence of fibrosis
- F1: perisinusoidal/portal fibrosis
- F2: perisinusoidal and portal/periportal fibrosis
- F3: septal or bridging fibrosis
- F4: indicating cirrhosis [25]

Loosely, the terms perisinusoidal, portal, and septal indicate the location of the fibrosis. F3 and F4 are considered

stages of advanced fibrosis. A NFS score below −1.455 identifies patients at a low risk for advanced fibrosis (F3/F4) and has a negative predictive value of 88 %. An NFS above 0.676 identifies patients who are at a high risk for advanced fibrosis (F3/F4) with a positive predictive value of 82 %. An NFS score between −1.455 and 0.676 falls in an indeterminate range [32]. Depending on the study, 25–30 % of patients have an indeterminate score [32, 33]. Nevertheless, the intermediate category in addition to high risk has been shown to increase the likelihood of liver-related events and outcomes, including mortality and liver transplantation [34]. Therefore, when the NFS score is used to choose candidates for liver biopsy, an intermediate or high-risk score (NFS score >−1.455) is used as the threshold for liver biopsy.

Advances in imaging technology have yielded elastography techniques that can estimate hepatic fibrosis noninvasively. Elastography is based on the principle that liver stiffness increases with worsening liver fibrosis. Transient elastography (TE) and magnetic resonance elastography (MRE) are the two most extensively studied liver elastography methods for NAFLD. TE is an ultrasound-based elastography technique that uses mechanical vibrations to estimate elastography. TE can be performed in an office setting and has reasonably good accuracy for predicting advanced fibrosis/cirrhosis, but its use is limited among morbidly obese individuals [35]. MRE is more reliable and more accurate [36] than TE for estimating liver fibrosis but is not routinely available for clinical use.

5.6 Management

The risk of cardiovascular disease is increased across the entire NAFLD spectrum. Therefore, management of cardiovascular risk factors (hyperlipidemia, hypertension, and diabetes) is of foremost importance. When indicated, statins should be used for treatment of dyslipidemia. Statins are safe among patients with NAFLD (even in the setting of elevated

liver enzymes) and are not associated with an increased risk of statin-induced hepatotoxicity [35]. All patients with NAFLD should be immunized against hepatitis A and hepatitis B and should be advised to avoid heavy alcohol intake (Table 5.2).

All patients should be directed to lose weight with the goal of achieving a normal BMI and waist circumference. Weight loss is associated with meaningful improvement in NASH histology. A recent prospective observational study among 293 patients with NASH demonstrated that 3–5 % weight loss is associated with improvement in steatosis, ≥7 % weight loss is associated with improvement in steatohepatitis (ballooning), and ≥10 % weight loss is associated with improvement in fibrosis and the highest likelihood of NASH resolution [37]. The challenge, however, is in motivating patients to achieve and maintain sufficient weight loss [38]. Cognitive behavioral therapy and frequent clinic visits counseling are possible strategies for encouraging weight loss. Bariatric surgery is associated with improvement in NAFLD, NASH, and fibrosis [39, 40]. Bariatric surgery should be considered among patients with severe obesity and complications but is not an established therapy for NASH at this time.

Exercise, independent of weight loss, is important for patients with NAFLD. At a minimum, the goal is for moderate-intensity exercise for ≥30 min daily at least 5 days per week, vigorous exercise for ≥20 min a day on 3 days a week, or some combination of both [41]. Exercise along these lines is associated with a significant reduction of hepatic fat [42]. Resistance training can improve muscle mass and thereby improve insulin resistance, a principle driver of NASH pathophysiology [42]. But the evidence for whether resistance training can improve hepatic fat is controversial. There is no evidence to show that any form of exercise improves hepatocyte ballooning or fibrosis. Patients with NAFLD, therefore, should be given recommendations to pursue regular aerobic exercise as outlined and may pursue resistance training as an additional intervention with the expectation that there might be improvements in insulin sensitivity and hepatic steatosis but not NASH or fibrosis.

The cornerstone of dietary recommendations is calorie restriction with the goal of weight loss. There is evidence to suggest that a Mediterranean diet is associated with reduction in hepatic steatosis and improvement in insulin sensitivity in the absence of weight loss [43]. However, there is not enough evidence to recommend a specific diet to patients with NAFLD [44]. Fructose intake is associated with greater risk of NAFLD, and "fast-food" diets consisting of high cholesterol, saturated fat, and fructose are associated with progressive fibrosis in animal models [45]. Therefore, intake of fructose and diets high in saturated fats and high cholesterol diet should be avoided.

In addition to lifestyle modifications and weight loss, liver-specific pharmacotherapy should be considered among patients with biopsy-proven NASH. Currently, there are no drugs approved by the US Food and Drug Administration (FDA) for the treatment of NASH, although vitamin E and pioglitazone are used off-label.

Vitamin E is an antioxidant that is recommended at a dose of 800 international units (IU) daily among nondiabetic non-cirrhotic patients with biopsy-proven NASH. Efficacy of vitamin E was initially demonstrated in the PIVENS trial where patients with NASH treated with 800 IU of vitamin E for 96 weeks had significant improvement in NASH histology as compared with placebo (43 % vs. 19 %, $P < 0.001$) [46]. These findings were confirmed in a subsequent trial [47]. The safety of long-term use of high-dose vitamin E in patients with NASH is still unknown. Data from outside of hepatology suggests that use of vitamin E at doses >400 IU daily is associated with a small increase in all-cause mortality, hemorrhagic stroke, and prostate cancer.

Thiazolidinediones (TZDs) are useful for treatment of NASH. Pioglitazone at a dose of 30–45 mg daily is recommended among non-cirrhotic patients with diabetes and biopsy-proven NASH. Pioglitazone was also examined in the PIVENS trial where it narrowly missed the primary end point but did show NASH resolution in 47 % of patients, as opposed to 21 % of placebo-treated patients

[46]. A later meta-analysis of four randomized controlled clinical trials (RCTs) demonstrated that TZDs improve steatosis, hepatocyte ballooning, and inflammation and may improve fibrosis [48]. More recently, in a single-center RCT among 101 patients with prediabetes or type 2 diabetes with NASH, pioglitazone was significantly associated with greater histologic improvement and NASH resolution when compared with placebo (histologic improvement: 58 % vs. 17 %, $P < 0.001$; NASH resolution: 51 % vs. 19 %, $P < 0.001$) [49]. Widespread use of pioglitazone has been limited due to concerns of associated weight gain (on average 3–5 kg) and concerns about the small but significant associated risks of heart failure, bladder cancer, and bone fractures among women [5]. Based on current evidence, however, pioglitazone is a treatment option for NASH in carefully selected patients with prediabetes and diabetes under close clinical monitoring for development of edema and weight gain and in conjunction with a hepatologist.

Obeticholic acid (OCA) and liraglutide are pipeline drugs that have shown promise for treatment of NASH in recent clinical trials. OCA is a synthetic bile acid and a farnesoid X nuclear receptor agonist. The FLINT trial, a recently completed phase III RCT, demonstrated that OCA-treated patients with NASH had significant improvement in NASH compared with placebo (45 % vs. 21 %, $P = 0.0002$). Importantly, patients treated with OCA also had more improvement in fibrosis and weight loss when compared to placebo. The most common adverse effect was pruritus and worsening dyslipidemia [50]. Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist approved for the treatment of type 2 diabetes and obesity. The LEAN trial, a recently completed phase II RCT, demonstrated that liraglutide-treated patients had greater resolution of NASH when compared to placebo (39 % vs. 9 %, $P = 0.019$) [51]. The drug was generally well tolerated, and adverse effects included mild to moderate diarrhea, constipation, and anorexia.

5.7 Summary

NAFLD is a highly prevalent condition with both hepatic and extrahepatic morbidity. Identifying the presence of NASH (a progressive NAFLD subtype) has therapeutic and prognostic implications. Currently, liver biopsy is the "gold standard" for diagnosis of NASH. Clinical markers that can be used to hone in on appropriate candidates to select for liver biopsy include the presence of metabolic syndrome features or an intermediate- to high-risk NAFLD fibrosis score. Cardiovascular risk reduction should be aggressively managed in all patients. Liver-specific therapies including vitamin E, pioglitazone, and/or consideration of clinical trials should be considered among patients with biopsy-proven NASH.

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