INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is an acquired metabolic stress-induced liver disease associated with insulin resistance (IR) and genetic susceptibility, sharing histological similarities with alcoholic liver disease (ALD) in the absence of substantial alcohol consumption or other causes of liver disease. The spectrum of NAFLD is from simple steatosis to nonalcoholic steatohepatitis (NASH) and eventually cirrhosis and hepatocellular carcinoma.\(^1,2\) NAFLD is one of the important public health problems worldwide in the 21st century and is also becoming more and more important in China.\(^3\) In order to further normalize the diagnosis and management of NAFLD, the Chinese National Consensus Workshop on NAFLD organized experts in this field to update the Guidelines for the diagnosis and treatment of nonalcoholic fatty liver diseases formulated in 2006 with reference to the latest worldwide research findings and related diagnosis and treatment consensus and in line with the principles of evidence-based medicine.\(^4-10\) The evidence bases are categorized into three grades and five levels,\(^11\) presented as roman digits in parentheses (Table 1).

The aim of this guideline is to help physicians to make correct decision in diagnosing and treating NAFLD. This guideline is not a mandatory standard and cannot involve or resolve all issues in the diagnosis and treatment program of NAFLD. Clinicians facing a specific patient should be able to make a reasonable diagnostic and therapeutic scheme based on the full understanding of the best clinical evidence and available medical resources and the comprehensive consideration of patient’s specific condition and wishes, and in accordance with their own knowledge and experience. The research work on NAFLD has been advancing rapidly, so the guidelines should be updated and improved continually based on the progress of the discipline and clinical requirements in near future.

EPIDEMOLOGY

NAFLD is now recognized as one of the most common causes of minor serum aminotransferase elevations and chronic liver diseases in developed countries such as Europe and America, and the prevalence of NAFLD...
is 20–33% in adults in the general population, among which NASH and cirrhosis account for 10–20% and 2–3%, respectively.1,2,11 The prevalence of simple steatosis, NASH and cirrhosis in obese patients was 60–90%, 20–25% and 2–8%, respectively. The prevalence of NASH in patients with type 2 diabetes mellitus (T2DM) and hyperlipidaemia were 28–55% and 27–92%, respectively.1,2,11,12 In parallel with the epidemiology of obesity and metabolic syndrome worldwide, the prevalence of NAFLD in Asian countries has increased rapidly with a trend to younger patients during the last two decades. The prevalence of NAFLD was about 15% in adults in Shanghai, Guangzhou and Hong Kong.3

The risk factors for NAFLD include a high-fat diet, a high-calorific diet, a sedentary lifestyle, insulin resistance, metabolic syndrome and its component disorders (obesity, hypertension, dyslipidaemia and T2DM).3,12,13 Although alcohol abuse and hepatitis C virus (HCV) infection are closely associated with steatosis, the global epidemic of fatty liver is mainly correlated with the rapid increase in the epidemic of obesity.3,12,14 NAFLD patients with normal body mass index (BMI) or a normal waist circumference, or both, are not uncommon in Asia–Pacific regions, even when the criteria put forth by the World Health Organization are used to diagnose obesity.3,12,13 A recent short-term weight gain and an increased waist circumference may be a cause of NAFLD and waist circumference predicts the presence of a fatty liver more accurately than BMI.3,12,13 Steatosis in patients with chronic HCV genotype 1 and 4 infection and hepatitis B virus (HBV) infection is highly likely to be related to insulin resistance and metabolic disorders. NAFLD is a common cause of minor serum aminotransferase elevation in hepatitis B surface antigen (HBsAg)-positive patients with serum HBV DNA level below 10⁴ IU/mL.3,4,16

### Table 1. Categorization of evidence bases

<table>
<thead>
<tr>
<th>Evidence grade</th>
<th>Definition</th>
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<tr>
<td>I</td>
<td>Randomized control study</td>
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<tr>
<td>II-1</td>
<td>Non-randomized control study</td>
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<tr>
<td>II-2</td>
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<tr>
<td>II-3</td>
<td>Serial studies at different times, with no controls</td>
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<tr>
<td>III</td>
<td>Opinions and experiences of experts and authorities, epidemiological description</td>
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### NATURAL HISTORY

The long-term liver-related prognosis of patients with NAFLD depends mainly on its histological type as shown by a liver biopsy at presentation. Simple steatosis develops slowly and the incidence of cirrhosis is low (0.6–3%) after 10 to 20 years follow-up; however, the rate of cirrhosis reaches 15–25% within 10 to 15 years in NASH patients.1,2 Some markers, including age over 50 years, obesity (especially visceral obesity), hypertension, T2DM, alanine aminotransferase (ALT) elevation, aspartate aminotransferase (AST)/ALT ratio greater than 1, and a decrease of platelet count are risk factors for NASH and advanced fibrosis.1,2,8,17 During the chronic protracted course of NAFLD, NASH is an inevitable stage in the development of simple steatosis into cirrhosis.1,2 Compared to chronic hepatic C and alcoholic hepatitis, the liver fibrosis of patients with NASH progresses relatively slowly and decompensated cirrhosis and hepatocellular carcinoma usually occur in elderly people.1,2,13,17 For individuals with IR, simple steatosis is a precondition of the development of NASH and cirrhosis, and a fatty liver decreases tolerance to hepatic toxins, ischemia and hypoxia. A liver with steatosis that is used for transplantation may easily cause the primary non-function of a liver graft.13,16 Furthermore, in patients with other chronic liver diseases, coexisting steatosis and its underlying disease may contribute to the development of cirrhosis and hepatocellular carcinoma and reduce the response to interferon-based anti-viral treatment in patients with non-genotype 3 hepatitis C.1,2,9,13,14

A few prospective cohort studies have found that the expected life span of patients with NAFLD, including patients with cryptogenic elevation of serum ALT or gamma-glutamyl transferase (GGT), or both, is shortened and the causes of death are mainly malignancy, atherosclerotic cardiovascular disease and cirrhosis.1,2,9 The all-cause mortality of patients with simple steatosis is not significantly lower than that of patients with NASH, but for the latter, liver-related mortality is markedly higher than that of a control group.1,2,9 NAFLD (including simple steatosis) and metabolic syndrome could be of reciprocal causation and NAFLD might be a better predictor of risk factor clusters when compared with the overall obesity reflected by BMI and the visceral obesity indicated by waist circumference.3,13,18,19 Even if the patients with NAFLD have normal body weight, the incidence of T2DM and cardiovascular disease still increase significantly after 6 to 15 years follow-up.2,3,9,13,18,19
**DIAGNOSTIC STRATEGY**

**Proposal 1: diagnostic criteria**

**Clinical diagnosis**

NAFLD can be diagnosed by the presence of three findings:1-5,9,10 (i) the histological findings of liver biopsy are in accord with the pathological diagnostic criteria of fatty liver disease; (ii) there is no history of alcohol drinking habit or the ethanol intake per week was less than 140 g in men (70 g in women) in the past 12 months; and (iii) specific diseases that could lead to steatosis, such as viral hepatitis, drug-induced liver disease, total parenteral nutrition, Wilson’s disease and autoimmune liver disease, can be excluded.

For epidemiological studies and in clinical settings, an operational definition of NAFLD is usually required because the histopathological diagnosis is usually difficult to obtain. The working definition is: (i) results of liver imaging study meet the diagnostic criteria of diffuse fatty liver and cannot be explained by other reasons;4 or (ii) patients with metabolic syndrome-related components show a persistent elevation of serum ALT or AST and GGT of unknown causes for more than 6 months, or both.4,5,9 NAFLD can be definitely diagnosed if an abnormal zymogram and fatty liver imaging has improved and even returned to normal after successful body weight reduction and the improvement of IR.4,5,9

**Pathological diagnosis**

Histologically, fatty liver disease can be diagnosed by the presence of parenchymal macrovesicular steatosis or mixed hepatocellular steatosis, with or without hepatocellular balloon-like degeneration, mixed inflammatory cell infiltration in the lobules and perisinus fibrosis in zone 3 of the liver acinus.4,5,9,20 NAFLD includes a spectrum of abnormalities from hepatic steatosis alone to steatosis associated with necroinflammatory changes and varying degrees of fibrosis. NASH in children is different from that in adults; the histology usually is characterized by more severe pathological changes such as inflammation and fibrosis in the portal area rather than in the lobules.21 It is recommended that the NAFLD activity score (NAS) and liver fibrosis stage should be assessed routinely to make a pathological diagnosis, and the effect of therapeutic in patients with NASH should be evaluated by referring to the National Institutes of Health NASH Clinical Research Website criteria.4,20 NAS is a semi-quantitative grading system but not a diagnosis procedure. NAS ≤ 3 were largely considered not to be diagnostic of NASH; patients with scores of >4 were diagnosed as having NASH; patients with scores between 3 and 4 were diagnosed as probably having NASH.20 It is stipulated that patients without lobular inflammation, ballooning and fibrosis but with more than 30% hepatic steatosis are diagnosed as having simple fatty liver, and with steatosis less than 30% as having hepatocellular steatosis.10

NASH-related cirrhosis includes NASH combined with cirrhosis, fatty cirrhosis and cryptogenic cirrhosis (due to liver steatosis and the alleviation of steatosis and inflammation with the progression of fibrosis). Cryptogenic cirrhosis without the histological features of steatohepatitis should not be rashly attributed to NAFLD and other likely causes that lead to cirrhosis must be sought.4,20

**Imaging diagnosis**

Diffuse fatty liver can be defined by the presence of at least two of three abnormal findings on abdominal ultrasonography: diffusely increased liver near field ultrasound echo (‘bright liver’), liver echo greater than kidney; vascular blurring and the gradual attenuation of far field ultrasound echo.4 The typical findings of fatty liver in computed tomography (CT) include a diffuse decrease of liver density. Portal and hepatic vein branches appear prominent in a scan unenhanced with contrast. A liver-to-spleen CT ratio less than 1 is defined as fatty liver: a mild degree of fatty liver has a liver: spleen CT ratio of less than 1 but more than 0.7; a moderate degree of fatty liver has a ratio of less than or equal to 0.7 but more than 0.5, and a severe degree of fatty liver has a ratio less than or equal to 0.5.10

**Diagnosis of the metabolic syndrome**

A diagnosis of metabolic syndrome components is recommended to adopt improved International Diabetes Federation (2005) criteria. Metabolic syndrome can be diagnosed if any three of the following five items coexist: (i) obesity: waist circumference >90 cm in male (>80 cm in female) or BMI > 25 kg/m² in both sexes, or both; (ii) elevated triglycerides: serum triglycerides ≥ 1.7 mmol/L or previously diagnosed as having hypertriglyceridemia; (iii) decreased high-density lipoprotein cholesterol (HDL-C): HDL-C < 1.03 mmol/L in males and <1.29 mmol/L in
females; (iv) elevated blood pressure: blood pressure \( \geq 130/85 \) mm Hg or having confirmed hypertension before; and (v) elevated fasting plasma glucose (FPG): FPG \( \geq 5.6 \) mmol/L or previously diagnosed as having T2DM.4,22

**Proposal 2: exclusion criteria**

2.1 Before ascribing fatty liver diagnosed by imaging or pathology to NAFLD, some specific liver diseases that can cause fatty liver such as ALD, chronic hepatitis C, autoimmune liver disease and Wilson’s disease should be excluded, together with some special conditions known to cause fatty liver such as intake of drugs (i.e., tamoxifen, amiodarone, valproate, methotrexate and glucocorticoid), total parenteral nutrition, inflammatory bowel disease, hypothyroidism, Cushing’s syndrome, hypo-\( \beta \)-lipoproteinemia and some IR-related syndromes (lipoatrophic diabetes and Mauriac syndrome) should also be excluded.4–10,16

2.2 Before ascribing raised ALT or GGT, or both, to NAFLD, other types of liver diseases including virus hepatitis, ALD, autoimmune liver disease, Wilson’s disease and alpha-1-antitrypsin deficiency should be excluded; patients with hepatic malignancies, infections and biliary tract disease and those who are receiving or have recently received drugs (Chinese traditional and western medicines) known to raise liver enzymes should not be regarded as NAFLD.4–10,16

2.3 For chronic HBV and HCV genotype 1 and 4 infection patients without excess alcohol intake, coexisting diffuse steatosis usually belongs to NAFLD.14–16. In HBsAg-positive patients with persistent abnormal serum transaminase, the abnormal liver function tests may be due to NAFLD if a serum HBV DNA level below 10^4 IU/mL and metabolic risk factors are present.4,15,16

2.4 In patients whose alcohol consumption lies between mild (less than 140 g/week in men and less than 70 g/week in women) and excessive, the causes of abnormal serum enzymes and fatty liver are usually difficult to determine and individual management should consider the potential of coexistence of alcohol abuse and metabolic factors.4,16 In patients with metabolic syndrome complicated by hepatotropic virus infection or alcohol abuse, or both, the diagnostician needs to be on the alert for the possibility of a coexistence of virus hepatitis and fatty liver disease and a coexistence of ALD and NAFLD.16

**Proposal 3: evaluation of the severity of the disease**

3.1 For patients with metabolic risk factors (i.e., visceral obesity, dyslipidemia, hypertension, T2DM, metabolic syndrome and a recent increase or rapid decrease of bodyweight), besides the need to evaluate heart, brain and kidney damage, liver function tests and the ultrasound scanning of the liver should also be routinely performed.4–10,13,23,24

3.2 For patients with asymptomatic hepatomegaly, a persistent and unexplained increase of serum transaminases or GGT, or both, and imaging findings of diffuse fatty liver denotes the need to take further medical history and related examinations to identify the existence of other liver-damaging factors, NAFLD and potential metabolic factors.4–10,17,23,24 Besides the detailed collection of data including recent changes of bodyweight and waist circumference, history of drinking alcohol, history of contacting drugs and hepatotoxic agents, family history of diabetes and coronary heart disease, the following routine examinations should also be undertaken: (i) anthropometry (height, bodyweight, waist circumference) and arterial blood pressure; (ii) complete blood count; (iii) serum enzymes, such as ALT, AST, GGT and alkaline phosphatase; (iv) serum HBsAg (also testing positive for HBV DNA), anti-HCV (also testing positive for HCV RNA), anti-nuclear antibody; (v) serum lipids profile including triglyceride, HDL-C, low-density lipoprotein cholesterol (LDL-C) and (vi) fasting plasma glucose (FPG) and glycated hemoglobin (HbA1C), and 75 g oral glucose tolerance test (OGTT) (in patients without a previous diagnosis of T2DM when their FPG is between 5.6 and 7.0 mmol/L or their HbA1C was between 6% and 6.5%, or both).

3.3 For patients with NAFLD established by clinical diagnosis, optional reference tests include:4–10,17,23,24 (i) their homeostatic model assessment IR may be calculated according to their FPG and fasting insulin; their postprandial blood glucose regulating capacity and insulin sensitivity should be estimated on the basis of OGTT; (ii) their whole blood viscosity, serum high sensitive C-reactive protein, serum uric acid and uric micro-albumin should be measured for the detection of metabolic syndrome relevant components; (iii) their serum total bilirubin, albumin and prothrombin time should be measured to reflect the liver reserve function. In patients with suspected cirrhosis gastroscopy should be considered to screen gastrointestinal varices and an alpha fetoprotein assay...
should be done for screening hepatocellular carcinoma; (iv) a carotid artery color Doppler ultrasonography should be conducted to detect atherosclerotic plaque; (v) an abdominal CT and magnetic resonance image should be performed if a properly conducted ultrasound is not informative, especially when malignancy cannot be excluded; (vi) related examinations should be performed to confirm the diagnosis of iron-overload, sleep apnea syndrome, polycystic ovarian syndrome, hypothyroidism, hypofunction of the anterior pituitary and other conditions; and (vii) a liver biopsy. This is not usually required for the clinical diagnosis of NAFLD, although, up to now, it has been the only method for distinguishing NASH from simple steatosis and judging the grade and stage of NAFLD.

3.4 It is suggested that a liver biopsy for histological assessment should be mainly used in: (i) patients unable to be definitely diagnosed by a routine examination and diagnostic therapy; (ii) those at risk of advanced hepatic fibrosis (in the absence of clinical or imaging evidence of cirrhosis); (iii) those enrolled in clinical trials and diagnostic tests; (iv) those subjected to a laparoscopy for other purpose (e.g., a cholecystectomy or gastric banding); and (v) those earnestly wanting to understand the nature and prognosis of liver disease.4–9,17,23,24 The expense and risks of a liver biopsy should be weighed against its value in evaluating prognosis and guiding treatment. Factors including sample and observer error should be considered in a liver histology evaluation.

3.5 Test items relevant only to research studies: (i) the determination of IR by the glucose clamp technique or using the product of fasting liver glucose output and insulin to calculate the liver IR index; (ii) quantification of hepatic triglycerides by proton magnetic resonance spectroscopy; (iii) estimation of body fat content and distribution pattern by dual energy X-ray absorptiometry scan or abdominal CT; (iv) examining heart and coronary artery by dual source CT; and (v) using non-invasive measures such as serum adiponectin, leptin, apoptosis-related markers and transient elastography to distinguish NASH from simple steatosis and to estimate fibrotic severity.4–10,17,23,24

**TREATMENT STRATEGY**

In view of the fact that NAFLD is one of the important components of metabolic syndrome and that the liver histology changes of most patients are at the stage of simple steatosis, the primary target of NAFLD therapy is to improve IR and prevent and treat metabolic syndrome components and related end-stage organ diseases so as to improve the patients’ quality of life and prolong their survival. The secondary target is to reduce liver fat deposition and avoid NASH and liver function decompensation caused by the two hits. In addition, for patients with NASH, measures for preventing liver disease progression and decreasing or preventing the development of cirrhosis, liver cancer and their related complications should be considered.4–10,17,23–25

**Proposal 4: therapeutic measures**

4.1 Implement health education to correct and change the patients’ behavior and lifestyle. Referring to the treatment suggestions for metabolic syndrome (III), moderate calorific restriction is recommended, consisting of a daily calorific intake of 2092–4184 KJ (500–1000 kcal) for obese adults; an alteration of the diet composition to a low carbohydrate and low-fat balanced diet, a reduction of drinks containing sugar, saturated fat and trans-fat intake and an increase in dietary fiber content; taking moderate aerobic exercise at least 4 times per week, with a minimum cumulated exercise time of 150 min.4–10,17,23,26–28 A modest weight reduction is usually desired, which will be beneficial for the recovery of components of metabolic syndrome including NAFLD (II-1, II-2).4–9

4.2 Control weight gain and decrease waist circumference: if patients are obese and fail to reach more than 5% weight reduction by changing their lifestyle for 6–12 months, they should be referred to drug use such as metformin, sibutramine and orlistat for secondary prevention (II-1 and II-2).4–10,17,23,26–28 Upper gastrointestinal bariatric surgery might be considered in patients with morbid obesity who do not respond to weight-reducing drug therapy, unless the patient has liver failure or moderate or severe gastroesophageal varices (II-1).4–10,17,23,24,27 An abnormal serum zymogram and histopathological injury in NAFLD patients usually improve significantly with weight loss (II-1). However, the most effective weight-reducing measure and the safety of anti-obesity drugs and how to prevent weight rebound remain to be further investigated.4,9,10

4.3 Improve IR and correct metabolic disorders: according to clinical requirement, related drugs can be adopted to treat metabolic risk factors and their complications (I). Unless in some conditions, including evident liver damage (such as serum transaminase more than thrice the upper normal limit) and hepatic...
insufficiency or decompensated cirrhosis, NAFLD patients may safely use angiotensin receptor blockers, insulin sensitizer (e.g. metformin, pioglitazone and rosiglitazone) and statins to decrease blood pressure, treat glucose and lipid metabolism disorder and atherosclerosis (III).4–10,17,23,24,29 However, the beneficial effect of these drugs on abnormal liver function tests and hepatic pathological changes in patients with NAFLD remains to be established by further clinical trials (I, II-1, II-2 and II-3).4–10,17,23,24

4.4 Reduce additional insults to prevent aggravation of liver damage (III): NAFLD, especially NASH patients, should avoid a drastic reduction of bodyweight and the use of very low calorie diet and a jejunal-ileal shunt operation for weight reduction is prohibited; avoid small intestinal bacteria overgrowth and contacting hepatotoxic agents; use Chinese traditional and western medicines with potential hepatotoxicity cautiously and strictly forbid excess alcohol intake.10

4.5 Use liver protective and anti-inflammatory drugs to prevent and treat steatohepatitis and advanced fibrosis: since there are still disputations on the role and position of liver-protective and anti-inflammatory drugs in prevention and treatment of NAFLD.4–10,17,23,24 At present there is not enough evidence to recommend the routine use of this kind of drug in patients with NAFLD and NASH. Under the premise of basic treatment, liver-protective and anti-inflammatory drugs could be used as adjunctive therapy mainly for the following conditions10,16,24 (III): (i) patients with NASH confirmed by liver histology; (ii) patients with significant liver injury or advanced hepatic fibrosis, or both, as shown by clinical features, laboratory findings and imaging examination, e.g. NAFLD patients with elevated serum transaminase, metabolic syndrome or T2DM; (iii) patients who are suspected of taking drugs which may induce liver injury and who are thereby affected the implementation of basic treatment or those who have serum transaminase elevation during the process of basic therapy; and (iv) patients with a coexisting current hepatotropic virus infection or other liver disease. One to two kinds of liver protective and anti-inflammatory drugs, including Chinese traditional and western medicines such as polyene phosphatidylcholine, silymarin, glycyrrhizin, bicyclol, vitamin E, ursodeoxycholic acid and S-ademetionine could be used, according to the disease activity, the stage of the disease, drug efficacy and cost (II-1, II-2 and II-3). The duration of treatment is usually 6–12 months or more (III).10

4.6 Manage cirrhosis complications actively: according to clinical requirements, related measures should be taken to prevent and treat cirrhotic portal hypertension and complications of liver failure (III). Liver transplantation could be considered for patients with NASH complicated by liver failure and decompensated cirrhosis and those with NAFLD complicated by hepatocellular carcinoma (II-2).9,10,17,23,24 Before a liver transplantation, an overall assessment of metabolic risk factors and related complications should be performed. After surgery, metabolic syndrome components still need enhanced treatment to reduce the recurrence of NAFLD and increase the survival rate of patients.9,10,17,23,24

Proposal 5: monitoring and follow up

5.1 Strengthen self-monitoring through health education. A self-record chart aiming at diet, physical exercise, bodyweight, waist circumference and other life-quality parameters associated with quality of life should be set up for communication between the physician and the patient and to perfect the individual’s diet and exercise program (III).9,10

5.2 Do a comprehensive evaluation on each of the components of metabolic syndrome, changes of serum biochemistry index and liver imaging and monitoring of the adverse effects so as to initiate and adjust drug treatment in time in order to make a judgment on the effect of the therapy. A dynamic examination of liver histology might be applicable only for clinical trials and patients for special purposes (III).4,5,10,17,23,24

5.3 It is recommended that patients with NAFLD should measure their bodyweight, waist circumference, blood pressure, liver function, serum lipids and blood glucose every 6 months and undergo an upper abdominal ultrasound examination involving the liver, gall bladder and spleen every year (III).6,9 It is suggested that malignancy, metabolic syndrome related end-stage organ diseases and complications of cirrhosis (such as liver carcinoma and gastroesophageal varices) are screened according to the patient’s condition and with reference to relevant diagnosis and treatment guidelines (III).9,10,13,25,29

REFERENCES


