

REVIEW

How should we manage patients with non-alcoholic fatty liver disease in 2007?

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Abstract

Evidence-based management guidelines for non-alcoholic fatty liver disease (NAFLD) are lacking in the Asia-Pacific region or elsewhere. This review reports the results of a systematic literature search and expert opinions. The Asia-Pacific Working Party on NAFLD (APWP-NAFLD) has generated practical recommendations on management of NAFLD in this region. NAFLD should be suspected when there are metabolic risk factors and/or characteristic changes on hepatic ultrasonography. Diagnosis by ultrasonography, assessment of liver function and complications, exclusion of other liver diseases and screening for metabolic syndrome comprise initial assessment. Liver biopsy should be considered when there is diagnostic uncertainty, for patients at risk of advanced fibrosis, for those enrolled in clinical trials and at laparoscopy for another purpose. Lifestyle measures such as dietary restrictions and increased physical activity (aerobic exercise) should be encouraged, although the best management strategy to achieve this has yet to be defined. Complications of metabolic syndrome should be screened for regularly. Use of statins to treat hypercholesterolemia is safe and recommended; frequent alanine aminotransferase (ALT) monitoring is not required. Obese patients who do not respond to lifestyle measures should be referred to centers specializing in obesity management; consideration should be given to bariatric surgery or gastric ballooning. The role of pharmacotherapy remains investigational and is not recommended for routine clinical practice. Non-alcoholic fatty liver disease should be recognized as part of the metabolic syndrome and managed in a multidisciplinary approach that addresses liver disease in the context of risk factors for diabetes and premature cardiovascular disease. Lifestyle changes are the first line and mainstay of management.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is highly prevalent in Asia.^{1,2} Some patients will develop histologic necroinflammation and fibrosis, that is, non-alcoholic steatohepatitis (NASH), and this may progress to cirrhosis and hepatocellular carcinoma (HCC). The management of NAFLD includes accurate diagnosis of the condition, careful assessment of risk factors associated with advanced liver disease, screening for metabolic syndrome and its complications, lifestyle modification (both physical activity and diet), consideration of obesity management including bariatric surgery, and, presently only in clinical trials, pharmacological treatment.

Diagnosis

Most patients are suspected to have NAFLD because of characteristic appearance on hepatic ultrasonography and/or elevation of

liver enzymes. Ultrasonographic examination for bright hepatic echotexture (compared with kidney and/or spleen), deep attenuation and vascular blunting¹ has adequate threshold for the detection of steatosis when more than 33% of hepatocytes contain fat, as shown by liver histology.^{3,4} Ultrasound is inexpensive and safe, but its accuracy may be limited in obese patients and by the occasional patchy distribution of steatosis through the liver. Computerized tomography (CT) scan and magnetic resonance imaging (MRI) are alternative imaging techniques for diagnosing fatty liver. These are applicable to obese patients and detect focal fatty changes more conclusively, but they are more expensive and access to them is limited in some parts of Asia.

Liver biopsy is not usually needed for the diagnosis of NAFLD, and is an invasive procedure with significant complications, particularly pain, some of which are occasionally dangerous, such as bleeding.^{5,6} Conversely, the diagnosis of NAFLD cannot be based solely on elevated serum aminotransferase (AT) levels, as AT

values can be within the normal range among patients with NAFLD.⁷⁻⁹ Congruent with this limitation, recent studies indicate that the upper limit of normal for serum alanine aminotransferase (ALT) may need to be lowered to ≤ 30 IU/L for men and ≤ 19 IU/L for women.¹⁰

The major challenge in the diagnosis of NAFLD is the distinction from alcoholic fatty liver. A careful history of alcohol intake is essential to exclude alcohol-induced fatty liver disease. None of surrogate markers for alcohol intake, including serum AT, gamma-glutamyl transpeptidase (GGT) or mean corpuscular volume are sufficiently accurate for this purpose.¹¹ The histologic features of alcoholic fatty liver disease and NAFLD are indistinguishable. Currently, it is not entirely clear whether there is a threshold of alcohol intake that can cause liver damage.¹¹ Alcohol intake less than 70 g/week in women and less than 140 g/week in men is generally regarded as non-hepatotoxic;¹² however, intakes somewhat higher than this but less than clearly toxic levels (more than 40 g/day for women, 60 g/day for men) comprise a gray zone in which the diagnosis of NAFLD cannot be made, as alcohol may be contributing to the symptoms. Abstinence of alcohol and repeated assessment may be needed to confirm the diagnosis, but there is no evidence in favor of (and there is some against) abstinence being an important part of long-term management of people with NAFLD. Whatever the difficulties in defining thresholds of alcohol intake for definition and practical management, it has been noted that a lifetime drinking history is more important in recognizing a pathogenic role of alcohol in chronic liver disease than is the recent history.¹³

Serology tests (hepatitis B surface antigen [HBsAg] and third-generation assay for hepatitis C antibodies [anti-HCV]) should be performed to exclude chronic hepatitis B and C, which are prevalent in Asian countries. Patients with a history of systemic illnesses known to cause NAFLD should be excluded,¹ as should those who are receiving or have received drugs known to cause NAFLD or raise ALT (this includes herbal and other non-prescribed medicines). Before ascribing abnormal liver test results to NAFLD, other less common liver diseases (autoimmune liver disease, celiac disease, alpha-1-antitrypsin deficiency, Wilson's disease), as well as hepatic malignancy, infections and biliary tract disease, should be excluded based on the local prevalence and clinical suspicion for these disorders.

Assessment of severity

Patients who have steatohepatitis have an increased risk of liver cirrhosis and liver-related death.¹ It is therefore important to determine the histologic severity of NAFLD.¹⁴ In one study in Hong Kong, nine of 17 (53%) patients with NAFLD who underwent a second liver biopsy had worsening of fibrosis stages over 6 years; eight of these nine patients had steatohepatitis on the first biopsy.¹⁵ Liver biopsy is the gold standard to assess the severity of NAFLD. The presence of moderate to severe necroinflammation, ballooning degeneration, Mallory hyaline and/or fibrosis indicates steatohepatitis.¹⁶ Although performing liver biopsy for all NAFLD patients is ideal to assess liver damage for the purpose of risk stratification, this is not feasible due to the large volume of NAFLD cases, the invasive nature of liver biopsy, with its risks of pain and bleeding complications, and the resultant unacceptability of this procedure to patients. We therefore recommend liver biopsy to be considered

when there is diagnostic uncertainty, for those with risk factors for advanced hepatic fibrosis and for those who are enrolled in clinical trials. Among patients who are subjected to laparoscopy for another purpose (e.g. cholecystectomy or gastric banding), liver biopsy is recommended as it provides valuable prognostic information without appreciably increasing the risks of these procedures.

Clinical factors including obesity, diabetes mellitus and older age are associated with advanced NAFLD.¹⁷ In a long-term follow-up study, diabetes mellitus was associated with increased risk of non-alcoholic liver disease and HCC.¹⁸ Imaging techniques including ultrasonography, CT scan and MRI cannot differentiate steatohepatitis or fibrosis from simple steatosis.³ Various biomarkers have been studied to predict necroinflammatory activity and/or liver fibrosis in NAFLD. Decreased platelet count may be related to underlying portal hypertension and is an indicator of severe liver fibrosis or early cirrhosis. Low serum albumin, elevated serum bilirubin and prolonged prothrombin time may indicate hepatic decompensation. Serum ALT level cannot accurately reflect the severity of NAFLD; a significant proportion of patients with normal ALT have bridging fibrosis and even cirrhosis on histology. An AST to ALT ratio more than 1.0,¹⁹ increased serum hyaluronic acid²⁰ and high homeostasis model assessment-insulin resistance (HOMA-IR) score, which is calculated by serum glucose \times serum insulin (both in mmol/L) divided by 22.5,²¹ are the common biomarkers associated with liver fibrosis. Other investigators have adopted panels of biomarkers to predict steatosis (Steatotest) and fibrosis (Fibrotest) among patients with NAFLD, but the use of these tests needs further validation.^{22,23} As the diagnostic accuracy of all biomarkers used to identify liver fibrosis seldom exceeds 75% to 80%, and these serum markers are not available in all laboratories and may be expensive, they are currently regarded as research tools and cannot substitute for liver biopsy in the management of NAFLD.²⁴

Metabolic syndrome

As introduced in the first of this series of articles on NAFLD in Asia¹, and explored in more detail in the fourth article,²⁵ insulin resistance is pivotal in the pathophysiology of NAFLD, and metabolic syndrome refers to the cluster of cardiovascular risk factors associated with insulin resistance. Recently, metabolic syndrome has been identified as a predictor for onset of NAFLD,²⁶ while ethnic differences in susceptibility of Asian-Indians to NAFLD are attributable to insulin resistance and its complications.²⁷ According to the recommendation of the International Diabetes Federation (IDF), central obesity, hypertriglyceridemia, low high density lipoprotein cholesterol (HDL-C), high blood pressure and high fasting glucose are features of metabolic syndrome.²⁸

The most important component of metabolic syndrome associated with liver disease is type 2 diabetes mellitus (T2DM). Approximately 44% of patients with NAFLD give the history of previously diagnosed diabetes mellitus,¹ while a similar proportion have an affected first-degree relative.²⁹ Therefore, personal and family history of diabetes mellitus should be sought carefully from all patients with NAFLD. Among patients who have no history of diabetes, the minimal test is a fasting blood glucose (FBG) level; FBG > 7.0 mmol/L is diagnostic of diabetes, whereas FBG ≥ 5.6 mmol/L may indicate glucose intolerance and is an

indication for an oral glucose tolerance test (OGTT).²⁸ A study in Hong Kong of 64 patients with no history of diabetes showed that 23% of patients were diagnosed with T2DM and 33% had impaired glucose tolerance on OGTT.³⁰ Moreover, in six of 15 patients with diabetes by OGTT, the diagnosis was based on an isolated elevated 2-h glucose level (with normal FBG). Hence, among patients who have NAFLD but no obvious feature of diabetes, OGTT with a standard 75 g glucose challenge is recommended. Other tests for insulin sensitivity including C-peptide, fasting and postprandial serum insulin levels (measured at 120 min after 75 g glucose challenge in OGTT) are optional investigations that give mechanistic insights into NAFLD; in clinical practice, especially in countries with scant health-care resources, these tests may be reserved for research purposes.

Body mass index (BMI), calculated as body weight (kg) divided by the square of body height (m), is commonly used to measure obesity; however, Asians have a higher percentage of adiposity at a lower BMI than Caucasians, so that for the same percentage adiposity, BMI is 3–5 units lower than Caucasian counterparts.³¹ According to the latest criteria set by the World Health Organization for Asians, BMI over 23 indicates overweight.³¹ We recommend using both waist circumference and BMI to define central obesity and metabolic syndrome in the Asian population. Waistline should be measured at the midpoint between the lower chest wall and the iliac crest when the patient is standing. In general, a waist circumference of >90 cm in male or >80 cm in female Asian subjects indicates central obesity. With this lower waist circumference cut-off, the prevalence of metabolic syndrome in Singaporeans, Chinese, Asian-Indians, Japanese and Koreans becomes comparable to that in the Western population.^{32–37} Imaging by dual-energy X-ray absorptiometry (DEXA) or abdominal CT can quantify visceral fat, and these tests can be reserved for selected patients or as research tools.

As metabolic syndrome and NAFLD can develop in non-obese subjects, other components of metabolic syndrome should be sought by careful investigations. Blood pressure should be measured and monitored. Fasting lipid profile should be included in the initial assessment; patients who have metabolic syndrome and NAFLD tend to have higher serum triglyceride and lower high density lipoprotein (HDL) cholesterol concentrations.^{7,38,39}

Lifestyle modification

Diet

Obesity, particularly central obesity, is strongly associated with hepatic steatosis. For this reason, lifestyle modification that includes dietary restriction and exercise to achieve judicious weight loss, in addition to the control of risk factors such as T2DM, obesity and dyslipidemia, is recommended as the first and most important approach to managing people with NAFLD.⁴⁰ The diet often recommended is one low calories and low in saturated fats. Unfortunately, however, little is known about effects of changes in dietary composition on liver histopathology in NAFLD. Few studies have addressed this issue, and for this reason the best dietary approach for treatment of NAFLD has not been established by experimental evidence. In the absence of such evidence, approaches used for T2DM and 'heart healthy' dietary composition seem prudent. These include some caloric restriction,

a diet low in saturated fats with relative enrichment of unsaturated fats, and low in rapidly absorbable carbohydrates (high glycemic index) but high in slowly absorbable carbohydrates (especially those high in dietary fiber).

In a study of 74 morbidly obese patients who had detailed dietary evaluation and a liver biopsy, no association was found between total caloric or protein intake and steatosis, inflammation or fibrosis. A higher carbohydrate intake was associated with significantly higher odds of inflammation, and a higher fat intake with significantly lower odds of inflammation.⁴¹ If this finding can be substantiated, the present recommendation of a low-fat diet could actually worsen NAFLD histopathology. Another study found that men with NASH had a significantly higher energy intake compared with age-matched men with chronic HCV infection or healthy controls.⁴² In this study, standardized nutritional counseling aimed at reducing insulin resistance included the following recommendations for calorie intake: 40–45% from carbohydrates, with emphasis on complex carbohydrates with fiber; 35–40% from fat with emphasis on mono- and polyunsaturated fats; 15–20% from protein. After 12 months, there was histologic improvement in nine out of 15 patients with biopsy-proven NASH, as measured by steatosis grade and NASH score.⁴³ In another study, a 500 kCal-restricted diet for 6 months changed body fat deposits and improved liver function tests in 10 patients with NAFLD, even though the average reduction in body weight was only 4%.⁴⁴ Low-carbohydrate diets (diets with a low glycemic index) have been shown to cause more short-term weight loss, greater lowering of BMI and greater improvement in insulin sensitivity than low-fat diets but, surprisingly, have not been evaluated in NAFLD.⁴⁵

Very few studies have investigated the effects of individual dietary components on NAFLD. Oligofructans are short-chain oligosaccharides containing D-glucose and D-fructose that are resistant to digestion. They are found in a variety of foods, including wheat, onions, garlic and bananas. A small cross-over study in seven patients with NASH has shown that oligofructans given for 8 weeks significantly reduce serum insulin and AT levels compared with placebo, but had no significant effect on plasma lipid levels.⁴⁶

Studies using an experimental rat model of hepatic steatosis have suggested that diets rich in olive oil⁴⁷ and fish oil (rather than corn oil)⁴⁸ and high-fiber diets,⁴⁹ but not fructose-enriched diets,⁵⁰ may be beneficial in hepatic steatosis. In the rat model, alternations of high-fat and normal-fat diets were shown to cause the same level of hepatic fat infiltration as a continuous high-fat diet;⁵¹ however, hepatic lipid content in rats seemed to increase in the early stages of high-fat feeding, and the development of non-alcoholic hepatic steatosis appears to be more linked to dietary fat ingestion than to gain in body weight.⁵² The possible relevance of these findings to humans remains to be investigated.

Physical activity

Physical activity (aerobic exercise) is beneficial in metabolic syndrome, T2DM, obesity, dyslipidemias and insulin resistance, all of which are risk factors for NAFLD. Exercise reduces weight by preferentially decreasing visceral obesity while preventing loss of muscle mass.⁴⁵ Aerobic exercise increases insulin sensitivity independent of weight loss,⁵³ and interferes with development of steatosis probably by decreasing peripheral lipolysis, inhibiting

hepatic lipid synthesis and stimulating fatty acid oxidation. A number of studies suggest that NAFLD improves after weight loss. Improvements in liver biochemistry and ultrasonographic appearances have been found with modest weight reduction, but few studies have evaluated the effects of weight reduction on hepatic histology.^{45,54,55}

Increased physical activity together with dietary restriction and control of risk factors appear to improve insulin sensitivity and liver disease in NAFLD.⁵⁵⁻⁵⁸ In a study of 25 obese Japanese subjects, significant reductions were seen in BMI, serum AT and hepatic steatosis on histology in the 15 subjects who underwent a program of diet and exercise for a period of 3 months, but these improvements were not evident in the 10 control subjects.⁵⁹ Effects of physical exercise independent of diet are difficult to assess in human studies, and there are no randomized controlled trials addressing this issue. Despite this, maintaining weight loss and continued exercise have been shown to be associated with improvement or normalization of ALT.^{60,61} There is an inverse association between NAFLD and cardiorespiratory fitness, and a positive association between NAFLD and BMI.⁶² In support of improving fitness, a recent study showed that moderate aerobic exercise helped normalize ALT in NASH; this normalization did not occur in the 15 patients who failed to comply with the exercise program.⁶³

Animal studies have shown independent beneficial effects of exercise in hepatic steatosis. Treadmill (exercise) training prevented hepatic steatosis in rats on high-fat diets, an effect not seen in sedentary rats.⁶⁴ Treadmill training introduced during a high-fat diet protocol decreased hepatic fat accumulation, which, again, was an effect not seen in sedentary rats.⁶⁵ In addition, swimming, especially in low temperatures (which results in more energy expenditure), has been shown to stimulate lipid-lipoprotein metabolism in fatty liver.⁶⁶

In summary, there is level II evidence to support the beneficial role of dietary restriction (mainly aimed at improving insulin sensitivity) and exercise in the management of NAFLD;^{67,68} however, rigorously conducted randomized controlled trials, especially with pre- and postintervention liver histology, are lacking in this area. Insulin resistance is a core feature of NAFLD, and dietary restriction and aerobic exercise have been clearly shown to improve insulin resistance, independent of weight loss. Therefore, lifestyle measures such as dietary modifications based on the metabolic profile (obesity, T2DM, hyperlipidemia, hypertension) and increasing physical activity in the form of aerobic exercise should be encouraged in all patients with NAFLD. The weight loss needed to reverse metabolic profile and fatty liver is only modest. In a large-scale, population-based study in Japan, a weight loss of approximately 2.5 kg over 1–2 years was associated with disappearance of ultrasonic features of fatty liver disease.²⁶ In obese diabetic patients, weight loss of 8% by a hypocaloric very-low-fat diet has been shown to reverse insulin resistance and normalize basal glucose production;⁶⁹ however, there is insufficient evidence to make prescriptive recommendations on how much exercise, the types of dietary modifications that are optimal, and how much (if any) weight loss is necessary to reverse the disorder. It is also a sobering reflection that many lifestyle regimens are successful at weight reduction in the short term, but recidivism occurs in the vast majority of cases. Thus, the most effective lifestyle regime

to prevent or reverse NAFLD, and how to achieve long-term adherence to it are crucial subjects for future research.

Pharmacological treatment

Emerging drug therapy for NASH is a hot topic of research. Specific therapies aimed at inhibiting the various pathways proposed for NASH pathogenesis have been studied. As NAFLD is strongly associated with insulin resistance, insulin-sensitizing drugs and those that affect hepatic lipid partitioning are the most appealing candidates of research. Metformin has been shown to consistently improve the ALT levels as compared with baseline in several uncontrolled, pilot studies;⁷⁰⁻⁷³ however, improvement in liver histology was rarely studied. In an open-label, randomized, controlled study of metformin versus vitamin E or dietary treatment, some improvement in hepatic steatosis, necroinflammation and fibrosis was seen as compared with the baseline liver biopsy in a small number of patients on metformin;⁷⁴ however, histologic improvement among patients on metformin and controls was not compared. In a more recent study, less than half the 24 metformin-treated subjects obtained histologic improvement, and these were those who lost weight, at least partly as a side-effect of metformin.⁷⁵

The thiazolidinediones (pioglitazone and rosiglitazone) are peroxisome proliferator-activated receptor gamma (PPAR γ) agonists that can improve insulin sensitivity, principally by acting on preadipocytes. Several small, open studies have shown encouraging results on the improvement of ALT levels as well as hepatic histology.⁷⁶⁻⁸⁰ One recent double-blind, placebo-controlled, randomized trial demonstrated that 6-month treatment with pioglitazone improved insulin resistance and glycemic control in 55 patients with NAFLD and glucose intolerance.⁸¹ More patients on pioglitazone than on placebo had improvement in hepatic steatosis (65% vs 38%, respectively) and necroinflammation (85% vs 38%, respectively), but the proportion of patients with improvement in hepatic fibrosis was not different between the two study groups (46% vs 33%, respectively). With encouraging results in this proof-of-concept study, a long duration of therapy may be required to see the true effect on liver fibrosis improvement.⁸² Another randomized, placebo-controlled, double-blind study reported in abstract form found that fewer than 50% of patients responded to rosiglitazone; improvement in insulin sensitivity was the most important correlate of a beneficial treatment response.⁸³ Weight gain (typically ~4% in first year) is a major unwanted effect of use of 'glitazones', and issues such as cost, long-term efficacy and other adverse effects need to be addressed before these agents can be routinely recommended for NASH.⁸²

Other agents including antioxidants (vitamin E, phlebotomy to remove iron), anti-inflammatory agents (pentoxifylline,^{84,85} etanercept, infliximab, thalidomide, misoprostol), pro- or prebiotics (to prevent bacterial overgrowth, which might increase endogenous ethanol production, produce endotoxin and increase hepatic oxidative stress), glutathione precursors (betaine⁸⁶), non-specific hepatoprotectants (ursodeoxycholic acid) and pancytopenia inhibitors (prevent apoptosis) have also been studied. Despite many clinical trials showing some degree of effect on ALT normalization, or even histologic improvement in small, open studies, few of these have been subjected to large-scale, placebo-controlled studies powered to show significant clinical efficacy and long-term

benefit.⁸⁷ In one randomized, placebo-controlled study including 166 patients with histologically diagnosed NAFLD, ursodeoxycholic acid was proven to be inferior to placebo in biochemical or histologic improvement.⁸⁸ A recent large randomized controlled trial of betaine also showed greater histologic improvement with placebo.⁸⁹ Therefore, the role of pharmacotherapy should be regarded as investigational and is not recommended for routine clinical practice.⁸²

Although the efficacy of pharmacological treatment for NASH has not yet been confirmed, treatment directed at associated comorbidity is important; these include overweight and central or overall obesity, T2DM, hypertension and dyslipidemias. Lipid-lowering drugs, that is, 'statins' (HMG-CoA reductase inhibitors), are frequently indicated among patients with metabolic syndrome. Many physicians are hesitant to use statins among patients with NAFLD due to the elevated liver enzymes. Recent evidence, however, shows that patients with raised liver enzymes are not at increased risk of hepatotoxicity with standard dose of statins.⁹⁰ Further, ALT monitoring is not effective at preventing rare instances of significant hepatotoxicity: minor changes in ALT levels are transient and of no clinical significance. It is therefore recommended that statins should be prescribed to patients with NAFLD whenever clinically indicated, and frequent monitoring of liver enzymes is not required (level I evidence).

Surgery

In the severely obese, the best therapeutic modality is bariatric surgery.⁹¹ It has been successful in producing a 61% weight loss overall. It is safe and improves diabetes mellitus, the metabolic syndrome, and therefore should prevent its sequelae. Early concern about deleterious effects of dramatic weight loss on aggravation of liver inflammation and fibrosis has been resolved with recent trials of more modest weight loss and less malnutrition. Bariatric surgery reduces steatosis, inflammation and even fibrosis in established NASH⁹²⁻⁹⁶ (level III evidence). It is also effective in ameliorating or resolving several of the most significant complications of obesity and metabolic syndrome, including T2DM, hypertension, dyslipidemia, sleep apnea, gastroesophageal reflux disease, degenerative joint disease, venous stasis, pseudotumor cerebri, urinary incontinence and infertility.⁹⁷ These promising procedures will undoubtedly increase and constitute the major therapeutic modality for those who are severely obese.

Follow up

Patients with NAFLD should be followed up to monitor progression of both liver disease and metabolic syndrome. Abdominal ultrasonography cannot determine the severity of hepatic necroinflammation and fibrosis, and should not be used for this purpose. Ultrasonography may be used for surveillance of HCC, particularly among patients with cirrhosis possibly or probably due to NASH (cryptogenic cirrhosis), but more data are needed to confirm survival benefit and cost-effectiveness of cancer surveillance in this patient population.

Although elevated ALT is a well-recognized feature of NAFLD, ALT elevation can be present or absent in both simple steatosis and

NASH. In most studies on lifestyle modification and pharmacological treatment in NAFLD, improvement in ALT is usually accompanied by improvement in histologic steatosis grading.^{59,72,76,77} The relationships between changes in ALT and changes in necroinflammation or fibrosis are less consistent.^{59,76,77,80,98} In a study in Hong Kong comparing patients with simple steatosis and NASH, patients with more advanced disease tended to have lower ALT levels.⁷ Lowering of ALT should not therefore be considered a valid marker for improvement of liver disease in the follow up of patients with NAFLD. At present, liver biopsy is the gold standard for monitoring the progression of liver diseases; however, follow-up or serial liver biopsies in NAFLD can only be recommended in the setting of clinical trials because they are unlikely to alter management. Other imaging techniques, including hepatic triglyceride quantitation using proton magnetic resonance spectroscopy, are research tools and not yet suitable for routine clinical practice.

The follow up of NAFLD patients should also focus on the components and complications of the metabolic syndrome; the latter include hypertension, premature cardiovascular disease, diabetes and certain cancers (breast, colon). Waist circumference and body weight should be measured regularly. Fasting blood glucose, lipid profile and blood pressure should be monitored periodically. The follow-up interval should be decided according to the perceived risk (age, family history, extent of obesity, previous findings), and management needs of the individual components of the metabolic syndrome.⁹⁹

Prevention

The worrying rise in the global prevalence of NAFLD/NASH and the slow progress in identifying effective medical therapy for this condition highlight the importance of preventive measures. Screening for early detection and proper management of insulin resistance is pivotal. Changes in lifestyle, which include an increase in physical activity (regular aerobic exercise appropriate for the age and health of the individual) and healthy dietary habits should be encouraged. Those at risk should be closely monitored to ensure the desired results, prevention of diabetes, cardiovascular disease, cirrhosis and cancer.

Conclusions

In summary, The Asia-Pacific Working Party for NAFLD makes the following recommendations on the management of NAFLD (Table 1). Non-alcoholic fatty liver disease should be suspected when there are metabolic risk factors or abnormal liver function tests and/or strong evidence of steatosis on hepatic ultrasonography. Diagnosis by abdominal ultrasonography, assessment of liver function and liver-related complications, exclusion of alcohol toxicity and hepatitis B and C, and screening for insulin resistance and metabolic syndrome are required for initial assessment. Liver biopsy should be considered in cases where there is diagnostic uncertainty, in patients at risk of advanced hepatic fibrosis (in the absence of clinical or imaging evidence of cirrhosis), in those enrolled in clinical trials, and in those subjected to laparoscopy for another purpose (e.g. cholecystectomy, gastric banding). Lifestyle measures such as dietary modification and increasing physical activity through regular aerobic exercise should be encouraged and

Table 1 Management algorithm for patients with non-alcoholic fatty liver disease

Diagnosis of NAFLD
Ultrasound abdomen
Computerized tomography (if ultrasound not diagnostic)
Liver biopsy (if uncertain diagnosis)
Exclusion of secondary causes of fatty liver
Alcohol use (less than 70 g/week in women and 140 g/week in men is acceptable)
Hepatitis B and C virus infections
Other liver and biliary diseases
Assessment of severity of NAFLD
Clinical factors: age, obesity (BMI \geq 25 kg/m ²), glucose intolerance or diabetes
Liver biopsy (diagnosis uncertain, or risk factors for advanced NAFLD present)
Evaluation of liver function and complications of cirrhosis
Screening for metabolic syndrome
Waist circumference (Asian criteria), body height and weight (BMI)
Fasting blood glucose and serum lipids
Blood pressure
Oral glucose tolerance test (if fasting blood glucose \geq 5.6 mmol/L, no history of diabetes)
Lifestyle modification
Diet low in simple carbohydrates, enriched in complex carbohydrates/dietary fiber, low in saturated fats, enriched in unsaturates (diabetic or 'heart healthy' diet)
Reduction in waist circumference, modest weight loss
Aerobic physical exercise (at least 20 min each day)
Sustained changes (need for reinforcement)
Drug treatment
Specific pharmacological treatment not recommended for routine practice
Treat metabolic syndrome, including the use of statins if clinically indicated
Bariatric surgery for morbidly obese, and those who fail to adopt or respond to lifestyle measures

NAFLD, non-alcoholic fatty liver disease.

sustained. Metabolic risk factors should be regularly screened for and treated. Use of statins is safe and is recommended for usual indications, and frequent ALT monitoring is not required. Obese patients who do not respond to attempted lifestyle measures should be referred to centers specializing in obesity management. In those refractory to medical measures, consideration should be given to bariatric surgery or gastric ballooning. The role of pharmacotherapy is currently investigational and is not recommended for routine clinical practice.

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