Recent Advances in the Management of Nonalcoholic Fatty Liver Disease

Dr. Vincent WS Wong
MBChB (Hons.), MRCP, FHKCP, FHKAM (Med)
Associate Professor, Department of Medicine and Therapeutics, The Chinese University of Hong Kong

Nonalcoholic fatty liver disease (NAFLD) has emerged as the most common chronic liver disease in affluent countries. Due to the adoption of Western diet and lifestyle, there is also an epidemic of NAFLD in Asia. In Japan and Indonesia, the prevalence of NAFLD is as high as 30%. In a population screening project in Shanghai, China, around 15% of the adults were also found to have NAFLD. Necroinflammation and fibrosis are common in Asian patients with NAFLD, and progression in fibrosis occurs in up to 50%. Progression to liver cirrhosis, liver failure and hepatocellular carcinoma has been reported. Besides, NAFLD patients have higher mortality than the general population, and the risk of cardiovascular diseases is doubled. Therefore, heightened awareness and proper management of this disease are important.

NAFLD has close relationship with the metabolic syndrome. Assessment of NAFLD patients should include both the evaluation of the liver condition as well as the associated features of metabolic syndrome. Healthy lifestyle remains the cornerstone for the management of NAFLD. Pharmacological treatment is under intensive investigations. Bariatric surgery is reserved for patients with morbid obesity.

Clinical evaluation

Severity of liver disease
NAFLD can be roughly divided into simple steatosis and nonalcoholic steatohepatitis (NASH). Patients with simple steatosis run a benign course. On the other hand, patients with NASH tend to have progressive disease and increased mortality. One of the goals is to differentiate simple steatosis from more severe disease.

Traditionally, the assessment of NAFLD severity depends on histology. However, liver biopsy is an invasive and expensive procedure. It carries a small but definite risk of bleeding, pneumothorax, haemothorax, and puncture of adjacent organs. Although liver biopsy has been considered the gold standard, emerging data challenged this concept. In one study, biopsies were taken from both the right and left lobe of the liver during bariatric surgery. Concordance was only 53% for liver fibrosis between the two samples, and even poorer for most features of necroinflammation.

Due to the limitation of liver biopsy, there is strong interest in the development of non-invasive tests for liver fibrosis. They can be divided into serum biomarkers and elastography techniques.

The first development of non-invasive tests for liver fibrosis is to construct a formula including factors associated with fibrosis. The BARD, BARG, BAAT and HAIR scores were all developed for this purpose. The factors used in these scores include body mass index, age, AST/ALT ratio, ALT, diabetes, HbA1c, insulin resistance index, triglycerides and hypertension. Recently, a group of hepatologists from the United States, Europe and Australia reviewed the clinical data of 733 patients with biopsy-proven NAFLD and identified 6 factors independently associated with advanced liver fibrosis - age, body mass index, impaired fasting glucose or diabetes, AST/ALT ratio, platelet count and albumin. The NAFLD fibrosis score was constructed from these 6 parameters, and high and low cutoff values were selected. When the score is below the low cutoff point (< -1.455 from the study), the sensitivity and negative predictive value are 82% and 93%, respectively. When the score is above the high cutoff point (> 0.676), the specificity and positive predictive value are 98% and 90%, respectively.

There are a few limitations to these prediction models. Firstly, none of the parameters chosen is a direct measurement of fibrogenesis or fibrinolysis. Secondly, fibrogenesis and fibrinolysis are dynamic process, while both the score and the 'gold standard' of liver biopsy are taken as a snapshot. Thirdly, the 'gold standard' of liver biopsy is also limited by sampling bias and interobserver variability. Therefore, it is unlikely that these prediction models will ever achieve close to 100% accuracy.

Fibroscan is a one-dimensional transient elastography. It is a rapid and non-invasive method to measure the stiffness of the liver. Early data show that the accuracy of Fibroscan is at least as good in NAFLD patients as in patients with other chronic liver diseases. In 67 Japanese NAFLD patients, the sensitivity, specificity, positive and negative predictive values of Fibroscan to exclude stage 3 and 4 fibrosis (optimal cutoff 8 kPa) were 88%, 84%, 64% and 96%, respectively. However, it is important to note that the success rate of Fibroscan is lower in obese patients, who often harbour NAFLD. In patients with thick subcutaneous fat, Fibroscan may fail to acquire any reading because ultrasound waves cannot penetrate deep enough.

Metabolic syndrome
Apart from evaluating the severity of liver injury, clinicians should not ignore common comorbid illnesses. The Metabolic syndrome is closely associated with NAFLD. As a minimum, anthropometric measurements, blood pressure, fasting glucose and
lipids should be checked. Both the body mass index and waist circumference are used to assess the degree of obesity. In particular, waist circumference is a reflection of central obesity and is strongly associated with the risk of myocardial infarction. Moreover, people of different ethnicity develop complications of metabolic syndrome at different body mass indices. Therefore, the definition of obesity is different in different ethnic groups. In Chinese, normal waist circumference is below 90 cm in men and 80 cm in women. In Asia, people with body mass index above 23 kg/m² are considered increased risk and those above 27.5 kg/m² are considered high risk. The definition of metabolic syndrome by the International Diabetes Federation also takes ethnic differences into account (Table 1).

The diagnosis of diabetes is made if the fasting plasma glucose is ≥7.0 mmol/l or the 2-hour plasma glucose is ≥11.1 mmol/l using a 75-gram oral glucose tolerance test. However, the American Diabetes Association discouraged performing oral glucose tolerance test because of cost and inconvenience. When oral glucose tolerance test was performed in NAFLD patients without history of diabetes, however, impaired glucose tolerance and diabetes were found in 29% and 33%, respectively. Moreover, post-challenge hyperglycaemia strongly predicted the presence of advanced liver fibrosis. According to the current guideline of the Asia-Pacific Working Party on NAFLD, oral glucose tolerance test should be considered in NAFLD patients.

Cardiovascular diseases
In addition to the association with metabolic syndrome, NAFLD also has close relationship with cardiovascular disease. Among 85 male volunteers in Italy, subjects with hepatic steatosis had significantly higher carotid intima-media thickness than those without steatosis (0.94 ± 0.12 mm vs. 1.15 ± 0.14 mm, p<0.001). The vasodilatory response of the brachial artery in response to ischaemia, a test of endothelial function, is also impaired in NAFLD patients. The strongest evidence for the association between NAFLD and cardiovascular disease came from the Valpolicella Heart Diabetes Study. Two thousand one hundred and three type 2 diabetic outpatients were followed up for a median of 6.5 years. After adjustment for sex, age, smoking, diabetes duration, HbA1c, LDL cholesterol and medications, NAFLD remained an independent factor predicting incident cardiovascular disease (hazard ratio 1.96, 95% confidence interval 1.4-2.7, p<0.001). Therefore, evaluation of NAFLD patients should include enquiry of symptoms and history of cardiovascular diseases. In positive cases, appropriate investigations should be arranged.

Treatment
Lifestyle management
Like most metabolic diseases such as type 2 diabetes and obesity, lifestyle modification remains the cornerstone of NAFLD treatment. In animal models, diets rich in olive oil, fish oil and fibre appear to improve hepatic steatosis. In one human study, 9 of 15 NASH patients undergoing 1 year of intense dietary intervention had histological improvement. The diet selected in that study was as follows: 40-45% of daily calories from carbohydrates with an emphasis on complex carbohydrates with fibre; 35-40% fat with emphasis on mono- and polyunsaturated fats; and 15-20% protein. It is however noteworthy that only 16 of 23 patients completed 12 months of dietary intervention, and only 15 had paired liver biopsies. This is a typical phenomenon in most lifestyle intervention studies. How one can achieve good compliance remains a major challenge to clinicians and allied health staff.

In another study involving 25 obese Japanese NAFLD subjects, diet restriction and exercise (walking or jogging) for 3 months resulted in improvement in metabolic parameters and liver histology. In 348 male employees with elevated ALT found during annual health checkup, weight loss and regular exercise were associated with ALT normalisation one year later.

While there is ample observational data showing that diet and exercise are beneficial for NAFLD patients, it is difficult to recommend the optimal dose and type. Further studies are required.

Pharmacological treatment
Drug treatment of NASH is under intense investigation. The studied drugs are acting on various targets central to the pathogenesis of NASH: insulin resistance, lipid metabolism, oxidative stress, inflammation, fibrosis, etc. The drugs that have attracted most attention are insulin sensitisers. Metformin was the first insulin sensitisers used to treat NASH. In a single-arm study involving 20 NASH patients, metformin 500 mg three times a day for 4 months resulted in ALT normalisation in 50% of the patients and improvement in insulin sensitivity. Subsequently, an open label, randomised trial showed that patients treated with metformin (2 g per day for 12 months) had a higher rate of ALT normalisation than controls. Metformin treatment also resulted in improvement in hepatic steatosis, inflammation and fibrosis. Unfortunately, only 17 patients receiving metformin had paired liver biopsies, and histological results of the control group were not presented.

Thiazolidinediones (pioglitazone and rosiglitazone) are another class of insulin sensitisers tested in NASH patients. In uncontrolled studies, both rosiglitazone and pioglitazone treatment for 12 months resulted in histological improvement in up to two-thirds of patients. Recently, a randomised controlled trial on pioglitazone has been completed. Fifty-five NASH patients with impaired glucose tolerance or type 2 diabetes were randomised to receive pioglitazone 45 mg daily or placebo for 6 months. The pioglitazone group had decreased ALT levels, increased hepatic insulin sensitivity, and improved hepatic steatosis, ballooning necrosis and inflammation. However, the beneficial effect was not durable. When pioglitazone was stopped, serum ALT and total hepatic fat worsened again. Therefore, NASH patients will need long-term therapy if this drug is approved for this indication. Another problem of thiazolidinedione treatment is weight gain. In NASH patients treated with pioglitazone for 6 months, the average weight gain was 2.5 kg. When further tests were performed, increase in whole body fat was found to be the main cause of weight gain. This casts doubt on the long-term safety of the drug. Indeed, although several meta-analyses provided conflicting
data, there was concern over the cardiovascular safety during long-term rosiglitazone treatment. Since oxidative stress is pivotal in the pathogenesis of NASH, anti-oxidants have also been tested. In a double-blind, randomised controlled trial involving 45 NASH subjects, vitamin E and vitamin C resulted in some improvement in liver fibrosis, but not in ALT normalisation or necroinflammation.

Ursodeoxycholic acid has been commonly used to treat primary biliary cirrhosis and other causes of cholestasis. In the largest clinical trial on NASH to date, 166 NASH patients were randomised to receive ursodeoxycholic acid or placebo for 2 years. However, ursodeoxycholic acid failed to demonstrate any superiority over placebo in all biochemical and histological assessments.

Other investigational therapies include phlebotomy, anti-inflammatory drugs (e.g. pentoxifylline, etanercept, infliximab, thalidomide, misoprostol), probiotics, betaine and pancaspase inhibitors. They need to be better evaluated in properly designed clinical trials.

Since NAFLD patients often have dyslipidaemia, one important question is whether lipid lowering drugs are safe in these patients. Among 68 NAFLD patients followed for 10.3 to 16.3 years, statin use was found to be safe and not to cause histological deterioration. In another observational study involving 166 chronic hepatitis C patients on statin, 332 chronic hepatitis C patients not on statin, and 332 patients on statin but without hepatitis C infection, statin use in chronic hepatitis C patients was associated with mild-to-moderate ALT elevation, but not severe liver dysfunction. Recently, a randomised controlled trial included 326 patients with hypercholesterolaemia and chronic liver disease. NAFLD was present in 64% and chronic hepatitis C in 23%. The patients were randomised to receive pravastatin 80 mg daily or placebo for 36 weeks. Not surprisingly, pravastatin was effective in lowering the total cholesterol, LDL cholesterol and triglycerides. Moreover, fewer patients in the pravastatin group had doubling of ALT or ALT rising above 2 times the upper limit of normal than controls. All data support the safety of statin use in patients with chronic liver disease. Current guideline also does not find close monitoring of liver function tests during statin therapy meaningful.

**Bariatric surgery**

Bariatric surgery is effective in achieving weight reduction. Long-term mortality was significantly lowered in patients with morbid obesity undergoing bariatric surgery than those on usual medical care. There was early concern that rapid weight loss might increase liver fibrosis in NAFLD patients. However, recent data showed that the risk is low if there was only modest weight loss and less malnutrition. Some observational studies also found improvement in steatosis, inflammation and fibrosis in NASH patients after bariatric surgery.

**Conclusion**

In summary, NAFLD is increasing in incidence. Although only a minority of NAFLD subjects eventually dies of liver complications, the absolute number is expected to be huge because the total number of NAFLD subjects is large. Serum biomarkers and transient elastography are potential non-invasive tests for liver fibrosis in NAFLD patients. Lifestyle modification is the most important management. Insulin sensitiser holds much promise as the pharmacological treatment of NASH, but long-term data are required. Statins and bariatric surgery are both safe in NAFLD patients, and should be provided if there is clinical indication.

Table 1. Metabolic syndrome definition by the International Diabetes Federation

<table>
<thead>
<tr>
<th>Central obesity</th>
<th>Waist circumference (ethnicity specific)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plus any two:</td>
<td></td>
</tr>
<tr>
<td><strong>Raised triglycerides</strong></td>
<td>&gt;1.7 mmol/l or specific treatment for this lipid abnormality</td>
</tr>
<tr>
<td><strong>Reduced HDL-cholesterol</strong></td>
<td>&lt;1.03 mmol/l in men or &lt;1.29 mmol/l in women or specific treatment for this lipid abnormality</td>
</tr>
<tr>
<td><strong>Raised blood pressure</strong></td>
<td>Systolic ≥130 mmHg or treatment of previously diagnosed hypertension</td>
</tr>
<tr>
<td><strong>Raised fasting plasma glucose</strong></td>
<td>Fasting plasma glucose ≥5.6 mmol/l or previously diagnosed type 2 diabetes</td>
</tr>
<tr>
<td>If above 5.6 mmol/l, oral glucose tolerance test is strongly recommended</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity specific definition of central obesity</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Ethnic group</strong></td>
<td><strong>Waist circumference</strong></td>
</tr>
<tr>
<td><strong>Europeans</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>≥94 cm</td>
</tr>
<tr>
<td>Women</td>
<td>≥80 cm</td>
</tr>
<tr>
<td><strong>South Asians and Chinese</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>≥90 cm</td>
</tr>
<tr>
<td>Women</td>
<td>≥80 cm</td>
</tr>
<tr>
<td><strong>Japanese</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>≥85 cm</td>
</tr>
<tr>
<td>Women</td>
<td>≥90 cm</td>
</tr>
</tbody>
</table>

Figure 1. NAFLD is characterised by macrovesicular steatosis.
References

1. Amarapurkar DN, Hashimoto E, Lesmana LA, Sollano JD, Chen PJ, Goh KL. How common is non-alcoholic fatty liver disease in the Asia-Pacific region and are there local differences? J Gastroenterol Hepatol 2007;22:788-93.


