Mistakes in nonalcoholic fatty liver disease and how to avoid them

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Nonalcoholic fatty liver disease (NAFLD) is defined as the accumulation of excess fat (triglyceride) in the liver in the absence of excessive alcohol consumption. Disease severity ranges from simple steatosis (nonalcoholic fatty liver [NAFL]) to nonalcoholic steatohepatitis (NASH), fibrosis, or cirrhosis, with the potential to develop hepatocellular carcinoma (HCC) or require liver transplantation.

NAFLD is believed to affect up to 25% of the Western population,^1^ and is fast becoming the leading reason for liver transplantation worldwide.^2^ It affects up to 70% of those who are obese,^3^ and is strongly linked to the metabolic syndrome. Management of NAFLD therefore requires a multidisciplinary approach, not only to identify those patients at risk of progressive liver disease, but also to improve long-term liver and cardiovascular morbidity and mortality. Here, we highlight some of the mistakes commonly made by medical practitioners when managing NAFLD, and give an evidence-based (where possible) or experience-based approach to management of the condition.

**Mistake 1** Assuming a normal alanine aminotransferase level means there is no significant liver disease

Abnormal concentrations of liver enzymes are probably the most frequent reason for a patient to be referred to a NAFLD clinic. However, several studies have shown that alanine aminotransferase (ALT) levels can be normal across the spectrum of disease in up to 30% of patients.^4^ Although steatosis is less marked in those who have ALT levels <30 IU/L than in those who have an ALT level of 30–75 IU/L, the full spectrum of fibrosis, including cirrhosis, can be seen in those with an ALT level <30 IU/L.^5^ The presence of a fatty liver on ultrasound, therefore, requires further investigation even in the presence of a normal ALT level.

**Mistake 2** Failing to check for other potential causes of liver disease in patients with risk factors for NAFLD

Even if a patient has all the features of metabolic syndrome, it is important to remember that other concomitant aetiologies may be responsible for their liver symptoms. A detailed alcohol history is essential; generally, an alcohol intake below national guidelines helps to rule out a diagnosis of alcohol-related liver disease. Alternative aetiologies may be treatable (e.g. hepatitis C infection) and so should be considered and ruled out. Conversely, if despite a negative liver screen the picture doesn’t quite ‘fit’ with NAFLD, you should have a low threshold for confirming the diagnosis with a liver biopsy sample.

**Mistake 3** Believing that if the results of noninvasive tests are normal, there is no fibrosis, or if they are elevated, there must be cirrhosis

Liver biopsy remains the gold standard for assessing fibrosis in patients with NAFLD; however, not all patients consent to biopsy samples being taken. Noninvasive methods of fibrosis assessment can be used in lieu of liver biopsy, facilitating more frequent assessment and avoiding biopsy-related risks. Transient elastography, or FibroScan^®^, has been utilised to this end, with a sensitivity of 91% and a specificity of 75% for the detection of significant (≥F3) fibrosis using a cut-off value of >7.9 kPa.^6^ However, the results of transient elastography may not always be correct and should always be correlated carefully with the clinical picture. If the results of noninvasive tests appear discordant with the clinical picture, then a staging biopsy should be considered.

**Mistake 4** Assuming because there is no pharmacological treatment for NAFLD, there is no benefit from specialist referral

Although there is currently no approved pharmacotherapy for NAFLD, that does not mean there is no treatment for patients who have NAFLD. Fibrosis stage is the best predictor of liver-related morbidity,^7^ and patients should undergo accurate staging so that those at risk of cirrhosis and HCC can be identified and appropriately managed. In addition, cardiovascular disease is the primary cause of mortality in individuals with NAFLD, estimated at 40%,^8^ requiring proactive management of the features of the metabolic syndrome (i.e. reducing blood pressure and cholesterol, weight loss) so as to reduce the risk of fibrosis progression as well as reducing long-term cardiovascular mortality.

Weight gain is one of the best predictors of fibrosis progression.^9^ By contrast, >7% weight loss has been shown to reduce fibrosis,^10^ and so referral to weight-management specialists for those patients with a BMI >30 is encouraged.^11^ Furthermore, drugs such as elafibranor and obeticholic acid for NAFLD are showing promise in phase 3 developments, and it is worth considering whether patients may benefit from participation in clinical trials.

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Mistake 5 Believing that if a patient is HIV positive, abnormal liver function test results must be due to antiretroviral drugs. Although antiretroviral medication is known to elevate serum transaminase levels, the prevalence of NAFLD in HIV-infected individuals is estimated to be as high as 35%, with fibrosis present in 22%. NAFLD should, therefore, not be overlooked in the HIV-infected population. The reasons for the pervasiveness of NAFLD in individuals with HIV are not fully understood but are likely to be multifactorial—the two most compelling reasons are, first, that the success of anti-retroviral therapy (ART) has resulted in an increasingly aged and obese population, and second, the prevalence of metabolic syndrome in HIV individuals is high (estimated to be twice that in healthy controls).

Mistake 6 Believing anyone with F2 fibrosis will progress while others will have benign disease only. Baseline fibrosis is believed to be an important predictor of progression to cirrhosis, but several factors contribute to fibrosis progression, and fibrosis regression is also seen in up to 30% of individuals. Risk factors that have been consistently demonstrated to affect disease progression are diabetes and BMI. Hence, a 35-year-old obese individual with diabetes who has stage 1–2 fibrosis and continues to gain weight may be of more concern than a 70-year-old patient with stage 3 fibrosis. Of note, the degree of steatosis has not been shown to correlate with fibrosis progression, nor convincingly a histological diagnosis of NASH.

Mistake 7 Assuming the patient is too old, obese or high risk for liver transplantation or bariatric surgery. Despite older age and comorbidities such as obesity, outcomes after liver transplantation for NAFLD are similar to outcomes after liver transplantation for other indications. For this reason, patients should not be dismissed as potential transplant recipients due to their age or obesity. A systematic review and meta-analysis supports this point, although it also demonstrated that there may be increased short-term (30 days) and medium-term (5 years) mortality rates after liver transplantation for those who have a BMI ≥40, and so these patients do require careful assessment and selection prior to listing for transplantation. Expertise in patient selection and post-operative care for those with obesity and NAFLD is increasing, and mortality rates are likely to improve further. Likewise, although the risk of bariatric surgery is higher in those who have compensated cirrhosis or portal hypertension, several studies have reported excellent outcomes for patients with compensated cirrhosis who underwent laparoscopic bariatric surgery. Even those who have significant liver disease should, therefore, not be excluded from weight-reducing procedures. In both cases, patients should be referred to centres with experience in this field so that the benefits and risks can be carefully considered.

Mistake 8 Being reassured that a patient with cirrhosis is finally losing weight. For patients who progress to cirrhosis, weight management becomes more challenging than it is for patients who do not. Whilst weight loss is desirable for most patients during disease progression, it may represent the onset of sarcopenia and protein calorie malnutrition in patients who have cirrhosis. The development of nonliver cancer and HCC should also be considered. Liver transplantation may be indicated for those patients who have end-stage liver disease; input from an experienced dietician is recommended to optimise the nutritional status in those who have sarcopenic obesity with the potential added complication of diabetes.

Mistake 9 Thinking that patients who undergo liver transplantation for NAFLD will need no further monitoring or treatment. Outcomes following liver transplantation for NASH match outcomes for those who undergo liver transplantation for other indications, with a 5-year survival of 76%. However, the risk of death from cardiovascular disease remains high in the post-transplant population and so clinicians must remain vigilant when treating patients with cardiovascular risk factors. Furthermore, NAFLD recurrence is common in the post-transplant population, with recurrent NASH seen in up to 40% of patients and bridging fibrosis in 20.6% of patients. For this reason, some experts advocate bariatric surgery at the time of transplantation.

Mistake 10 Not tailoring the choice of anti-diabetes agent to patients with NASH. While improving glycaemic control is important in NAFLD patients who have diabetes, the use of weight-neutral medications, or even those that promote weight loss, is preferred. Sodium glucose co-transporter 2 (SGLT2) inhibitors facilitate urinary glucose excretion, and are used in patients who have type 2 diabetes mellitus (T2DM) to both improve their plasma glucose levels and encourage weight loss. In mouse models of NAFLD, SGLT2 inhibitors have also been shown to be beneficial, by improving steatosis, inflammation and fibrosis. Studies in patients with T2DM have shown that ipragliflozin and canagliflozin improved ALT levels. Glucagon-like peptide-1 (GLP-1), which is a gut-derived hormone analogue that stimulates secretion of insulin, reduces secretion of glucagon, suppresses appetite, and delays gastric emptying. Aside from improving glycaemic control and inducing weight loss in patients with diabetes, a clinical trial demonstrated that liraglutide increases resolution of NASH. The use of semaglutide in patients with NASH and fibrosis is currently being investigated in a phase 2 trial. Furthermore, both the SGLT2 and GLP-1 drug classes have shown potential for improving cardiovascular mortality.

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**Your NAFLD briefing**

**Mistakes in...**

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