



Nonalcoholic fatty liver: an independent predictor of heart disease?

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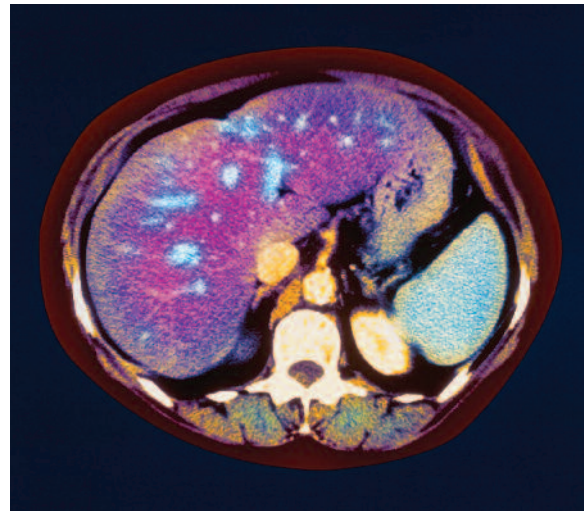
According to recent emerging data, nonalcoholic fatty liver disease has been suggested to be a predictor of heart disease independent of the metabolic syndrome and traditional cardiovascular risk factors.

Nonalcoholic fatty liver disease (NAFLD) is becoming more prevalent in the western world with the parallel increase in obesity and type 2 diabetes mellitus.¹ NAFLD is made up of a pathological spectrum in disease severity ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) associated with varying degrees of fibrosis and subsequently cirrhosis (Figure 1).² NAFLD has been recognised as the hepatic representation of the metabolic syndrome.³ More recently, there are reports of its strong associations with ischaemic heart disease (IHD).



Figure 1. Gross specimens showing healthy liver, fatty liver and cirrhotic liver.

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Key points

- Nonalcoholic fatty liver disease (NAFLD) is the major cause of chronic liver disease.
- NAFLD is the hepatic representation of the metabolic syndrome.
- Ischaemic heart disease (IHD) is the main cause of mortality among patients with NAFLD, and there is a higher prevalence of IHD in patients with NAFLD than in those without the disorder.
- Statin therapy is generally safe in patients with NAFLD.
- GPs have a key role in the diagnosis and management of patients with NAFLD.

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About 30% of the adult population has NAFLD and about 3% has NASH. In the morbidly obese population, the prevalences increase dramatically to 90% and 37%, respectively.^{4,5} Among the paediatric population, up to 10% has NAFLD, with the prevalence rising to 40% among obese children.⁶ NAFLD is also widespread in those with diabetes, with 70% found to have fatty liver.⁷

Liver histology findings of hepatocyte ballooning degeneration, mixed acute and chronic inflammation, Mallory–Denk bodies and pericellular fibrosis is the definitive diagnosis for NAFLD. However, most patients are not biopsied. The diagnosis is then based on clinical suspicion supported by liver enzyme derangement in a patient with an imaging finding (usually on liver ultrasound) of fatty infiltration of the liver if steatosis is at least 30% (ultrasound sensitivity drops sharply when steatosis is less than 30%). Classically, the alanine transaminase (ALT) level is greater than the aspartate transaminase (AST) level. The gamma glutamyl transferase (GGT) level is also frequently elevated. Liver biopsy is recommended in our clinic if elevated transaminases persist longer than six months.

Diet and exercise remains the mainstay treatment for patients with NAFLD, and this is often difficult to sustain. To date, there is no reliable pharmacological intervention to prevent NASH progression to cirrhosis.

This article focuses on the relation between NAFLD and IHD, rather than the management or diagnosis of NAFLD.

NAFLD and metabolic syndrome

The metabolic syndrome is a cluster of cardiovascular risk factors highly associated with insulin resistance. These include dyslipidaemia (elevated triglycerides level and reduced HDL cholesterol level), hypertension, dysglycaemia and abdominal obesity. Insulin resistance has been identified as one of the main contributors of steatosis formation in NAFLD and is almost universal in patients with NASH.³

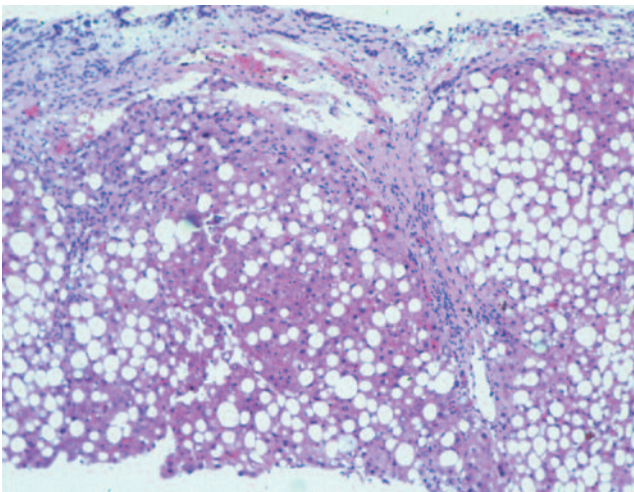


Figure 2. Liver histology showing steatosis with cirrhosis features and focal inflammation. Courtesy of Associate Professor Martin Weltman, Sydney, NSW.

Each of the individual features of the metabolic syndrome carries significant risk for future IHD. It has been shown that there is an increased degree of hepatic fibrosis with increased number of features of the metabolic syndrome.¹⁷

There is some controversy regarding the nature of the pathophysiology of the association between metabolic syndrome and IHD and it is unlikely that there is a single underlying pathophysiological defect. However, it is useful to identify patients with metabolic syndrome so they can be screened and treated for IHD and possibly also NAFLD.

Increased IHD prevalence and mortality

Multiple studies on patients with NAFLD who have been followed up for long periods of time concluded that such patients have a higher prevalence of IHD. These studies observed that the increases in fatal and nonfatal IHD events seem to be independent of the metabolic syndrome influence.⁸ The increased risk is two-fold compared with the general population (over 14 years follow-up).²

Among type 1 and type 2 diabetic cohorts, patients with NAFLD have been observed to have a higher incidence of coronary artery disease.⁸ In another community-based study looking at 2088 male workers, NAFLD was independently associated with higher CVD incidence.⁸ In patients referred for coronary angiogram, those with NAFLD had more severe angiographic findings.⁸ All current data, however, were derived from retrospective, small-sized studies and therefore need to be reproduced in larger randomised trials.

Importantly, IHD has also been identified as the number one cause of mortality among NAFLD patients, IHD-related mortality being as high as 25% in one NASH cohort (Figure 2).⁹ This is quite different when compared with chronic liver disease of any other aetiology, where the main causes of mortality are cirrhosis and its complications.

In 2009, the Cleveland Clinic Foundation, Ohio, reviewed the national death records for the number one cause of death among patients with liver biopsy-proven NAFLD. They found that almost 13% of these patients died of coronary artery disease.¹⁰ Similar data from Duke University, North Carolina, was presented recently at Digestive Disease Week 2011, held in Chicago.

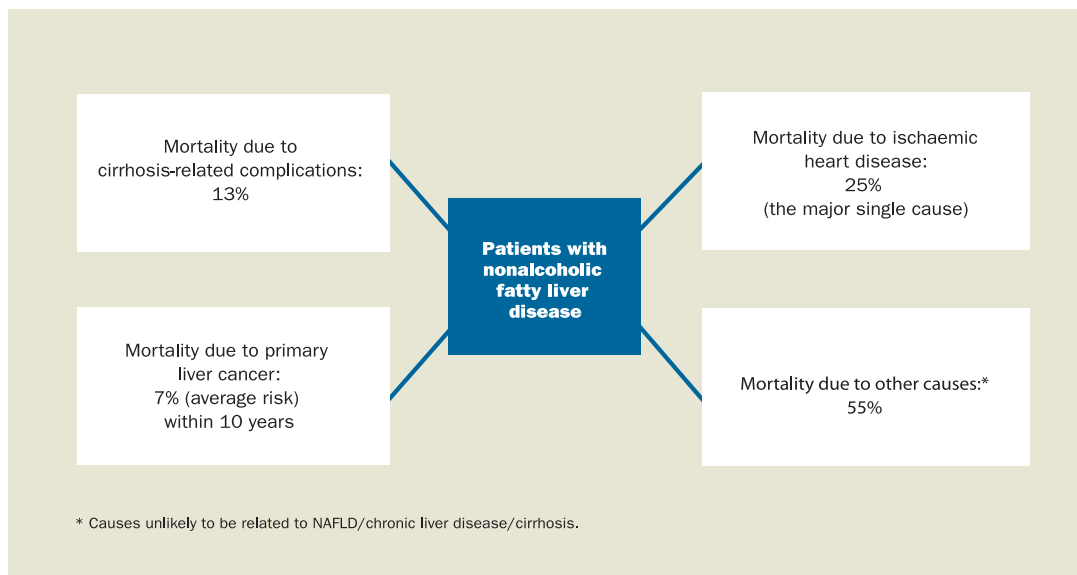
In another study, 358 consecutive patients who received multi-slice coronary CT to assess for coronary plaques also had their liver assessed for NAFLD.⁵ This study found that NAFLD was a novel risk factor for vulnerable plaques.

Similarly, in a study of 524 Chinese patients with a suspected acute coronary syndrome who underwent coronary angiogram, the finding of NAFLD on a CT abdomen was associated with greater severity of coronary artery disease.¹⁵

Increased atherosclerosis risk

Patients with NAFLD have an increased risk for higher carotid intimal thickness, which is an established marker for underlying atherosclerosis elsewhere. In particular, these patients have both

Figure 2. Causes of mortality among patients with NAFLD.^{1,9}



increased carotid artery intimal medial thickness and increased prevalence of atherosclerotic plaques compared with their age- and sex-matched controls.^{12,13}

Furthermore, there appears to be a linear relation between increasing liver fibrosis staging and carotid intimal medial thickness. One study showed that increasing severity of liver histology in patients with NAFLD is associated with increasing carotid intimal medial thickness. This hints at NAFLD being a possible independent predictor for atherosclerotic vascular disease.

Lipid lowering therapy

There may be some reluctance among physicians to prescribe statins to patients with NAFLD because of concerns about hepatotoxicity. There is increasing supportive evidence in the literature that statin therapy in these patients is safe and appropriate to prescribe. Hepatotoxicity from statins is likely to be idiosyncratic.

Statin therapy has been shown to reduce cholesterol levels as well as the degree of hepatic steatosis (on imaging as well as biopsy proven) in patients with NAFLD.¹⁸ Consequently it should be prescribed when clinically appropriate.

Clinical implications in general practice

NAFLD is a growing epidemic that requires a multidisciplinary approach from different specialties. GPs are often the first point of contact for patients with NAFLD and therefore play a key role in the diagnosis and management of these patients.

With the higher IHD risk of patients with NAFLD, a more aggressive approach to addressing the metabolic syndrome is needed. In particular, aggressive control of other cardiovascular system risk factors, including hypertension and hyperlipidaemia, is warranted in these patients. Therefore, as well as screening for diabetes in patients identified as having a nonalcohol-related fatty liver, it is also prudent to seek cardiovascular symptoms. **CT**

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