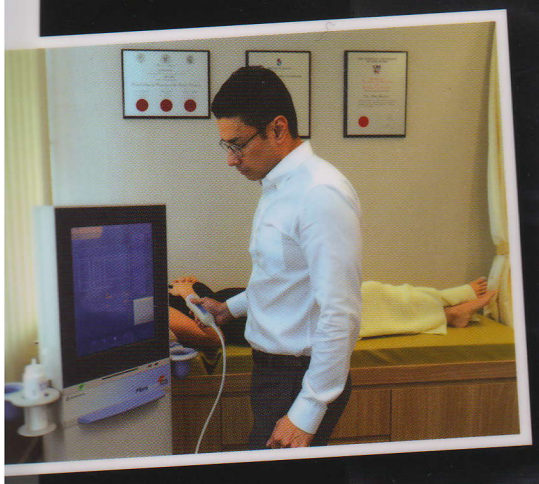
Non-Alcoholic Fatty Liver Disease



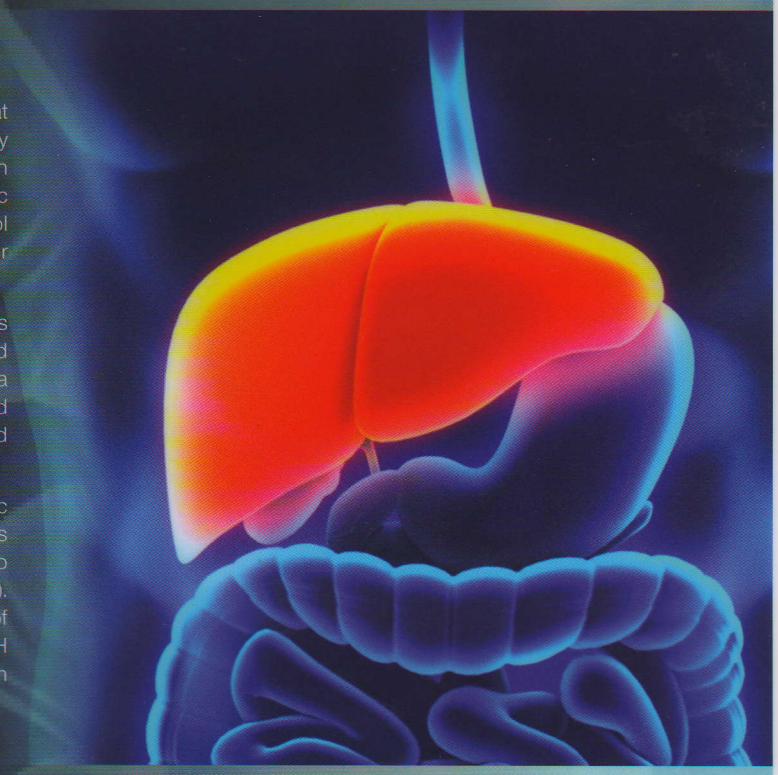
NAFLD is the single most prevalent cause of liver disease in the developed world. With the advent of effective medications to treat hepatitis B and C, it is likely this statistic will only increase. NAFLD is associated not only with liver related mortality but also cardiovascular mortality and screening for risk factors associated with the metabolic syndrome is essential. To date specific targeted therapies remain few and lifestyle modification and weight loss remain the main stay of treatment. Early evaluation for the progression of liver disease is essential so that patients are screened for complications of cirrhosis and treatment instituted early.

WHAT IS NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

The definition of non-alcoholic fatty liver disease (NAFLD) requires that (a) there is evidence of fat within liver cells (hepatic steatosis), either by radiological imaging (e.g. ultrasound, CT scan or MRI scan) or based on a histology of liver tissue and (b) no other causes of secondary hepatic fat accumulation in the liver can be identified such as significant alcohol consumption, hepatitis C infection, use of steatogenic medication or hereditary disorders.

A recent consensus meeting concluded that, for NASH clinical trials candidate eligibility purposes, significant alcohol consumption be defined as 21 drinks per week in men and 14 drinks per week in women over a 2-year period prior to baseline liver histology. However, it must be stressed that the definition of alcohol consumption amongst trials so far has varied considerably.

In the majority of patients, NAFLD is associated with the metabolic syndrome which is characterised by risk factors such as obesity, diabetes mellitus, and dyslipidemia. NAFLD is histologically further categorized into non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). NAFL is defined as the presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes. NASH is defined as the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis.



Prevalence of NAFLD

The prevalence of NAFLD is highest in patients with obesity and type 2 diabetes mellitus. Advanced age, male gender and race are also other factors that have been associated with a higher prevalence of NAFLD. The prevalence of histologically-defined NAFLD was 51% in one study from Korea comprising potential living liver donors. The reported prevalence of NAFLD when defined by liver ultrasound ranged between 17% and 46% depending on the population studied. Alcohol and NAFLD.

Natural History of NAFLD

Several longitudinal studies have shown that patients with simple steatosis have very slow, if any, histological progression, while patients with NASH can exhibit histological progression to cirrhotic-stage disease. Patients with NAFLD have increased overall mortality compared to matched control populations.

The most common cause of death in patients with NAFLD, NAFL and NASH is cardiovascular disease, and patients with NASH (but not NAFL) have an increased liver-related mortality rate. Patients with NAFLD are at increased risk for hepatocellular carcinoma (HCC), but this risk is likely limited to those with advanced fibrosis and cirrhosis. However, studies have shown that patients with NASH cirrhosis are at significantly lower risk for HCC than patients with hepatitis C cirrhosis.

Evaluation of NAFLD

Patients with hepatic steatosis detected on imaging should be evaluated for metabolic risk factors (e.g., obesity, glucose intolerance, dyslipidemia) and alternate causes for hepatic steatosis such as significant alcohol consumption or medications. The presence of metabolic syndrome is a strong predictor for the presence of steatohepatitis in patients with NAFLD and may be used to best identify patients with persistently abnormal liver biochemistries who would benefit diagnostically and prognostically from a liver biopsy. Liver biopsy should be considered in patients with NAFLD who are at increased risk to have steatohepatitis and advanced fibrosis. The presence of metabolic syndrome and the NAFLD Fibrosis Score may be used for identifying patients who are at risk for steatohepatitis and advanced fibrosis.

Non-invasive Assessment of Steatohepatitis and Advanced Fibrosis in NAFLD

NAFLD Fibrosis Score is a clinically useful tool for identifying NAFLD patients with higher likelihood of having bridging fibrosis and/or cirrhosis. Alternatively, Fibroscan a non-invasive technology which measures the sheer velocity of a mechanical wave propagated through the liver correlated to a liver stiffness measurement may be helpful in evaluating patients for significant liver fibrosis in patients reluctant to undergo a liver biopsy.

Screening for complications of liver disease

Patients with NASH cirrhosis should be screened for the complications of cirrhosis such as gastroesophageal varices and hepatocellular carcinoma.

ARE THERE TREATMENTS AVAILABLE FOR NAFLD?

Lifestyle modification

Many studies indicate that lifestyle modification may reduce aminotransferases and improve hepatic steatosis when measured either by imaging studies. Weight loss generally reduces hepatic steatosis, achieved either by hypocaloric diet alone or in conjunction with increased physical activity. Loss of at least 3–5% of body weight appears necessary to improve steatosis, but a greater weight loss (up to 10%) may be needed to improve necroinflammation. However, the ability of exercise and weight loss alone to improve other aspects of liver histology remains unknown.

Insulin Sensitizing Agents

Metformin has not been shown to have a significant effect on liver histology and is not recommended as a specific treatment for liver disease in adults with NASH.

Pioglitazone can be used to treat steatohepatitis in patients with biopsy-proven NASH. However, it should be noted that majority of the patients who participated in clinical trials that investigated pioglitazone for NASH were nondiabetic and that long term safety and efficacy of pioglitazone in patients with NASH is not established. A meta-analysis of 5 randomised trials showed that pioglitazone improved steatosis, necroinflammation but not fibrosis. Weight gain is also a significant side effect of pioglitazone.

Vitamin E

Vitamin E (-tocopherol) administered at daily dose of 800 IU/day improves liver histology in non-diabetic adults with biopsy-proven NASH, however it is not recommended in diabetic patients. There is also an ongoing debate as to whether Vitamin E increases the risk of prostate cancer. Hence patient selection may be important in choosing whom to start Vitamin E in.

Use of Statins in Liver Disease

Given the lack of evidence to show that patients with NAFLD and NASH are at increased risk for serious drug-induced liver injury from statins, statins can be used to treat dyslipidemia in patients with NAFLD and NASH. Until RCTs with histological endpoints prove their efficacy, statins should not be used to specifically treat NASH.

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Dr Fernandes graduated with honours from the University of Edinburgh. He was admitted as a Member of the Royal College of Physicians of the United Kingdom in 2003 and obtained his specialist accreditation in 2007. Dr Fernandes pursued an Advanced Fellowship in Interventional Hepatology at the Chang Gung Memorial Hospital in Taiwan and furthered his exposure to Liver Transplantation Medicine at the King's College Hospital, London. He was the first Gastroenterologist in Singapore to perform Radiofrequency Ablation for liver cancer. In 2009, he established the Liver Tumour Ablative Service at National University Hospital (NUH), in collaboration with the Departments of Diagnostic Imaging. He was also part of liver transplantation team at National University Hospital Singapore.

Dr Fernandes has also extensive experience in monitoring the progression of liver disease using Fibroscan®, one of the services provided by gutCARE Digestive • Liver • Endoscopy Associates.

Dr Fernandes has a strong research background and is on the committee of the National Foundation For Digestive Diseases.

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