World Gastroenterology Organisation Global Guidelines

Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

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1 Introduction

On May 21, 2010, the 63rd World Assembly of the World Health Organization adopted a resolution that established a World Hepatitis Day on July 28, and stated that "This endorsement by member states calls for WHO to develop a comprehensive approach to the prevention and control of these diseases." The diseases were the viral hepatitides A through E. This resolution, and a second one relating to alcoholic liver disease, represent the first formal declaration by WHO that the burden of liver disease represents a major global public health problem. However, although viral hepatitis and alcoholic liver disease are critical to global health, they do not encompass all—or even the most important—of the conditions contributing to the global health burden due to liver diseases. Over the past couple of decades, it has become increasingly clear that nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are now the number one cause of liver disease in Western countries. The prevalence of NAFLD has doubled during last 20 years, whereas the prevalence of other chronic liver diseases has remained stable or even decreased. More recent data confirm that NAFLD and NASH play an equally important role in the Middle East, Far East, Africa, the Caribbean, and Latin America.

NAFLD is a condition defined by excessive fat accumulation in the form of triglycerides (steatosis) in the liver (> 5% of hepatocytes histologically). A subgroup of NAFLD patients have liver cell injury and inflammation in addition to excessive fat (steatohepatitis). The latter condition, designated NASH, is virtually indistinguishable histologically from alcoholic steatohepatitis (ASH). While the simple steatosis seen in NAFLD does not correlate with increased short-term morbidity or mortality, progression of this condition to that of NASH dramatically increases the risks of cirrhosis, liver failure, and hepatocellular carcinoma (HCC). Cirrhosis due to NASH is an increasingly frequent reason for liver transplantation. While the morbidity and mortality from liver causes are greatly increased in patients with NASH, they correlate even more strongly with the morbidity and mortality from cardiovascular disease.

Table **1** Mortality in NAFLD/NASH

	Liver	Cardiac
General population	0.2%	7.5%
Simple Steatosis	0%	8.6%
NASH	1.6–6.8%	12.6–36%

NASH is widely considered to be the liver expression of the metabolic syndrome—diseases related to diabetes mellitus type 2, insulin resistance, central (truncal) obesity, hyperlipidemia (low high-density lipoprotein cholesterol, hypertriglyceridemia), and hypertension. There is at present a worldwide epidemic of diabetes and obesity. At least 1.46 billion adults were overweight or obese and 170 million of the world's children were overweight or obese in 2008. In some parts of Africa, obesity afflicts more children than malnutrition. The numbers are continuing to rise, indicating that NASH will become an increasingly common liver problem in both rich and poor countries, increasing the global burden of liver disease

and affecting public health and health-care costs globally. It is estimated that NAFLD/NASH will increase 5-year direct and indirect medical costs by 26%.

Table **2** Clinical identification of the metabolic syndrome (scientific statement by the American Heart Association and National Heart, Lung, and Blood Institute in the United States)

Risk factors—any three of the five constitute a diagnosis of metabolic syndrome		Defining levels
Abdominal obesity (waist circumference)	Men	> 102 cm (> 40 inches)
	Women	> 88 cm (> 35 inches)
Elevated triglycerides		≥ 150 mg/dL
Reduced HDL cholesterol	Men	< 40 mg/dL
	Women	< 50 mg/dL
Blood pressure	Systolic	≥ 130 mmHg
	Diastolic	≥ 85 mmHg
Fasting glucose		≥ 100 mg/dL

HDL, high-density lipoprotein.

The exact cause of NASH has not been elucidated, and it is almost certainly not the same in every patient. Although it is most closely related to insulin resistance, obesity, and the metabolic syndrome, not all patients with these conditions have NAFLD/NASH, and not all patients with NAFLD/NASH suffer from one of these conditions. However, as noted above, NASH is a potentially fatal condition, leading to cirrhosis, liver failure, and HCC.

There is no established therapy and there are no evidence-based clinical guidelines. There have not been any adequate prospective, double-blind, controlled trials to provide the data necessary to create an evidence-based guideline. This Global Guideline is intended to provide the best opinions of a group of experts from all areas of the globe concerning every aspect of this problem and the best approaches to diagnosing and treating this condition, taking locally available resources into account.

Cascades—a resource-sensitive approach

A gold standard approach is feasible for regions and countries in which the full scale of diagnostic tests and medical treatment options are available for the management of NASH. However, such resources are not available throughout much of the world. With their diagnostic and treatment cascades, the World Gastroenterology Organisation guidelines provide a resource-sensitive approach.

Cascade: a hierarchical set of diagnostic, therapeutic, and management options to deal with risk and disease, ranked by the resources available.

2 Epidemiology

NASH is an increasingly common chronic liver disease with worldwide distribution that is closely associated with diabetes and obesity, which have both reached epidemic proportions. It is estimated that there are at least 1.46 billion obese adults worldwide. Approximately 6 million individuals in the USA are estimated to have progressed to NASH and some 600,000 to NASH-related cirrhosis. There are significant cultural and geographic differences in the prevalence of obesity.

Whereas in most Western countries, the preferred body image, especially in women, is very thin with minimal body fat, that is not necessarily true globally. In many other cultures, obesity is considered desirable and also regarded as a distinct sign of prosperity (see, for example, the data from Egypt given below).

In the USA, obesity is particularly epidemic in those from lower socio-economic groups who rely heavily on diets provided by high-fat, high-calorie fast food outlets ("junk food"). The opposite is true in many poorer countries, where it is the well-to-do, better-educated population that has the highest prevalence of obesity.

Regional obesity/overweight data

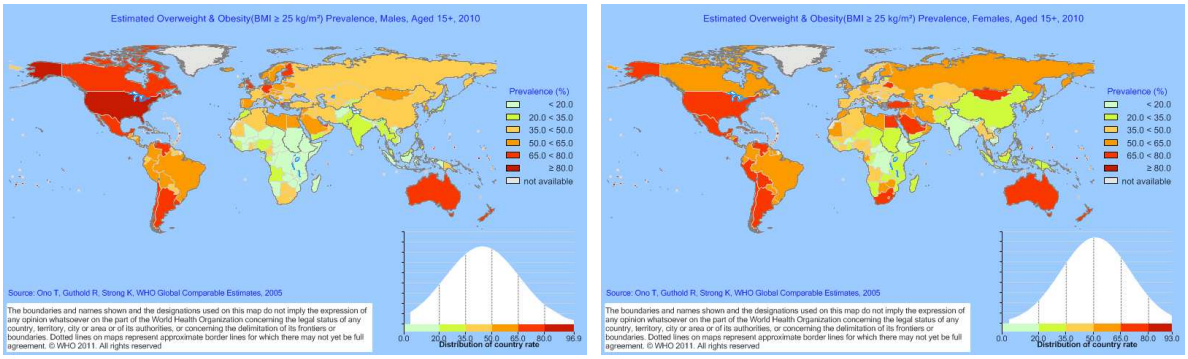
Table **3** Regional obesity/overweight data (representative examples)

Country	Details	Obese/overweight	Female (%)	Male (%)
Egypt	Urban	Obese (BMI 30–39.9)	45.2	20.0
	Rural	Obese (BMI 30–39.9)	20.8	6.0
	Youth (11–19 y)	Overweight	18.0	7.0
	Youth (11–19 y)	Obese	8.0	6.0
Mexico	Youth (11–19 y)	Overweight	21.0	18.0
	Youth (11–19 y)	Obese	9.0	11.0
Russia	–	Obese (BMI > 30)	18.0	7.0
		Overweight (BMI 25.0–29.9)	32.0	47.0
Croatia	Urban and rural	Obese	20.6	20.1
		Overweight	33.6	43.2
Pakistan	Age 25–64	Overweight (BMI > 25)	22.6	13.2
	General population	Overweight (incl. obese)	25.0	
		Obese	10.3	
	Children	Overweight/obese	6.4	4.6
	Children aged 13–14 y	Overweight/obese	11.0	7.0
	Rural—lower class	Overweight	9.0	
	Rural—middle class		15.0	
	Rural—upper class		27.0	

Country	Details	Obese/overweight	Female (%)	Male (%)
	Urban—lower class		21.0	
	Urban—middle class		27.0	
	Urban—upper class		42.0	

BMI, body mass index.

Fig. **1** Estimated prevalence of obesity (BMI > 25) in males and females aged 15+ (2010).



Source: WHO InfoBase.

Table **4** Overweight and obesity—summary of prevalence by region (2004)

		Population (millions)	Mean BMI (age 30+ y)	BMI > 25 (%)	BMI > 30 (%)
World	Both sexes	6,437	24.5	42	12
	Males	3,244	24.3	40	9
	Females	3,193	24.6	43	15
Region	Income				
Africa	Low and middle	738	23.0	30	6
South-East Asia	Low and middle	1,672	22.1	22	2
The Americas	Total	874	27.9	70	33
	High	329	29.0	76	43
	Low and middle	545	27.0	65	26
Eastern Mediterranean	Total	520	25.2	48	18
	High	31	28.5	74	37
	Low and middle	489	25.0	46	16
Europe	Total	883	26.9	65	24
	High	407	26.8	65	23
	Low and middle	476	27.0	65	25
Western Pacific	Total	1,738	23.4	31	3
	High	204	24.1	39	7
	Low and middle	1,534	23.3	30	2

Source: WHO 2009 [25]. Click here to link to the source.

Prevalence of NAFLD and NASH

Table **5** Estimated prevalences of NAFLD and NASH. Reports on the prevalence of NAFLD and NASH vary substantially due to varying definitions, differences in the populations studied, and the diagnostic methods used

Region	Population studied	Prevalence of NAFLD in these populations (%)
USA	Pediatric population	13–14
	General population	27–34
	Morbid obesity	75–92
	European-Americans	33
	Hispanic-Americans	45
	African-Americans	24
Europe	Pediatric population	2.6–10
	General population	20–30
Western countries	General population	20–40
	Obesity or diabetes	75
	Morbid obesity	90–95
Worldwide	Obese population	40–90
Middle East	General population	20–30
Far East	General population	15
Pakistan	General population	18
Population with NAFLD studied		**Prevalence of NASH in these populations (%)**
Selected healthy liver donors		3–16%
No inflammation or fibrosis		5%
General population		10–20%
High-risk, severe obesity		37%
Patients at tertiary care centers		40–55%

3 Pathogenesis and risk factors

NASH represents the most severe histologic form of nonalcoholic fatty liver disease (NAFLD), which is defined by fat accumulation in the liver exceeding 5% of its weight. Uniform criteria for diagnosing and staging NASH are still debated (see details in later sections).

Insulin resistance is related to obesity and is central to the pathogenesis of NAFLD. In addition, oxidative stress and cytokines are important contributing factors, together

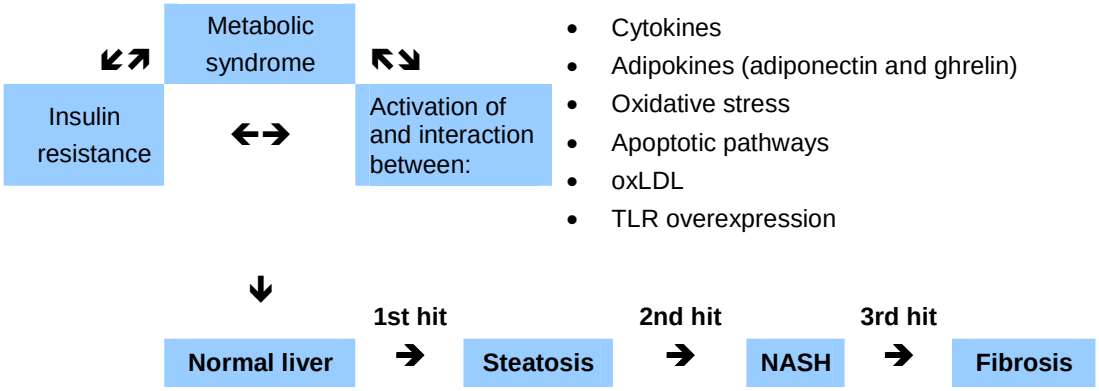
resulting in steatosis and progressive liver damage in genetically susceptible individuals.

Key histologic components of NASH are steatosis, hepatocellular ballooning, and lobular inflammation; fibrosis is not part of the histologic definition of NASH. However, the degree of fibrosis on liver biopsy (stage) is predictive of the prognosis, whereas the degree of inflammation and necrosis on liver biopsy (grade) are not.

The disease can remain asymptomatic for years, or can progress to cirrhosis and hepatocellular carcinoma.

One global hypothesis for the pathogenesis of NASH is the "multi-hit hypothesis," with metabolic syndrome playing a major role, due to insulin resistance and the proinflammatory process mediated by different proteins and immune components. The identities of the multiple "hits" are different in each patient and largely undefined at present.

Fig. **2** The "multi-hit" hypothesis for nonalcoholic steatohepatitis (NASH). oxLDL, oxidized low-density lipoprotein; TLR, Toll-like receptor.



Risk factors and associated conditions

The characteristics of a low-risk population are: young, healthy, with low alcohol consumption, and not obese.

Table **6** Risk factors and associated conditions

Risk factors	Disease progression	Associated conditions
• Insulin resistance/metabolic syndrome • Jejunoileal bypass surgery • Age—highest risk in 40–65-year-olds, but it does occur in children < 10 y old • Ethnicity—higher risk in Hispanics and Asians, lower risk in African-Americans • Positive family history—genetic predisposition • Drugs and toxins—e.g., amiodarone, coralgil, tamoxifen, perhexiline maleate, corticosteroids, synthetic estrogens, methotrexate, IV tetracycline, highly active antiretroviral drugs (HAART)	• Obesity, Increased BMI and waist circumference • Uncontrolled diabetes, hyperglycemia, hypertriglyceridemia • Sedentary lifestyle, lack of exercise • Insulin resistance • Metabolic syndrome • Age • Genetic factors	• Hyperlipidemia • Insulin resistance/metabolic syndrome • Type 2 diabetes • Hepatitis C • Rapid weight loss • Total parenteral nutrition • Wilson's disease, Weber–Christian disease, a beta lipoproteinemia, diverticulosis, polycystic ovary syndrome, obstructive sleep apnea

Table **7** Calculation of insulin resistance

Name	Formula	Level suggesting insulin resistance
HOMA	$\frac{\text{Fasting insulin (mU/L)} \times \text{fasting glucose (mmol/L)}}{22.5}$	> 1.8–2.0
QUICKI	1 / (log(fasting insulin µU/mL) + log(fasting glucose mg/dL))	< 0.35
Rough estimate	Fasting insulin × fasting glucose	> 700

HOMA, homeostasis model assessment; QUICKI, quantitative insulin-sensitivity check index.

Table **8** NASH scoring system in morbid obesity

Factor	Points
Hypertension	1
Type II diabetes	1
AST ≥ 27 IU/L	1
ALT ≥ 27 IU/L	1
Sleep apnea	1
Nonblack	2
Point total	**Risk of NASH**
0–2	Low
3–4	Intermediate
5	High
6–7	Very high

Prognosis and complications

- Disease progression from NAFLD to NASH to cirrhosis/liver failure and HCC.
- NAFLD does not exacerbate hepatotoxicity, and side effects of pharmacologic agents, including HMG-CoA reductase inhibitors, are not more likely to occur,
- NAFLD and coexistent obesity and related metabolic factors may exacerbate other liver diseases—e.g., alcoholic liver disease.
- Concurrence of NAFLD with hepatitis C or human immunodeficiency virus (HIV) worsens their prognoses and decreases their responses to therapy.
- Hepatitis C, genotype 3, is commonly associated with hepatic steatosis, which may confuse a diagnosis of hepatitis C vs. NASH vs. both together.
- Liver biopsy may indicate the severity of disease, but only fibrosis, and not inflammation or necrosis, has been confirmed to predict the disease prognosis.
- Histologic progression to end-stage liver disease may occur: NASH + bridging fibrosis or cirrhosis.
- End-stage NASH is an often under-recognized cause of cryptogenic cirrhosis; progressive fibrosis may be obscured by stable or improving steatosis and serologic features, especially in older NASH patients.
- NASH-related (cryptogenic) cirrhosis increases the risk of hepatocellular carcinoma (HCC).
- Causes of mortality in cirrhotic NASH patients:
  — Liver failure
  — Sepsis
  — Variceal hemorrhage
  — HCC
  — Cardiovascular disease

Table **9** NASH survival rates in comparison with simple steatosis and alcoholic steatohepatitis (ASH)

Survival	Simple steatosis	NASH	ASH
5-year	Normal	67%	59%
10-year	Normal	38%	15%

Table **10** Disease progression from NAFLD to NASH to cirrhosis/liver failure and HCC. The results of prevalence and incidence studies vary substantially due to varying definitions, different populations studied, and diagnostic methods used

Population studied	Prevalence of disease progression
NAFLD → NASH	
General population	10–20%
No inflammation or fibrosis	5%
High-risk, severe obesity	37%
NAFLD → cirrhosis	
Simple steatosis	0–4% over 10–20 y

Population studied	Prevalence of disease progression
NASH → fibrosis	
Patients at tertiary referral centers	25–33% at diagnosis
High-risk, severe obesity	23%
NASH → cirrhosis	
High-risk, severe obesity	5.8%
Patients at tertiary referral centers	10–15% at diagnosis
General population	3–15% over 10–20 y
General population	5–8% over 5 y
NASH → liver failure	
Cirrhosis	38–45% after 7–10 y
NASH → hepatocellular carcinoma	
Cirrhosis	2–5% per year

- Independent predictors for progression of fibrosis:
  — Age > 45–50
  — BMI > 28–30 kg/m^2
  — Degree of insulin resistance
  — Diabetes
  — Hypertension
- Negative impact on NASH survival:
  — Diabetes and elevated serum alanine (ALT) and aspartate aminotransferase (AST)
  — Older age and presence of necrotic inflammation on initial liver biopsy
  — Older age, impaired fasting glucose, and presence of cirrhosis

4 Diagnosis

Patient history and clinical evaluation

- Patient symptoms:
  — In most cases, NASH does not cause any specific symptoms.
  — There are sometimes vague symptoms of fatigue, malaise, and abdominal discomfort.
- The presence of any of the following, especially with a history of abnormal AST/ALT, should lead to a work-up for NAFLD/NASH:
  — Presence of obesity, especially morbid obesity (BMI > 35)
  — Diagnosis of type 2 diabetes mellitus
  — Diagnosis of metabolic syndrome
  — History of obstructive sleep apnea

— Presence of insulin resistance (see below and Table 7)
— Chronic elevation of AST/ALT, otherwise unexplained

- Detailed patient history of alcohol consumption—threshold < 20 g/day in women, < 30 g/day in men. *This is critical, as no diagnostic test can reliably distinguish between ASH and NASH.*
  — Appropriate specialized questionnaires or scoring systems for the evaluation of alcohol consumption should be used.
  — CAGE questionnaire: CAGE is the acronym for the four questions: have you ever felt you needed to *C*ut down on your drinking, that people *A*nnoyed you by criticizing your drinking, felt *G*uilty about drinking, needed a drink first thing in the morning (*E*ye-opener)? CAGE is a widely used method of screening for alcoholism, and confirms clinically relevant alcohol consumption if at least one of the questions is answered positively and if the Alcohol Use Disorders Identification Test (AUDIT) score is higher than 8.
- Although it is generally recommended that one should avoid all alcohol if one has underlying liver disease, this can raise problems in patients with the metabolic syndrome who have documented coronary artery disease, for whom modest wine consumption has been shown to be beneficial. Limited studies have suggested that modest wine drinking (0.12 L / 4 fluid ounces per day) may be associated with a decreased prevalence of NAFLD. Its effectiveness as treatment for preexisting NAFLD has not been addressed.
- Central obesity correlates with severity of inflammation on biopsy, and dorsocervical lipohypertrophy (buffalo hump) correlates with hepatocyte injury.
- Physical findings in case of progression/advanced liver disease: spider angiomas, ascites, hepatomegaly, splenomegaly, palmar erythema, jaundice, hepatic encephalopathy.

Routine laboratory findings and imaging tests

- Elevated ALT and AST:
  — In 10% of NASH patients, ALT and AST may be normal, especially with simple steatosis.
  — An abnormal ferritin level in the presence of normal transferrin saturation should always suggest a need to rule out NASH.
- AST/ALT ratio < 1—this ratio is usually > 2 in alcoholic hepatitis.
- Typical imaging test results confirming fat accumulation in the liver:
  — The magnetic resonance imaging (MRI) test has a quantitative value, but cannot distinguish between NASH and ASH.
  — Ultrasound is the usual screening test for fatty liver.

No imaging study can identify fat accurately if it is < 33% or distinguish NASH from ASH.

Tests to exclude:

- Viral hepatitis—hepatitis B surface antigen, hepatitis C virus antibody or HCV-RNA, hepatitis A antibody IgM, hepatitis E antibody (in an appropriate geographical setting); it should be noted that the patient may have coexisting viral hepatitis as well as NAFLD/NASH.
- Alcohol-related liver disease including alcoholic steatohepatitis.
- Autoimmune liver disease.

- Congenital causes of chronic liver disease: hereditary hemochromatosis, Wilson's disease, alpha-1-antitrypsin deficiency, polycystic ovary syndrome.
- Drug-induced liver disease.

Investigational laboratory tests, scoring systems, and imaging modalities

A wide variety of attempts have been made to develop scoring systems or imaging techniques that will allow noninvasive diagnosis of NASH and avoid the need for a liver biopsy. Currently, none has been tested rigorously enough in prospective, double-blind studies, nor has their ability to predict the prognosis or response to therapy been proven. The majority of speciality serum tests/scores are available from single laboratories or research laboratories and only at significant cost, so they are of little value in countries with limited resources. Specialized imaging modalities, including FibroScan, using a novel "controlled attenuation parameter," and positron emission tomography (PET) scanning suffer from the same limitations of limited availability, high cost, and lack of sufficient controlled data.

An extensive review of the various modalities and the data currently available can be found in the article by Dowman et al. [7]. Another detailed discussion of the issues was published in Ratziu et al. [11]. The methods involved show great promise for the future, but cannot at present be recommended at this time for general use.

Liver biopsy

Although it is invasive and has a potential for sampling errors and inconsistent interpretation of the histopathology, liver biopsy is required in order to establish the diagnosis and to stage NASH. The currently most commonly used histological scoring system is summarized in Table 11. It is used primarily in controlled trials to evaluate the effects of experimental therapies, rather than to establish the diagnosis of NASH. It has been independently validated and is applicable to both adult and pediatric NAFLD/NASH. There is no reliable way of distinguishing between NAFLD/ALD and NASH/ASH without a liver biopsy. Because of the difficulties in proper interpretation of the liver biopsy, it is best if it can be read by a specialized hepatopathologist with experience in making the histopathologic diagnosis.

Table **11** NASH Clinical Research Network histological scoring system

NASH activity grade: grade = total score: S + L + B (range 0–8)					
Steatosis	S score	Lobular inflammation	L score	Hepatocyte ballooning	B score
< 5%	0	None	0	None	0
5–33%	1	< 2	1	Few ballooned cells	1
34–66%	2	2–4	2	Many ballooned cells	2
> 66%	3	> 4	3		

NASH fibrosis stage	Stage
None	0
Mild, zone 3 perisinusoidal fibrosis	1a
Moderate, zone 3 perisinusoidal fibrosis	1b

Portal/periportal fibrosis only	1c
Zone 3 perisinusoidal and portal/periportal fibrosis	2
Bridging fibrosis	3
Cirrhosis	4

Source: Kleiner et al., Hepatology 2005;41:1313–21 [35].

Liver biopsy and histology are indicated in order to confirm a NASH diagnosis, to grade and stage the disease, and to rule out other diagnoses in the presence of one or more of the following findings:

- Abnormal serum ferritin in the absence of an elevated transferrin saturation
- Cytopenia
- Splenomegaly
- Clinical signs of chronic liver disease
- Diabetes and abnormal persistently elevated AST/ALT
- Obesity and age > 45 or abnormal AST/ALT
- Unexplained hepatomegaly

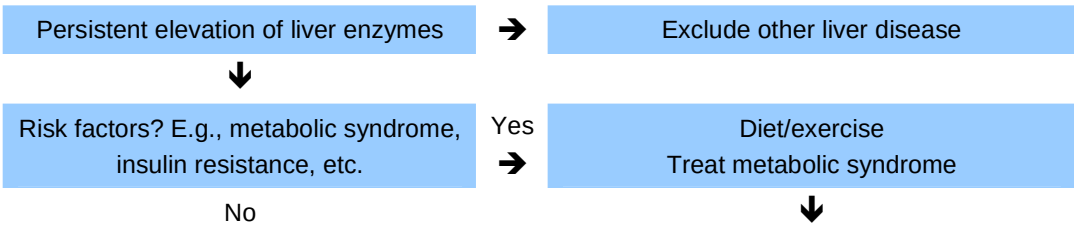
Table **12** Diagnostic tests for fatty liver

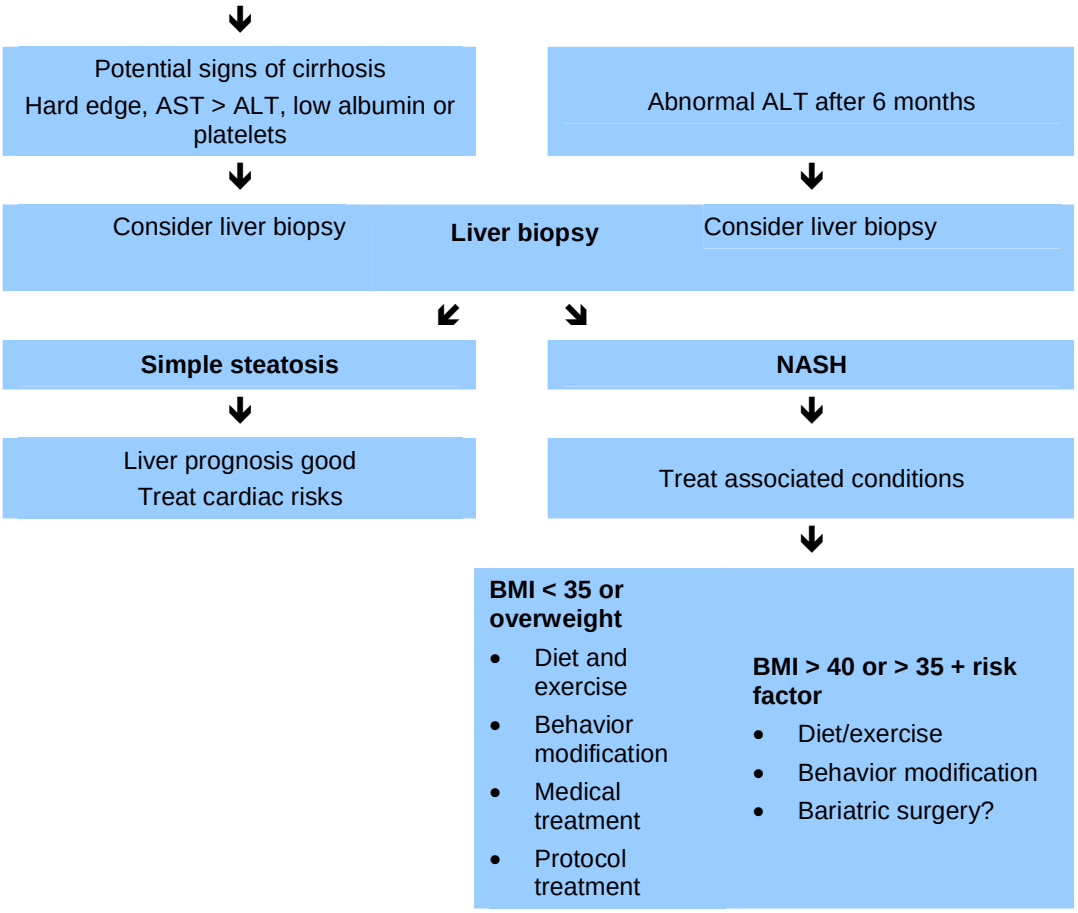
Test	Sensitivity	Specificity	Remarks
Histology, liver biopsy	The gold standard	Cannot reliably distinguish between ASH and NASH	Significant variability between pathologists' reading of the same sample; a highly experienced hepatopathologist is best
Liver enzymes	Low	Low	AST/ALT usually < 1.0; values may be normal
Imaging			
Ultrasound	Limited	Limited	Insensitive unless steatosis > 33%; operator-dependent
MRI, MRS, CT scan ± contrast enhancement	Results are variable and not well verified		Test are costly, less available, cannot distinguish steatosis and fibrosis or NASH/ASH or stage disease, and are insensitive if there is < 33% steatosis; see reference list and extended reference list

ALT, alanine aminotransferase; ASH, alcoholic steatohepatitis; AST, aspartate aminotransferase; CT, computed tomography; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NASH, nonalcoholic steatohepatitis.

Diagnostic strategy for NASH

Fig. **3** Management algorithm for NAFLD. Based on Rafiq and Younossi [10].





Liver enzyme tests and liver ultrasound:

- In patients who seek medical help in relation to insulin resistance/metabolic syndrome/diabetes

Imaging procedures to evaluate for steatosis:

- In patients with elevated liver enzymes

Liver biopsy:

- May be indicated if there is a strong suspicion for advanced fibrosis, when liver enzymes are elevated and ultrasound is positive for steatosis.
- To determine the severity of disease/fibrosis when noninvasive tests are indeterminate.
- Indicated in patients with chronic liver disease (other than NAFLD) and positive tests for metabolic risk factors, insulin resistance, and steatosis on ultrasound.
- If elevated ferritin with normal transferrin saturation, must rule out NASH.
- During surgical procedures in other high-risk groups—e.g., anti-obesity surgery, cholecystectomy.

None of the noninvasive tests will rule out other possible underlying diseases or stage the disease for prognostic purposes.

Ultimately, NAFLD/NASH is a diagnosis of exclusion, and liver biopsy will often be required to confirm the diagnosis, stage the disease, rule out other liver diseases, and determine the need for and urgency of aggressive therapy.

Fig. **4** Algorithm for liver biopsy in patients with suspected NAFLD after exclusion of other liver diseases.

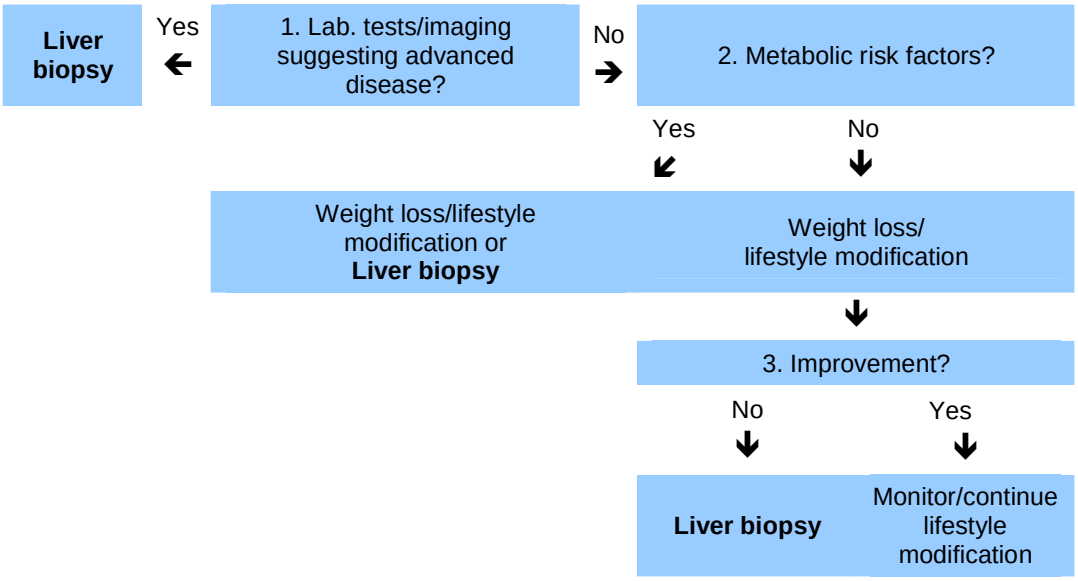


Fig. **5** Diagnostic options for NAFLD

Suspected NAFLD

- Central obesity, diabetes mellitus, dyslipidemia, metabolic syndrome
- Abnormal LFTs and/or changes on ultrasound consistent with fatty liver

Minimal assessment

- Bilirubin, ALT, AST, GGT, albumin, and fasting serum lipids
- Complete blood count
- Anti-HCV, HB_sAg, ANA
- FBG; if FBG is ≥ 5.6 mmol/L, 75 g OGTT
- Anthropometry: height, weight, BMI, waist circumference
- Blood pressure measurement
- Imaging: abdominal ultrasound

Optional tests

- Abdominal CT, if ultrasound is not informative
- Liver biopsy in cases of diagnostic uncertainty and in patients who are at risk of advanced hepatic fibrosis

Additional tests	• Hereditary hemochromatosis, Wilson's disease, alpha-1-antitrypsin deficiency, polycystic ovary syndrome • Autoimmune liver diseases (ANA, ASMA, AMA, anti-LKM Ab)

ALT, alanine aminotransferase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; anti-LKM Ab, anti-liver–kidney microsomal antibody; ASMA, anti-smooth muscle antibody; AST, aspartate aminotransferase; BMI, body mass index; CT, computed tomography; FBG, fasting blood glucose; GGT, gamma-glutamyl transferase; HB_sAg, hepatitis B surface antigen; HCV, hepatitis C virus; LFT, liver function tests; OGTT, oral glucose tolerance test.

Cascade—options for diagnosis in patients with suspected NAFLD/NASH

Table **13** Diagnostic cascade for extensive, medium, and limited resources

Level 1—extensive resources		Availability	Feasibility	Remarks
1	Medical and family history to evaluate for risk factors; alcohol intake is a critical part of the patient history	Limited medical training required	Access to patients. Reliable history may be problematic	First step to identify potential patients: > 20 g/day in females > 30 g/day in males
2	General physical examination to evaluate for risk factors, BMI, and waist–hip ratio	Limited medical training required	Access to patients	
3	Test serum liver aminotransferases	Yes	Generally available	May be normal
4	Radiologic evaluation	Ultrasound; MRI more quantitative	Generally available	Insensitive if < 33% fat; cannot distinguish ASH from NASH
5	Serology to exclude viral hepatitis	HB_sAg, HCV Ab, HEV Ab when appropriate	Generally available	May coexist with NASH and exacerbate progression
6	Fasting blood sugar, lipid profile, HbA_{1c}	Readily available		
7	Screen for insulin resistance	Should be readily available		Would require further NAFLD/NASH evaluation if screen was positive
8	Rule out other chronic liver diseases	Optional and additional tests (see Fig. 5)	Generally available; expensive but important to rule out treatable coexistent diseases	Cost may be limiting

Level 1—extensive resources		Availability	Feasibility	Remarks
9	Liver biopsy and histology	Generally available	Requires experienced pathologist	The definitive test to rule out other diseases, grade and stage disease; cannot reliably distinguish NASH from ASH

Ab, antibody; HbA_{1c}, glycosylated hemoglobin; HB_sAg, hepatitis B surface antigen; HCV, hepatitis C virus; HEV, hepatitis E virus; MRI, magnetic resonance imaging.

Level 2—medium resources	
1	Medical and family history and history of alcohol intake
2	General physical examination to evaluate for risk factors, BMI, and waist–hip ratio
3	Test serum liver aminotransferases
4	Imaging evaluation: ultrasound
5	Serology to exclude viral hepatitis: HB_sAg, HCV Ab, HEV Ab
6	Fasting blood sugar, lipid profile, HbA_{1c}
7	Screening for insulin resistance
8	Rule out other chronic liver diseases: optional/additional lab tests (see Fig. 5; not all may be available)
9	Liver biopsy and histology

Ab, antibody; HbA_{1c}, glycosylated hemoglobin; HB_sAg, hepatitis B surface antigen; HCV, hepatitis C virus; HEV, hepatitis E virus.

Level 3—low resources	
1	Medical and family history and history of alcohol intake
2	General physical exam to evaluate for risk factors, BMI and Waist hip ratio
3	Test serum liver aminotransferases
4	Radiologic evaluation: ultrasound
5	Serology to exclude viral hepatitis: HB_sAg, HCV Ab, HEV Ab
6	Fasting blood sugar, cholesterol, triglycerides

5 Management

Therapeutic rationale

Targets for therapy are insulin resistance and oxidative stress. Although several treatment options are being evaluated, the value of most treatments remains uncertain, or the effects reverse when they are discontinued. The goals of treatment for NASH are to reduce the histologic features and improve insulin resistance and liver enzyme levels.

At the present time, there is no evidence-based approved drug therapy for NAFLD/NASH. Lifestyle change is critical in any attempt to reverse the course of NAFLD/NASH.

In the absence of a treatment that would represent a standard of care, the management of NASH focuses on associated conditions. NASH should be treated aggressively in order to prevent progression to cirrhosis, as these patients are frequently not candidates for liver transplantation due to their morbid obesity, cardiovascular disease, or other complications of their underlying condition.

The overall goal of lifestyle change is to reduce excess weight: even a gradual 5–10% weight loss has been shown to improve liver histology and enzymes, but not fibrosis. This is usually most successful if combined with an active exercise program and elimination of a sedentary lifestyle. This may also require a sensitive approach to explaining the problems of obesity in certain cultures in which it may be considered a mark of beauty/desirability and/or prosperity.

Liver transplantation is appropriate in the face of liver failure. Some 30–40% of patients with NASH-related cirrhosis require liver transplantation. Most programs will decline patients with an elevated BMI (which varies from > 35 to > 45, depending on local program criteria). NASH can recur in the transplanted liver, or a new occurrence may even develop.

Treatment options for NASH

As emphasized above, lifestyle changes are critical in any attempt to reverse the course of NAFLD/NASH, and an evidence-based approved drug therapy for NAFLD/NASH is not available at present.

Treatment of metabolic conditions

Proper control of diabetes, hyperlipidemia, and cardiovascular risks is recommended. Studies with atorvastatin and pravastatin have shown improvement in histology in patients with NASH. NAFLD patients with dyslipidemia should be treated with statins. Patients with underlying liver disease do not seem to have any additional risk of statin toxicity. Serious hepatotoxicity from statins is rare.

Improving insulin sensitivity—weight reduction

- *Diet:* A weight loss of 5–10% should be aimed for, and a 25% decrease in calories from the normal diet (ca. 2500 calories per day) for the patient's age and sex. A moderately calorie-restricted diet with modified macronutrient composition produces better results in comparison with a very low-caloric diet. Attention should be given to the role of a hypocaloric diet and counseling about the type of foods to be consumed—avoiding fructose and trans-fats present in soft drinks and fast foods, and increasing omega-3/omega-6 polyunsaturated fatty acids in diet. This may be difficult for the patient to adhere to, and many patients regain weight after an initial loss.
- *Exercise:* A moderate exercise program three to four times a week should be encouraged to achieve a heart rate of 60–75% of the age-based maximum.

- The efficacy of dietary and exercise measures should be assessed after a 6-month period; if they have been ineffective, additional therapeutic options such as pharmacologic therapy may then be considered.
- *Weight loss (bariatric) surgery* may be beneficial for patients with morbid obesity; again, this should be considered early, as most programs will decline such surgery for patients who are already cirrhotic. Limited studies have reported a dramatic improvement in liver disease, as well as other complications of metabolic syndrome/insulin resistance, following successful bariatric surgery.
- Drugs targeting insulin resistance, such as thiazolidinediones and metformin, are approved for diabetes therapy but not for NAFLD/NASH, and should be considered experimental (see the reference list below for more information and detailed discussion).

Antioxidants and antifibrotic agents

Antioxidants and antifibrotic agents, such as vitamin E and pentoxifylline, have not been approved for NASH/NAFLD treatment. For all of them, there are limited data and few if any data from double-blind controlled trials. They are all considered experimental (see the reference list below for more information and detailed discussion).

Monitoring strategy

Disease progression and complications can be detected during the follow-up as indicated in Table 14.

Table **14** Follow-up tests and their timing

Follow-up	Recommended
Evaluate weight loss, exercise, diet and lifestyle changes	After 6 months
Blood and platelet count	2 × annually
Liver biochemical tests	2 × annually
Prothrombin time	2 × annually
Consult hepatologist	At 6 months and then yearly, depending on the response
Screening for cardiovascular risk	Every 1–2 years, depending on risk factors
Liver biopsy	Every 3–5 years, depending on response
Imaging tests	When indicated

Cascades—options for therapy

Table **15** Therapy cascades for extensive, medium, and limited resources

Level 1—extensive resources	Availability	Feasibility	Remarks
1 Weight loss diet (individually planned diet, based on measurements of total and resting	Well-trained health-care providers available	Well-trained doctors, nurses, dietitians, exercise/physiotherapy providers available	*Lifestyle changes are the single most effective weapon in treating NASH; an* enthusiastic support

Level 1—extensive resources		Availability	Feasibility	Remarks
	energy expenditures), exercise, education			group is very helpful
2	Diabetes control	One of the key risk factors; well-recognized health problem	Physicians, nurses, dietitians readily available with appropriate training	Essential to control if present
3	Lipid-lowering agents	Readily available; dietary changes also essential	Physicians, nurses, dietitians readily available with appropriate training	Essential to control if present
4	Weight loss—bariatric surgery	Widely, although not universally available	Major surgery; still requires extensive lifestyle changes; likely not available if the patient is already cirrhotic or has portal hypertension	Should be considered early, before the patient has cirrhosis/portal hypertension; has been shown to reverse many of the problems of NASH/metabolic syndrome
5	Liver transplantation	Generally available in high-resource countries, but not in all centers or cities	Generally not available to patients with BMI > 45 (> 35 in some centers)	NASH may recur or develop de novo in the transplanted liver

Level 2—medium resources		Availability	Feasibility	Remarks
1	Weight loss diet (25% calorie restriction from recommended value), exercise, education	Limited training required for health-care provider	Limited training required for health-care provider	*Lifestyle changes are the single most effective weapon in treating NASH; an* enthusiastic support group is very helpful
2	Diabetes control	One of the key risk factors; well-recognized health problem	Physicians, nurses, dietitians more often available with appropriate training	Essential to control if present
3	Lipid-lowering agents	May be less available due to cost; dietary changes will also help if hyperlipidemia is present	Physicians, nurses, dietitians more often available with appropriate training	Important to control if present

Level 3—limited resources		Availability	Feasibility	Remarks
1	Weight loss diet, exercise, education	Limited training required for health-care provider	Limited training required for health-care provider	*Lifestyle changes are the single most effective weapon in treating NASH; an* enthusiastic support group is very helpful
2	Diabetes control	One of the key risk factors; well-recognized health problem	Generally available	Essential to control if present
3	Lipid-lowering agents	Becoming more widely available with good and cheaper generics; dietary changes will also help if hyperlipidemia is present	Require resources for medications, training of health-care providers	Important to control if present

6 Summary

- NAFLD and NASH represent a major global public health problem, which is pandemic and affects rich and poor countries alike.
- There is insufficient evidence to justify screening for NASH/advanced liver disease in the general population.
- The diagnosis should be sought in all patients who present with risk factors for NASH. Not all patients with risk factors will have NAFLD or NASH, and not all patients with NASH will have standard risk factors.
- Not every person with fatty liver needs aggressive therapy.
- Diet and exercise should be instituted for all patients.
- Liver biopsy should be reserved for those patients who have risk factors for NASH and/or other liver diseases.
- Patients with NASH or risk factors for NASH should first be treated with diet and exercise. Vitamin E or pentoxifylline may be added in these patients. Experimental therapy should be considered only in appropriate hands and only in patients who fail to achieve a 5–10% weight reduction over 6 months–1 year of successful lifestyle changes.
- Bariatric surgery should be considered in patients in whom the above approaches fail, and it should be performed before the patient becomes cirrhotic.
- Liver transplantation is successful in patients who meet the criteria for liver failure, but NASH may recur after transplantation and is likely to be denied to patients with morbid obesity.
- NAFLD and NASH are also becoming an increasingly serious problem in pediatric patients, including those under the age of 10.
- Ultimately, NAFLD and NASH are diagnoses of exclusion and require careful consideration of other diagnoses. Just as the clinician cannot diagnose NASH on the basis of clinical data alone, the pathologist can document the histological

lesions of steatohepatitis, but cannot reliably distinguish those of nonalcoholic origin from those of alcoholic origin.

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Position statements and reviews

Insufficient randomized, controlled, double blind studies are available to provide evidence-based data for a formal guideline, as discussed in the Introduction above. The following is a listing of selected position statements, reviews, and expert opinion articles.

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Further reading

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