

ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease in the world. Overall improvement in public health, active screening of blood products, universal vaccination of hepatitis B have led to a drop in the incidence of hepatitis B and C worldwide. NAFLD is strongly associated with metabolic syndrome. With the rise in overweight status and obesity worldwide, it is not surprising that NAFLD is on the rise. Diagnosis of NAFLD requires confirmation of fatty infiltration in the liver, as well as liver damage like elevated liver enzymes and the presence of fibrosis. Currently the best treatment for NAFLD is weight loss, and the proven method would be dieting with regular exercises. Vitamin E and pioglitazoles are promising medications for treating NAFLD, but each has its shortcoming. Until more studies are conducted, lifestyle modification remains the only reliable way to treat NAFLD. Family physicians also ought to look out for cardiovascular diseases, as well as be vigilant in cancer screening, as NAFLD is associated with higher risks of ischemic heart disease and cancer. Besides, NAFLD is associated with a long list of extrahepatic manifestation and Family physicians ought to look out for them when managing patients with NAFLD.

Keywords: Fatty Liver, metabolic syndrome, diabetes mellitus, cirrhosis

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WHAT IS NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)?

There must be evidence of fat in the liver of ≥ 5 percent, usually confirmed by imaging studies, with no secondary causes such as significant alcohol consumption, medications, or genetic disorders.¹

NAFLD comprises of a spectrum of diseases, depending on the degree of inflammation, and extent of liver fibrosis.

NAFLD can be categorised histologically into:

1. Non-alcoholic fatty liver (NAFL), which refers to the presence of fat in liver without significant inflammation

or fibrosis. Risk of progression to cirrhosis or liver failure is minimum.¹

2. Non-alcoholic steatohepatitis (NASH), which refers to presence of fat with inflammation. NASH can progress to cirrhosis.^{1,3}
3. NASH cirrhosis, which refers to cirrhosis with current or previous histological of steatosis or steatohepatitis.¹

HOW PREVALENT IS NAFLD?

No population study has been done in Singapore. But judging from some cohort studies, NAFLD is common locally. One local study showed that NAFLD is present in 56 percent of patients undergoing cholecystectomy. Another local study showed that among attendees to a public health forum, 40 percent had ultrasonic evidence of NAFLD.

These studies are biased and could have over-estimated the prevalence of NAFLD in Singapore.

Population studies in Asia like Hong Kong, China, Bangladesh, showed NAFLD to be present in about 25-40 percent of the general population. Fortunately, less than five percent of NAFLD patients have significant fibrosis. Hence, we can postulate that NAFLD is prevalent in 25-40 percent of the Singapore population, with the majority (about 95 percent) without significant fibrosis.

NAFLD is particularly common in patients with metabolic syndrome. NAFLD is present in more than 95 percent of obese patients undergoing bariatric surgery, two-thirds of diabetics have NAFLD, and half the patients with dyslipidaemia.

WHAT IS THE NATURAL HISTORY OF NAFLD?

Generally speaking, patients with NAFL alone have a very low risk of progression to liver cirrhosis. But patients with steatohepatitis, especially those with fibrosis, may progress to cirrhosis or even liver cancer. The progression is believed to take more than a decade, with weight gain being an important predictor of progression.

Interestingly, longitudinal follow-up studies have shown that cancer and cardiovascular diseases are the top 2 causes of death in patients with NAFLD. Liver complications such as hepatocellular carcinoma, liver cirrhosis and liver failure are only ranked as the third cause of death for patients with NAFLD.

Possible explanations are first, overweight status and metabolic syndrome are risk factors for certain cancers,

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such as pancreatic, breast, and colon cancer. Besides, patients having NAFLD would have concurrent metabolic syndrome, which in itself is a risk factor for cardiovascular disease.

HOW DO I CONFIRM THE DIAGNOSIS OF NAFLD?

Firstly, there must be documentation of fat in the liver, which is usually diagnosed on an ultrasound scan. Most of my patients with NAFLD have their disease diagnosed via routine screening. Rarely, fatty liver is diagnosed on CT or even laparoscopy when patients undergo abdominal or pelvic surgeries.

Secondly, there may be liver inflammation so their liver profile may show elevated GGT or ALT.

Third, alternative causes of liver injuries, such as viral hepatitis B or alcohol, should be excluded. The safe limit of alcohol has been of much debate. The consensus is that the safe limit of alcohol consumption for a man is 21 units a week, and 14 units for a woman. One unit of alcohol is approximately one can of beer, one glass of wine, or one shot of hard liquor.

Fourthly, NAFLD is almost always associated with a metabolic syndrome so clinicians ought to look out for overweight status, hypertension, dyslipidaemia, diabetes or pre-diabetes. On the other hand, in patients without any evidence of metabolic syndrome, nor significant alcohol consumption, a diagnosis of NAFLD is unlikely.

HOW CAN I STAGE THE SEVERITY OF NAFLD?

NAFLD progresses into the following stages: pure fat, steatohepatitis, fibrosis, then cirrhosis.

The ideal method to stage the disease is percutaneous liver biopsy^{1,3}, which could tell the degree of inflammation and stage of fibrosis. But as the biopsy is associated with a small risk of complications, about one percent, such as hemoperitoneum, patients rarely agree to it.

While transaminases such as ALT and GGT may reflect the degree of liver inflammation, they can only act as a guide as they do not correlate accurately with inflammation in liver histology.³

Several non-invasive methods of assessment for NAFLD are available commercially.

Hepatic steatosis can be quantified by MR imaging accurately.³ Besides MR Elastography can also stage the amount of liver fibrosis, as well as identifying any focal liver lesions. But its limited availability and high-cost make it difficult for general use in primary care.

Several panels utilise laboratory and clinical markers, such

as platelets, albumin, BMI, age, ALT, etc. to insert into a particular formula to estimate the risk of liver fibrosis. Some are available for use in Singapore.

Fibroscan®, which measures liver stiffness^{1,3}, is also available locally to estimate the amount of liver fibrosis. Fibroscan® is cheaper than MR Elastography. But of note is that 10-25 percent of fibroscan studies may fail to obtain reliable readings due to patient factors. Besides, an appropriate probe size is needed for different patient sizes.

HOW SHOULD I MANAGE AT A PRIMARY CARE CLINIC?

Establishing the diagnosis, i.e., confirming the presence of fat in the liver, with the exclusion of alternative liver diseases is the first line of management. One also ought to look for other components of metabolic syndrome as they almost always present in all patients with NAFLD. Next step is to establish the severity of liver damage by non-invasive methods. Those with advanced fibrosis or cirrhosis should be referred for specialist care. Lifestyle modification is the mainstay of treatment for NAFLD, and should be done at primary care level.

The most proven management of NAFLD is weight loss.⁴ Weight loss of 3-5 percent from baseline often leads to improvement in hepatic steatosis. Further weight loss of 7-10 percent would lead to improvement of inflammation and fibrosis histologically.^{2,4}

Exercises alone may not be sufficient in improving stage of NAFLD so exercises should be combined with dieting.² A hypocaloric diet, i.e., creation of a calorie deficit, plus moderate-intensity exercise, is likely to provide the best likelihood of sustaining weight loss.

Other forms of dieting such as intermittent fasting, low fat diet, the Mediterranean diet, etc work in losing weight as well.

In fact, metaanalysis has consistently show that most dieting work. But the problems are sustainability of dieting, and rebound of weight when dieting stops.

Family physicians play an important role in enforcing dieting and exercise regimes to patients.

My personal experience is that constant reminders and regular reviews of patients, providing insights, going through patient's dietary and social history, are important in helping patients adhere to a hypocaloric diet and a regular exercise regime.

Metformin has been discarded as a treatment of choice as meta-analysis showed no benefits in improvement in liver histology.⁴

Pioglitazone, vitamin E at 800 IU/day have been shown to improve liver histology in NASH patients.² But Pioglitazone use is associated with weight gain, increased bone loss,

as well as a small risk of bladder cancer.¹ So, pioglitazone should be used only for those with biopsy-proven NASH and with informed consent.

Vitamin E at a dose of 400 IU/day has been associated with an increased risk of prostate cancer and all-cause mortality in some studies.^{1,2} Hence, their benefits and risks ought to be discussed with patients before starting it. Vitamin E is not recommended for NAFLD patients with liver biopsy, with cirrhosis, or with diabetes.

Newer diabetic medications like GLP-1 agonists have shown promising results in managing weight loss but their use in NAFLD is currently not recommended yet.

Bariatric surgeries, which lead to significant weight loss, can lead to an improvement in liver histology.¹ But careful patient selection, as well as long-term postop support, are important in ensuring maintenance in weight loss.

HOW TO DO DIETING?

There is no simple answer to this. I often joke with my patients that if there is a simple method to lose weight, there will be no fat doctors!

But a few points can be written on losing weight.

Firstly, there must be a calorie deficit whereby a patient's calorie intake is less than his requirement. The type of diet, be it in low-carbohydrate diet, ketogenic diet, Mediterranean diet, Subway diet etc., is not important. Studies have shown that these diets can all help reduce weight. The most important part of dieting is its sustainability, as many studies showed only a quarter to one-third of participants can complete a one year program to lose weight.

Many of my patients lost weight on a ketogenic diet. But being Asians, it is difficult not to consume rice or bread so most cannot sustain a ketogenic diet.

Secondly, the patient must have enough insight into the problem to improve self-motivation. And emotional support from his family members is essential for success.

Thirdly, food containing simple sugar, like desserts, soft drinks, snacks should be minimised, or rationed.²

Fourthly, a low-calorie diet leads to reduced metabolic rate and muscle loss. So, any form of dieting should be accompanied by a moderate amount of exercises to avoid

loss of lean mass and maintenance of metabolic rate.

Finally, we, as physicians, must be aware of the adverse effects of different types of diets. For instance, intermittent fasting, i.e., eating only for eight hours over a 24-hour period, can lose weight significantly. But patients often feel lethargic, cold, dizzy when they first started doing intermittent fasting. So, patients who operate heavy machinery, drive a taxi, for instance, may not be suitable for intermittent fasting. Besides, skipping breakfast has been shown to be associated with gallstones formation so we must first warn patients on all these before recommending to them.

Extrahepatic manifestations of NAFLD

Patients with NAFLD have been shown to develop other components of the metabolic syndrome over time, if their weights are unchecked. For example, an overweight patient with NAFLD may develop diabetes mellitus, hypertension, dyslipidemia over time unless he can control his weight.

NAFLD patients have more cancer in pancreas, breasts, endometrium, colon than the general public.

Knee and hip joints degenerative diseases, obstructive sleep apnea, chronic kidney injury also occur more often in NAFLD patients

Family physicians ought to look out for all these during their follow up of NAFLD patients.

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LEARNING POINTS

- **NAFLD is now the most common cause of liver disease in Singapore, as well as the rest of the world. It will emerge as the leading cause of cirrhosis, liver cancer, and liver-related mortality in the time to come.**
- **NAFLD is associated with metabolic syndrome, and the family doctor ought to look out for and treat different components of metabolic syndrome.**
- **There is currently no magic way to lose weight. Much effort in taking a low-calorie diet and doing daily exercises must be preached to all patients constantly.**