Fatty liver disease

Lifestyle factors other than alcohol intake can lead to insidious outcomes from this surprisingly common condition. **Assoc Prof David Cameron-Smith** reviews current and potential management strategies.

Many of the more subtle health risks directly related to obesity, the metabolic syndrome (syndrome X or the insulin-resistance syndrome) and type 2 diabetes are now being identified. Recent attention has focused on the prevalence and health impacts of non-alcoholic fatty liver disease (NAFLD), in which fat accumulates to account for more than five per cent of the weight of the affected liver.

In the absence of a history of excessive alcohol intake (more than two standard drinks daily for women and three for men), three-quarters of obese individual and 60 per cent of those with type 2 diabetes experience NAFLD.[1,2] These figures translate to 15–20 per cent of the adult population having the condition.

Alarmingly, NAFLD has been observed within one study to be present in almost 50 per cent of obese children.[3] The longer-term risks posed by the disease in these obese children is yet to be understood, but are likely to contribute to the overall decline in health that may occur in early- to mid-adulthood.

Health implications

Under most conditions, the fat accumulated in the liver poses little immediate risk to affected individuals. The symptoms, if present at all, may vary from abdominal discomfort (due to hepatomegaly) to fatigue and weakness.[4]

The disturbances in liver fat metabolism impose a more sinister underlying risk in that there is greater incorporation of triglycerides (fats) into the secreted very low-density lipoproteins (VLDLs). Triglyceride-rich VLDLs become small, dense, low-density lipoproteins (LDLs) — the most potent lipid particles implicated in atherosclerosis growth.[5]

In those affected with NAFLD, there is a risk of progressive fibrosis and cirrhosis. NAFLD with significant inflammatory and fibrotic damage is termed non-alcoholic steatohepatitis (NASH)[4], which is present in approximately 18 per cent of the obese, and correlates closely with the severity of insulin resistance.[6,7]

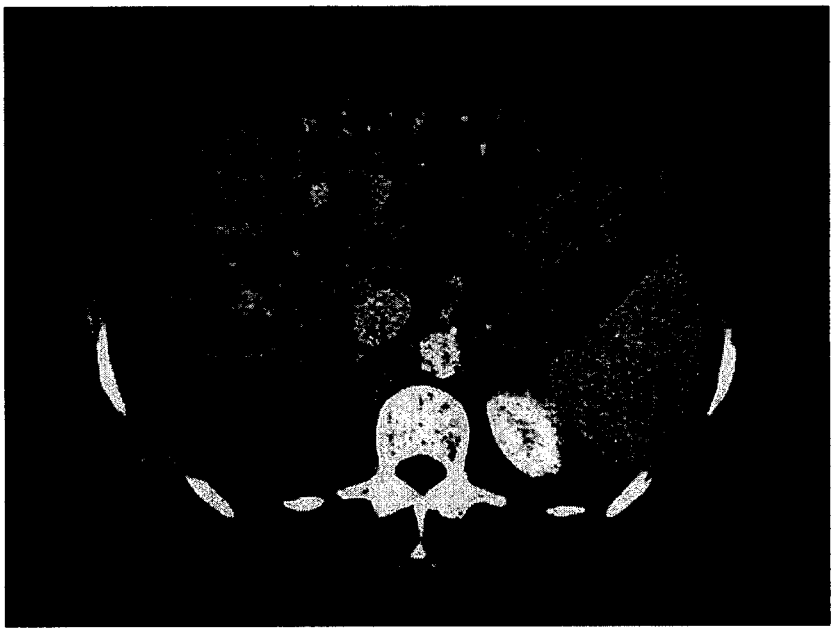
In these cases, there are real risks to the health of the affected individuals, with a significant risk factor for the development of liver-related morbidity and mortality.[8]

Aetiology of fatty liver

The liver is significant in the control of lipid metabolism. The liver stores blood-borne fats as triglyceride, which can be used either for the synthesis of cholesterol, or can be repackaged and exported as VLDL particles. Conversely, the liver is the major site for the uptake and clearance of both cholesterol-laden LDL and high-density lipoprotein particles.

The supply of fatty acids to the liver is dramatically increased in states of central (visceral) obesity. Visceral adipocytes, which have a high lipolytic (fat-releasing) capacity, drain their fat load directly into the portal vein.[9] It is therefore not surprising then that there is a very close relationship between visceral fat mass and NAFLD.[10]

Considerable recent research has identified the accumulated fats as playing an important role in the development of



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cirrhosis and fibrosis. It is hypothesised that the accumulating fat participates in a 'two hit' process, resulting in fibrosis.[11]

The 'first hit' is explained by the increased supply of fatty acids to the liver in people with central or visceral obesity. The augmented fat supply causes greater hepatocyte fat accumulation, thus impairing insulin action in the liver. The reduced insulin sensitivity and greater fat supply promotes increased liver fat oxidation and the generation of reactive oxygen species (ROS) within the hepatocyte.

The 'second hit' results from ROS acting to facilitate an inflammatory cascade, causing the progressive fibrosis and cirrhosis observed in NASH.

In addition to the increased supply of fatty acids, the adipocytes in the visceral region also secrete a range of cytokines (adipokines), including tumour necrosis factor–alpha (TNF–α), leptin and adiponectin.[9] The exact role of each adipokine on liver function is yet to be fully elucidated; although more recent research points to a complex interplay within the liver with the promotion of pro-inflammatory — and inhibition of anti-inflammatory — pathways.[12]

Diagnosis

The detection of NAFLD and NASH is difficult, and ultimately requires an invasive biopsy and histochemical analysis of the harvested liver sample.[4] Non-invasive imaging techniques (including ultrasonography, computer tomography and MRI) can all detect the presence of NAFLD in combination with clinical or biochemical observations of obesity and/or impaired insulin function, yet fail to determine the extent of NASH.[4]

Liver enzymes are commonly applied to a range of diseases affecting liver function; however, in individuals with NALFD, the levels tend to fluctuate, and normal liver enzyme concentrations are present in the majority of cases.[13] When abnormal liver enzymes levels are present, the most common is a modest rise in alanine aminotransferase (ALT).[13] However, ALT is a poor diagnostic marker and concentrations rarely correlate with the severity of fat accumulation.[4]

Management

The overall strategy for managing NAFLD is to improve insulin action and reduce body weight. Very few long-term, well-controlled interventions focusing on NAFLD or NASH have been published. The majority of the available data are derived largely from observation, or are opportunistically collected in the pursuit of other clinical endpoints.

Despite the paucity of data, it is likely that modest lifestyle changes that lower visceral fat mass and improve insulin action may also slow the progression of NAFLD to NASH, potentially lower liver fat accumulation and ease the burden posed by NAFLD.

Weight loss and physical activity

Three studies have now addressed weight loss that can be achieved through either energy restriction (very low-calorie diet or lifestyle change) or pharmacotherapy (orlistat).[14–16] To date there is very limited data on the promotion of physical activity. The only available literature suggest that increased physical activity is able to reduce hepatomegaly and plasma ALT concentrations. Importantly, however, this study failed to assess liver steatosis of fibrosis.[15]

Several studies have cautioned against rapid weight loss via gastric bypass surgery. Very rapid weight loss has been suggested to worsen the risk for inflammation and fibrosis.[17]

However, these risks may be overstated. A further Australian study utilising the lap-banding technique, which provides modest constriction of the upper portion of the stomach and

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dramatically lowers food intake, failed to provide any evidence for a worsening of liver function with rapid weight loss.[18] In the study cohort of 36 very obese patients, initial biopsies revealed 12 cases of NASH, which fell to only four following an average weight loss of 34 kg over 26 months.

A major deficiency in our current understanding of NAFLD and NASH is exactly how amenable they are to lifestyle change. Studies are urgently needed to examine how rapidly liver fat stores respond to changes in body weight and physical activity. These studies also need to establish how much weight loss is required, what impact exercise has alone or together with diet, and importantly, what impact dietary change may have on liver fat concentrations.

It is not yet known whether saturated fat poses a greater risk than other forms of fat, or — as is being discovered with mono- and polyunsaturated fats for heart disease risk — may prove to be beneficial.[19] An additional point of concern is sugar, particularly the fructose component, which is well established in animal studies to increase liver fat levels.[20]

Insulin sensitisation

Other strategies have been applied to improve insulin sensitivity, using either metformin or the thiazolidinedione (TZD) class of drugs.[11] Metformin is able to lower liver lipid accumulation; however, in the two trials published to date, the impact on inflammation and fibrosis was variable.[21,22]

Vitamin E (and C)

An alternative strategy is to address the oxidative and inflammatory components involved in the progression from NAFLD to NASH. The use of vitamin E (α–tocopherol), a potent anti-oxidant, has been examined in three clinical trials.[23–25] These studies provide inconsistent results, with the two trials that used vitamin E alone failing to show improvements in either liver enzymes or histology.

Emerging and experimental observations

In animal models, dietary zinc and conjugated linoleic acid (CLA) have been shown to regulate liver lipid levels.[26,27]

Zinc is a constituent of many hundreds of liver proteins involved in metabolism. Animals with low-zinc diets demonstrate increased liver fat concentrations, but it is premature to suggest that increasing zinc intake may improve liver fat levels in humans.

CLA is a mixture of positional and geometric isomers of linoleic acid found in high levels in meat and dairy products. The potential beneficial roles of CLA for atherosclerosis, improving blood glucose and lowering body fat levels is an area of intense research. In an obese and insulin-resistant rodent model (Zucker rat), CLA supplementation reduced liver size and liver fat deposits, and also lowered liver enzymes.[27] Again, clinical data are lacking.

Conclusions

Despite the considerable risks posed by NAFLD and NASH, these conditions remain an enigma. The emerging picture is that NAFLD is far from benign, adding yet another burden to the already compromised health status of obese and insulin-resistant individuals, although the extent to which NAFLD adds to

this health burden remains unclear.

Within the next few years, considerable research will be published providing valuable new insights into the most effective dietary, physical activity and complementary medical strategies to target both liver fat concentrations and inflammation. ◗

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