**Non alcoholic fatty liver disease (NAFLD): an overview**

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ABSTRACT Non alcoholic fatty liver disease is an extremely common and under-recognised disorder. The term encompasses a spectrum of histological abnormality ranging from simple steatosis, through NASH to cirrhosis. Insulin resistance is central to its pathogenesis and is the liver manifestation of the Metabolic Syndrome. The natural history and the risk factors for disease progression are incompletely understood but the severity of insulin resistance and having multiple components of the Metabolic Syndrome appears important. Understanding the pathogenesis is crucial as it provides possible targets for therapeutic intervention. Management of the other components of the Metabolic Syndrome such as weight, hypertension and insulin resistance is important and helps both that component and the liver problem. A general, rather than an organ-specific, approach to treating NAFLD and its comorbidity is essential.

KEYWORDS NAFLD, NASH, cirrhosis, insulin resistance, metabolic syndrome

LIST OF ABBREVIATIONS Alanine aminotransferase (ALT), aspartate aminotransferase (AST), body mass index (BMI), c-jun N-terminal kinase (cJNK), free fatty acids (FFA), gamma glutamyl transferase (GGT), hepatocellular carcinoma (HCC), homeostasis model assessment of insulin resistance (HOMA-IR), hepatic steatosis (HS), inhibitor of kappa kinase-β (IKK-β), insulin resistance (IR), insulin receptor substrate (IRS), liver function test (LFT), metabolic syndrome (MS), non alcoholic fatty liver disease (NAFLD), non alcoholic steatohepatitis (NASH), nuclear factor-κβ (NF-κβ), peroxisome proliferator-activated receptor gamma (PPARγ), protein kinase C (PKC), reactive oxygen species (ROS), type 2 diabetes mellitus (T2DM), triacylglycerol (TAG), tumour necrosis factor α (TNFα), randomised controlled trial (RCT)

DECLARATION OF INTERESTS No conflict of interests declared.

**What is NAFLD?**

Non alcoholic fatty liver disease is the term for the liver disorder, similar histologically to alcoholic liver disease, which is seen in patients with the MS. Non alcoholic fatty liver disease encompasses the various stages of the disorder from fatty liver or hepatic steatosis through NASH to cirrhosis. It is important that fatty change of the liver is a reactive pathological response to a variety of other conditions (see Table I), and it is therefore important that causes other than insulin resistance are excluded. The term NAFLD should only be applied to the fatty liver that occurs with insulin resistance.

**Who gets it?**

Non alcoholic fatty liver disease and the metabolic syndrome are closely related, with obesity and T2DM the most common associations. Hepatic steatosis is almost invariable in morbid obesity. Most patients with NAFLD will have other features of the MS, and more severe steatosis and advanced liver disease is associated with more features of the MS. Although the large majority of NAFLD patients are obese, a few are thin or have a normal BMI and waist to hip ratio. In these patients, it is believed that genetic rather than environmental factors play a key role.

Worryingly, probably reflecting our increasingly sedentary lifestyle, NAFLD, which may progress to cirrhosis over a relatively short period, is now recognised in teenagers. In adults, more advanced liver disease tends to occur above 45 years of age.

**How is it diagnosed?**

Most patients are asymptomatic and are referred for investigation of deranged LFTs, mainly in the form of isolated increases in ALT or GGT. It should be noted that the normal reference range for transaminase activity has been questioned recently, with the ALT in healthy women being <19 IU/L and in healthy men <30 IU/L. Needless to say, when these new reference ranges are applied, many more patients with NAFLD are identified. Indeed, using these new reference values, 73% of patients had abnormal LFTs.
Not all patients with NAFLD have abnormal LFTs. Patients with cirrhosis may have normal plasma liver enzyme activity, with reduced serum albumin, prolonged prothrombin time, or features of hypersplenism such as leucopenia and thrombocytopenia. A cholestatic variant of NAFLD is also recognised with elevation of alkaline phosphatase and GGT rather than transaminases. Imaging, particularly ultrasound which is most readily available, is the most useful, non-invasive way of examining the liver itself. Diagnosis is optimal once fatty change has involved more than 33% of the liver cells, but differentiation of NASH from other forms of NAFLD is not possible. Ultrasound, CT and MRI all give similar results. The demonstration of IR is the key to the diagnosis once other causes of liver disease have been excluded (see Table 1). Insulin resistance should be confirmed by calculation of HOMA-IR index (see Figure 1). Insulin resistance is a pre-diabetic state, and HOMA-IR is therefore not applicable in patients with T2DM where IR has already been established.

A liver biopsy is only necessary where there is diagnostic doubt. For example, non organ specific autoantibodies (especially antinuclear antibodies) are present in up to 30% of NAFLD patients, and a biopsy may be required to exclude treatable autoimmune liver disease such as autoimmune hepatitis. It has been argued that a liver biopsy is necessary to diagnose NASH or cirrhosis but serum fibrosis markers, such as hyaluronic acid, in combination with other biochemical markers of advanced disease such as an AST/ALT ratio of greater than unity and a high HOMA-IR, has made histology less important than previously. Serum hyaluronic acid has been shown to differentiate accurately between significant fibrosis, severe fibrosis and cirrhosis. Furthermore, recent studies have questioned the reliability of liver biopsy. For example, Ratziu et al examined 102 liver biopsies taken from 51 patients with a clinical diagnosis of NAFLD. Each patient underwent a liver biopsy from both the left and right lobes of the liver. The discordance rate for hepatocyte ballooning was reported as 18% with ballooning being missed in 24% if only one biopsy had been taken. Alarmingly, a discordance of one stage or more in the fibrosis grade was reported in 41% of patients, with 35% of patients having bridging fibrosis on one biopsy with only mild or no fibrosis on the other.

The diagnosis of NAFLD is generally made on the evidence outlined in Table 2.

TABLE 1 Causes of fatty change in the liver.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Example</th>
</tr>
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<tbody>
<tr>
<td>Drugs</td>
<td>Tamoxifen, methotrexate, glucocorticoids, oestrogens, amiodarone, diltiazem, sodium valproate, tetracycline, aspirin, antiretrovirals</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Hypopituitarism</td>
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<td>Wilson's disease</td>
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<td>Insulin resistance syndromes</td>
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<td>metabolic syndrome</td>
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<td>Dysbeta lipoproteinemia</td>
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<tr>
<td>Nutritional</td>
<td>Rapid, profound weight loss</td>
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<td>Prolonged starvation</td>
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<td>Parenteral nutrition</td>
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<td>Surgica</td>
<td>Jejuno-ileal bypass</td>
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<td></td>
<td>Jejunal diverticulosis</td>
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<td>Extensive intestinal resection</td>
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<td>Viral</td>
<td>Hepatitis C Virus</td>
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<td>Human immunodeficiency virus</td>
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<td>Toxins</td>
<td>Alcohol</td>
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<td>Phosphorus poisoning</td>
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<td>Petrochemicals</td>
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How common is it?

Until around five years ago, NAFLD was perceived as being relatively uncommon, but it is now one of the most common reasons for referral to gastroenterology clinics. This increase is due largely to previous underdiagnosis, but other factors include increasing obesity and the routine measurement of LFTs in patients started on statins.

Information on the prevalence of NAFLD depends on the diagnostic criteria used, and the population studied, and prevalence rates vary from 5–29%, which is in keeping with the reported prevalence of the MS of 22%. Most studies have used ultrasonography to estimate the prevalence of NAFLD (see above), and prevalence is related to the frequency of obesity, dyslipidemia and T2DM in the population studied. The prevalence of HS identified using ultrasound increases with age from 12·2% in subjects in their third decade, to 25·5% in the sixth decade. Unlike the MS, however, the prevalence appears to decline thereafter.

Natural history of NAFLD

Hepatic steatosis and NASH are generally asymptomatic, and it is only cirrhosis that is important for the patient. As most data has been derived from cross-sectional rather than prospective studies, the true natural history of NAFLD has not been established. It is, however, generally believed that, like alcoholic liver disease, the pathological progression is from HS through NASH with increasing...
inflammation and fibrosis advancing to cirrhosis. It is also believed that HS is benign, and that those with NASH are at most at risk of developing cirrhosis. Currently, it is unclear which patients with HS will progress to NASH within the following 10 years, and without this information it is difficult to reassure young patients. Patients with more features of the MS and those with worse IR (see below) are more likely to progress. By analogy with alcoholic liver disease, progression to cirrhosis may not always go through an inflammatory stage and regression, particularly of HS, may occur. This was highlighted in a longitudinal study by Adams et al.\textsuperscript{12} in which 103 patients with NAFLD underwent sequential liver biopsies, with a mean interval of approximately three years between biopsies. They reported that fibrosis progressed in 37% of patients, was unchanged in 34% and regressed in 29%. A higher rate of fibrotic progression was associated with T2DM and a low fibrosis score on initial biopsy.

Once cirrhosis has developed, the natural history of NAFLD is probably broadly similar to other causes of cirrhosis, with complications arising secondary to portal hypertension, liver failure and HCC. This latter may be particularly important as obesity is an independent risk factor for HCC development.\textsuperscript{13} A recent comparison of the outcome for patients with compensated cirrhosis due to NAFLD, compared to those due to hepatitis C, found that the former had a lower mortality and less frequent ascites, hyperbilirubinaemia and HCC but a higher cardiovascular mortality.\textsuperscript{14}

**Why does it develop?**

Although the pathogenesis of NAFLD remains uncertain, it is clear that several independent pathways may be involved including dysregulation of fatty acid metabolism with increased hepatic uptake and synthesis as well as impaired storage or export by hepatocytes resulting in accumulation of fat within the liver. Insulin resistance is believed to be the predominant cause of this steatosis, but hepatic steatosis itself can in turn cause IR.

**What causes insulin resistance?**

The precise mechanisms underlying IR are unknown and both peripheral (i.e. impaired uptake of glucose by peripheral tissues such as skeletal muscle or adipose tissue with failure of insulin to suppress lipolysis) and hepatic (i.e. failure of insulin to adjust hepatic glucose production appropriately by suppression of gluconeogenesis or stimulation of glycogenesis) IR are probably involved.

**Peripheral IR**

Several theories have been postulated for peripheral IR, but the majority involve defects in insulin binding or IRS proteins in muscle or fat cells. Figure 2 shows the factors which modulate insulin signalling. In general, once insulin has bound to its receptor, autophosphorylation of tyrosine residues occurs which triggers an intracellular signalling cascade that involves several molecules, the most important being IRS 1 and IRS 2.\textsuperscript{15} The autophosphorylation of tyrosine residues occurs which triggers an intracellular signalling cascade that involves several molecules, the most important being IRS 1 and IRS 2. The autophosphorylation of tyrosine residues occurs which triggers an intracellular signalling cascade that involves several molecules, the most important being IRS 1 and IRS 2.\textsuperscript{15}

Obesity is now widely regarded as a low-grade inflammatory state, with adipose tissue being a reservoir for a large number of hormones and inflammatory factors. The trigger for the release of these active factors...
substances is unknown. Recently, it has been shown that macrophage cell infiltration of adipose tissue occurs, and this may cause the release of cytokines or macrophage factors, some of which affect insulin signalling directly in addition to altering glucose transport proteins on adipocytes and therefore exacerbate IR.

Hepatic IR
An important role of the liver is to regulate the supply and storage of energy by the manipulation of glucose and lipid metabolism. Alterations in the balance between intracellular glucose and lipids occurs with accumulation of FA metabolites, and impairs insulin signalling as a result of abnormal phosphorylation of insulin receptors. This is the result of direct activation of tissue kinases such as PKC, cJNK and IKK-β, resulting in failure of insulin to suppress gluconeogenesis and adjust hepatic glucose production accordingly. Insulin receptor signalling in the liver is mainly via IRS 2 and any alteration of this regulator has detrimental effects on the intracellular actions of insulin. Reduced hepatic clearance of insulin from the blood, which occurs in cirrhosis, may also contribute to hepatic IR.

The consequence of IR is an influx of FFAs into the liver as a result of decreased suppression of lipolysis and increased de novo hepatic lipogenesis in the liver. The ongoing production of FFAs not only worsens peripheral insulin sensitivity by inhibiting insulin-stimulated peripheral glucose uptake, but it also provides substrate for oxidative stress (see below).

In NAFLD patients, accumulation of fat within the liver cells occurs in the form of TAG. Donnelly et al recently demonstrated that the fatty acids required for TAG synthesis come predominantly from the plasma nonesterified FFA plasma pool. Triacylglycerols may be stored in liver cells or secreted into the blood as VLDL. Dysregulation of VLDL metabolism has been shown to occur in NAFLD patients resulting in accumulation of TAGs within the liver cells.

Additional factors
Since only a minority of patients with HS progress to NASH and cirrhosis, it is believed that additional factors such as oxidative stress, mitochondrial dysfunction, inflammation and adipocytokines are important.

(i) Oxidative stress
Increased fat storage within hepatocytes leads to excess generation of ROS as the increased intracellular FFAs act as substrates for a number of pathways such as microsomal cytochrome P450 lipoxygenases in addition to peroxisomal and mitochondrial beta-oxidation. Reactive oxygen species production leads to activation of hepatic stellate cells which are responsible for collagen production and fibrogenesis. Oxidative stress may also occur due to reduced antioxidant defences such as reduction in the selenium-dependant enzymes, glutathione peroxidases and thioredoxin reductases.

(ii) Mitochondrial dysfunction
Mitochondrial beta-oxidation is believed to account for the majority of FFA oxidation with the generation of ROS by three mechanisms: lipid peroxidation, cytokine induction and induction of Fas ligand. Lipid peroxidation within the liver cells causes cell death, with the release of byproducts such as MDA and 4-hydroxy-2-nonenal which trigger activation of hepatic stellate cells and nuclear factor-κβ (NF-κβ) which regulates the expression of several proinflammatory cytokines such as tumour necrosis factor-α (TNF-α) and interleukin 6 (IL-6). TNF-α itself has been shown to impair insulin signalling directly in addition to decreasing the expression of the insulin-dependent glucose-transport molecule GLUT 4. Elevated TNF-α levels therefore exacerbate IR and promote further production of free radicals which cause further cell death and activation of hepatic stellate cells responsible for liver fibrosis.

The theory that mitochondrial dysfunction is important in the pathogenesis of NAFLD, is supported by presence of hepatocyte megamitochondria in NASH which contain linear crystalline inclusions, and the demonstration of altered activity of mitochondrial respiratory chain complexes. The relationship between IR and mitochondrial dysfunction remains unclear with further work required to clarify whether mitochondrial dysfunction is a primary or a secondary event.
Adipocytokines
As mentioned previously, adipose tissue is a rich source of physiologically active hormones known collectively as adipocytokines. These hormones can be proinflammatory (leptin, resistin, tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)) and Interleukin 6 (IL-6)), or anti-inflammatory and anti-steatotic, (adiponectin). All are involved in the regulation of adipocyte metabolism and some have a direct role in insulin-mediated processes.

Adiponectin, in particular, appears important as it promotes mitochondrial \(\beta\) oxidation of FFAs, contests FA synthesis in the liver and reduces synthesis and release of TNF-\(\alpha\) within adipose tissue. It is regarded as an insulin sensitizer. Serum adiponectin concentrations are markedly decreased in obesity and T2DM; levels are also lower in patients with NASH than with HS. Recently, it has also been reported that reduced expression or down regulation of adiponectin’s hepatic receptor, adipoR2, occurs in patients with NASH,\(^22\) and preliminary animal studies have suggested that recombinant adiponectin relieves the liver damage.\(^22\)

Secretion of adipocytokines is thought to be closely integrated and, although the triggering factor or signalling mechanism remains unknown, macrophages infiltrating the adipose tissue are thought to play a key role. It remains unclear whether the primary defect is a reduction of adiponectin leading to IR or IR leading to adiponectin reduction.

Do genetic factors have a role to play?
Although several genetic factors have been linked with T2DM, no genetic links have yet been identified in patients with NAFLD. Current genetic studies are focusing on factors affecting oxidative stress and adipocytokines. For example, a recent study of genetic polymorphisms of MnSOD (an enzyme critical in detoxifying ROS generated by mitochondria) in patients with NASH, suggests that functional polymorphisms of MnSOD might be involved in determining susceptibility to NAFLD.\(^24\) It is, however, yet to be determined whether detection of this polymorphism might be useful in clinical practice.

Dietary factors
It is widely recognised that certain diets, such as high fat or high calorie, induce obesity and IR. The mechanism is thought to be multifactorial, and it has been established that dietary factors can trigger several pathological cascades, such as TNF\(_{\text{alpha}}\), which promote IR and the development of HS. Current studies suggest that dietary factors can have a major influence, not only in determining...
the amount of fat in the liver; but the ratio of saturated to unsaturated fat in the diet may be another key factor in the pathogenic process. Capanni et al have recently demonstrated that dietary supplementation with n-3 long chain polyunsaturated fatty acids improves the biochemical and ultrasonographic features in patients with NAFLD.

**Treatment of NAFLD**

Treatment other than dietary measures remains limited. The main goal of treatment is to prevent the development of cirrhosis and its complications. Most treatment aims to correct the MS (particularly to reduce IR), and so minimise the oxidative stress that promotes progression of hepatic steatohepatitis, and to reduce overall cardiovascular risk. This approach alone may not be adequate in reversing NASH, necessitating other possible treatments such as antioxidants or cytoprotective agents to induce regression of steatosis, inflammation and fibrosis.

**Non-pharmacological approach for insulin resistance weight reduction**

Given that the majority of patients with NAFLD are obese, gradual weight reduction with diet and exercise is a logical initial approach. Weight loss improves insulin sensitivity, and glucose homeostasis in obese patients and some of these effects may be related to changes in adipocytokines production. Similarly, regular exercise, independent of weight loss, improves insulin sensitivity in muscle, liver and adipose tissue. Weight reduction of 5% or greater for one year has been shown to decrease ALT, and sustained improvement can be achieved if weight loss is maintained. Several other studies have shown a beneficial effect of weight loss on ALT activity and/or hepatic pathology in patients with NASH (see Table 1). By contrast, rapid weight loss is not recommended as this potentially could lead to an overwhelming influx of free fatty acid which could aggravate the underlying hepatic inflammation and fibrosis.

Recently, there has been interest in the combination of lifestyle modification as above and anti-obesity drugs such as orlistat and sibutramin. The role of these agents in NASH is not well established and requires further evaluation.

**Bariatric Surgery**

A more aggressive approach for patients with morbid obesity is bariatric surgery which improves liver biochemistry and reduces HS. The principles underlying these procedures are restrictive (stomach size reduction limiting the amount of food intake), malabsorptive (reducing calorie absorption) or a combination of both. All appear effective in achieving long-term weight reduction, and it has been suggested that post-operative suppression of ghrelin, a mediator of growth hormone release and one of the appetite-stimulating humoral signals to the hypothalamus, may play an important role in maintaining long-term weight loss. A recent study showed that gastric bypass surgery successfully reduced weight and normalised the metabolic abnormalities involved in the pathogenesis of NAFLD and the hepatic expression of factors involved in inflammation and fibrosis. However, these procedures are not without risks. Major complications include anastomotic ulcer; closed-loop obstruction, intestinal bacterial overgrowth, possible iron, calcium and vitamin B12 deficiencies and gallstones associated with rapid weight loss. Furthermore, it remains to be established whether these procedures are cost-effective.

**INSULIN SENSITISING AGENTS**

**Metformin**

As insulin resistance is thought to play an integral part in the pathophysiology of NAFLD, treatment with insulin-sensitising agents has been the main focus of pharmacological treatment of NAFLD. Metformin, a biguanide widely used in the treatment of type 2 diabetes, reduces hepatic gluconeogenesis and increases glucose uptake in skeletal muscle and adipose tissue. Several studies have shown reduction of ALT activity with metformin, and a return to pre-treatment activity levels on treatment withdrawal. However, histological data from these studies are limited and inconsistent (see Table 3). A recent randomised controlled trial comparing metformin with vitamin E or prescriptive diet showed that metformin significantly reduced plasma transaminase activity and improved liver histology.

**Thiazolidinediones**

Thiazolidinediones are a novel class of insulin-sensitisers that exert their effect by acting as ligand to PPARγ. The initial PPARγ agonist used in NASH was troglitazone which was withdrawn due to hepatotoxicity. Nevertheless, the study did show improvement of both plasma ALT and liver histology after six month. A recent randomised control trial comparing rosiglitazone and metformin has demonstrated a significant improvement in peripheral and hepatic insulin sensitivity with both agents. However, a reduction in hepatic fat content was only observed in the group receiving rosiglitazone and this was associated with an increase in serum adiponectin concentrations. Several other observational studies using either rosiglitazone or pioglitazone have also demonstrated beneficial effects on plasma ALT and liver histology (see Table 4). Similar to the effects seen with metformin, ALT activity returned to pre-treatment levels on withdrawal of TZD treatment. Weight gain is a recognised side-effect
of TZDs, and improvement in insulin sensitivity despite the increase in body weight was thought to be, in part, caused by redistribution of fat from visceral tissue to subcutaneous tissue.49

Fibrates

The use of fibrates as lipid-modifying agents led to the characterisation of peroxisome proliferator-activated receptor alpha (PPARα) and, subsequently, fibrates were identified as its synthetic ligands. Activation of PPARα enhances the expression of enzymes involved in lipid metabolism. In animal studies, fibrates have been shown to induce the regression of hepatic steatosis and upregulate a wide array of genes involved in fatty acid oxidation.50,51 However, data from clinical studies have been inconclusive (see Table 4).52,53

Anti-oxidant/anti-cytokine agents

A number of these agents exist including ursodeoxycholic acid (UDCA), Vitamin E, beta-carotene, pentoxifylline, selenium and S-adenosyl-methionine (SAMe). None yet has a proven role in NAFLD. A recent randomised two-year controlled trial of UDCA at a dose of 13 to 15 mg/kg/day found it well tolerated but no better than placebo for NASH.54 Interestingly, ALT activities improved in both the treatment and placebo groups, underlining the necessity for placebo-controlled trials.

Vitamin E was shown to have some benefit in a pilot study, but robust evidence for its use is lacking.55 SAMe was also associated with improvements in ALT and histology in a small study.56 The TNFα inhibitor pentoxifylline, widely used in the treatment of alcoholic hepatitis, has also been investigated in a pilot study which noted an improvement in ALT.57

THE USE OF HMG CO A REDUCTASE INHIBITOR (STATINS) IN NAFLD

There has been uncertainty about the use of statins in patients with elevated transaminases activities, including those with NAFLD, but the recent consensus of the American Liver Expert Panel suggest that statins can be used safely in NASH.58 Small observational studies have demonstrated beneficial effects on ALT activities and on lower histology.59,60 Even though the role of statins in NAFLD is unclear, the association of NAFLD with metabolic syndrome and increased vascular risk would suggest a cardioprotective benefit of statin therapy in these patients. Recently, it has been suggested that NAFLD itself predicts future cardiovascular events independently from other cardiac risk factors and is associated with increased mortality.41

OTHER POTENTIAL THERAPIES

Intestinal bacterial overgrowth increases cytokine concentrations in the portal vein and increases hepatic inflammation. This has led to the use of antibiotics and probiotics to alter bowel flora and therefore hepatic cytokine load. In rodents, probiotics reduced TNF concentrations and hepatic inflammation.42 There are no randomised trials of antibiotics or probiotics in patients with NAFLD.

Hypertension is common in NAFLD. Interestingly, a pilot study of an angiotensin receptor blocker, losartan, showed improved transaminases and liver histology in patients with NAFLD.43 Similarly angiotensin II receptor blockade has also been associated with an anti-fibrotic effect in NASH.44

So far, there have been no large prospective randomised control trials demonstrating the efficacy of any of these treatments in NAFLD. Until these data are available, treatment should be directed at managing risk factors and minimising hepatic oxidative stress. Most studies so far have, however, provided positive preliminary data that should become the basis of future clinical trials.

CONCLUSIONS

NAFLD, the hepatic manifestation of the metabolic syndrome, is common, under-diagnosed, and increasing in prevalence. It is generally asymptomatic and may progress through to HS to NASH, and eventually cirrhosis presenting with such complications as variceal haemorrhage, liver failure or hepatocellular carcinoma. It is usually, although not invariably, associated with features of the MS, with more severe NAFLD seen in patients with increasing components of the MS. The pathogenesis remains to be fully understood but IR appears to be the primary driving force. Improving insulin resistance IR and treating the components of the MS appears to improve NAFLD but there is a clear need for prospective, randomised controlled trials in this area. A general, rather than organ-specific, approach to treating NAFLD and its related comorbidity is essential.

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