

Review

Non-alcoholic fatty liver disease: The mist gradually clears[☆]

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Non-alcoholic fatty liver disease (NAFLD) is now the commonest liver disorder in the developed world affecting up to a third of individuals. It is closely associated with features of the metabolic syndrome, particularly obesity and diabetes. It can progress to cirrhosis, hepatocellular carcinoma and liver failure and is an increasing indication for transplantation. Dietary and genetic factors determine susceptibility to NAFLD and its progression. NAFLD may also be involved in the pathogenesis of cardiovascular disease. Most patients present with incidentally found abnormal liver blood tests. Diagnosis is usually one of exclusion. Liver biopsy is required for disease staging, but new imaging modalities and biomarkers are emerging which may eventually fulfil this role. There is, as yet no firm evidence-based treatment for NAFLD. Therapy is currently directed at treating components of the metabolic syndrome which may also be beneficial for the liver. The recent elucidation of the mechanisms leading to progressive disease suggests a variety of novel targets worthy of testing in animal models of NAFLD and subsequently in pilot studies in humans.

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Keywords: NAFLD; NASH; Steatosis

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Abbreviations: AIH, autoimmune hepatitis; ALT, alanine transaminase; ANA, anti-nuclear antibody; Apo-B, apolipoprotein B; AST, aspartate transaminase; BMI, body mass index; CB₁, cannabinoid-1; FFA, free fatty acids; GGT, gamma glutaryl transpeptidase; HCC, hepatocellular carcinoma; HMGCoA, 3-hydroxy 2-methyl glutaryl-coenzyme A; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OSA, obstructive sleep apnoea; PCOS, polycystic ovarian syndrome; PPAR α , peroxisome proliferator-activated receptor alpha; PPAR γ , peroxisome proliferator-activated receptor gamma; RCT, randomised control trial; SMA, smooth muscle antibody; T2DM, type 2 diabetes mellitus; TNF α , tumour necrosis factor alpha; TGFB β , triglyceride transfer factor beta; TZD, thiazolidinediones; UDCA, ursodeoxycholic acid.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is increasingly diagnosed worldwide and considered to be the commonest liver disorder in Western countries. It comprises a disease spectrum which includes variable degrees of simple steatosis (fatty liver), non-alcoholic steatohepatitis (NASH) and cirrhosis. Simple steatosis is benign, whereas steatohepatitis (NASH) is characterised by hepatocyte injury, inflammation and fibrosis which can lead to cirrhosis, liver failure and hepatocellular carcinoma (HCC).

NAFLD is strongly associated with obesity, insulin resistance, hypertension and dyslipidaemia and is now regarded as the liver manifestation of the metabolic syndrome. Rapid spread of the obesity 'pandemic' in adults and children, coupled with the realisation that the outcomes of obesity-related liver disease are not entirely benign, has led to rapid growth in clinical and basic studies in NAFLD. This review will concentrate on an update of clinical aspects of this increasingly important disease.

2. Epidemiology

NAFLD is often an asymptomatic illness in which the liver blood tests may be completely normal. This has made studies on prevalence extremely difficult with most relying on ultrasound which is known to be sensitive only when more than a third of the liver is affected by steatosis. With this proviso the prevalence of NAFLD appears to be around 20–30% in Western adults [1,2] and 15% in Asians [3]. Due to the lack of prospective studies, the true incidence of NAFLD is not well defined, although from the information available, it appears to be low [4]. Since liver biopsy is the only method of accurately diagnosing steatohepatitis, incidence/prevalence studies of NASH are rare. According to available data, NASH is much rarer than NAFLD, affecting 2–3% of the general population [5]. NAFLD and NASH are strongly associated with the presence and severity of obesity. Studies in severely obese patients (BMI > 35 kg/m²) undergoing bariatric surgery have reported prevalences of NAFLD and NASH of 91% and 37%, respectively [6] while a post-mortem study reported NASH to be present in 3% of non-obese, 19% of obese and 50% of a morbidly obese individuals [7]. A recent novel observational study in NAFLD patients has demonstrated that while central obesity correlates with the severity of inflammation, dorsocervical lipohypertrophy correlates with hepatocyte injury, inflammation and fibrosis [8]. Type 2 diabetes mellitus (T2DM) is the other major association of NAFLD with a prevalence of 70% recently reported from an ultrasound survey of almost 3000 unselected Italian T2DM patients [9,10]. Even in the absence of obesity and T2DM, NAFLD is closely associated with other features of the metabolic syndrome, with one study of non-diabetics with NAFLD reporting that 18% of normal weight patients and 67% of obese fulfilled criteria for the metabolic syndrome [11].

There are no accurate data regarding temporal changes in the prevalence of NAFLD, however, the rising prevalence of obesity, diabetes and the metabolic syndrome seems likely to be reflected in an increasing prevalence of NAFLD. This trend is of particular concern in the paediatric population where the reported increase in obesity will undoubtedly result in a higher incidence and prevalence of paediatric and adult NAFLD in the future. To date, studies in children have reported a prevalence of NAFLD of 3% in the general paediatric population and 53% in obese children [12,13]. Reports of toddlers with NAFLD and primary school children with NAFLD-related cirrhosis are clearly a cause for alarm [14].

3. Natural history of NAFLD

In marked contrast to alcoholic steatohepatitis, the short-term prognosis of NAFLD is good. The largest pro-

spective histological study of the natural history of NAFLD, with a mean follow-up of 13 years, has recently been published [15]. Data from this and other studies suggest that the long-term hepatic prognosis of patients with NAFLD depends on the histological stage of disease at presentation [16] (Fig. 1). Among patients with simple steatosis 12–40% will develop NASH with early fibrosis after 8–13 years. For patients presenting with NASH and early fibrosis, around 15% will develop cirrhosis and/or evidence of hepatic decompensation over the same time period, increasing to 25% of patients with advanced pre-cirrhotic fibrosis at baseline. In the most recent study, weight gain and the presence of portal tract fibrosis on index biopsy were the only significant predictors of fibrosis progression [15]. About 7% of subjects with compensated cirrhosis associated with NAFLD will develop a hepatocellular carcinoma (HCC) within 10 years, while 50% will require a transplant or die from a liver-related cause [17]. The risk of HCC in NAFLD-related cirrhosis is comparable to that in cirrhosis associated with alcohol or hepatitis C [18]. This may partly explain the recently reported associations of HCC with high BMI and T2DM [19]. Liver transplantation is increasingly available to those with chronic liver failure and about 10–12% of liver transplants in the United States are for NAFLD cirrhosis [20]. Unfortunately, the condition can recur in transplanted organs. The overall survival of patients with NAFLD is less than that of an age- and sex-matched population, with liver disease the 3rd leading cause of death in NAFLD patients compared to the 13th leading cause in a general population [21].

4. Susceptibility

While the vast majority of individuals with obesity, insulin resistance and the metabolic syndrome will have

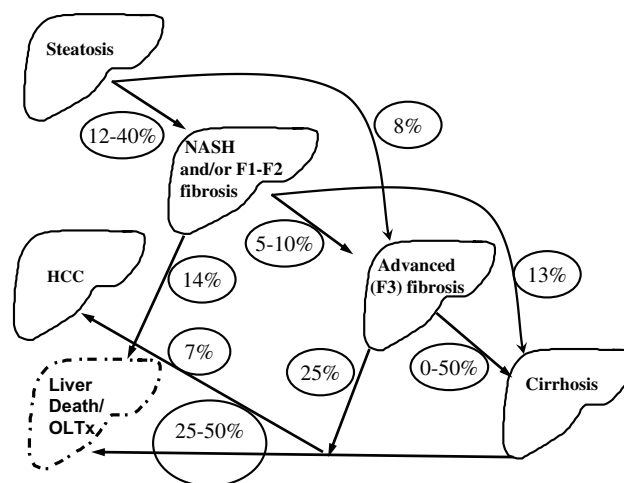


Fig. 1. Natural history of NAFLD over 8–13 years. HCC, hepatocellular carcinoma; OLTx, liver transplantation. Source Refs. [15,16].

steatosis, only a minority will ever develop steatohepatitis, fibrosis and cirrhosis. Potential environmental determinants of NAFLD are dietary factors and small bowel bacterial overgrowth [22]. Recent studies have shown that diets high in saturated fat, soft drinks and meat and low in anti-oxidants and omega 3-containing fish are associated with an increased risk of NAFLD/NASH [23,24]. With respect to alcohol intake, while there is no doubt that obesity increases risk of cirrhosis in heavy drinkers [25] emerging evidence suggests that “sensible” light alcohol intake may be protective versus NAFLD/NASH [26,27], an effect that appears likely to be due to the beneficial effect of light alcohol intake on insulin sensitivity. Family studies and inter-ethnic variations in susceptibility suggest that genetic factors may be important in determining disease risk. Although no genetic associations with advanced NAFLD have been replicated in large studies, preliminary data suggest that polymorphisms in the genes encoding microsomal triglyceride transfer protein, phosphatidylethanolamine transferase, superoxide dismutase 2, the CD14 endotoxin receptor, TNF α , TGF β and angiotensinogen may be associated with an increased risk of steatohepatitis and/or fibrosis [28]. With the advent of high-throughput gene analyses and the reduced cost of whole genome wide scans it seems likely that genes contributing to inherited susceptibility to this common disease will be identified in the near future.

5. Disease associations with NAFLD

5.1. Cardiovascular disease

Given the close association between NAFLD and classical cardiovascular risk factors it is perhaps not surprising that, when compared to controls, patients with NAFLD have a higher prevalence of atherosclerosis, as shown by increased carotid wall intimal thickness, increased numbers of atherosclerotic plaques and increased plasma markers of endothelial dysfunction [9,29,30]. This association also extends to children with the prevalence of coronary and aortic atheroma higher in children with fatty liver compared to controls in an autopsy-based report [31]. Consistent with these observations two natural history studies have reported that the increased age-related mortality observed in patients with NAFLD is attributable to cardiovascular as well as liver-related deaths [15,17]. Although an indirect association between NAFLD and cardiovascular disease is expected, a growing body of evidence supports a direct role for NAFLD in the pathogenesis of atheromatous cardiovascular disease. A recent study of unselected patients with T2DM reported that the prevalence of cardiovascular, cerebrovascular and peripheral vascular disease was significantly greater in those with NAFLD

than in those without independent of the individual components of the metabolic syndrome [10]. A similar finding has been observed for microvascular diseases, nephropathy and retinopathy [32]. The mechanism of any direct effect of NAFLD on cardiovascular risk remains unclear; possibilities include the release of atherogenic inflammatory cytokines and pro-coagulant factors from the steatotic liver [33].

5.2. Polycystic ovary syndrome (PCOS)

As with the association between NAFLD and the metabolic syndrome, the now well-established association between NAFLD and the PCOS seems likely to be indirect as a result of both conditions being characterised by insulin resistance. Up to 30% of females with PCOS have elevated alanine transaminase (ALT) levels [34] and a NAFLD prevalence of 42% has been reported in a series of PCOS patients with a mean age of 25 years [35]. More recently, advanced fibrotic liver disease has been reported in patients with PCOS [36] suggesting that women with this syndrome require careful hepatic evaluation.

5.3. Obstructive sleep apnoea (OSA)

Chronic intermittent hypoxia, as seen in obstructive sleep apnoea (OSA), has been associated with cardiovascular disease, the metabolic syndrome and insulin resistance [37]. As might be expected, therefore, a proportion of patients with OSA have elevated liver enzymes and histological features of NASH independent of body weight [38]. The severity of histology and the associated insulin resistance both correlate with the severity of OSA, strongly implicating insulin resistance as the pathogenic mechanism linking OSA to NASH although not entirely excluding a role for hypoxic liver injury. As with PCOS, this and other similar reports suggest that patients with OSA require hepatic evaluation, and that the diagnosis of OSA should be considered in NAFLD patients reporting daytime somnolence, sleep disturbances or any other symptoms suggesting a diagnosis of OSA.

6. Clinical features

NAFLD is a largely asymptomatic condition that may reach an advanced stage before it is suspected or diagnosed. Symptoms such as right upper quadrant discomfort, fatigue and lethargy have been reported in up to 50% of patients but are uncommon modes of presentation. Most patients with NAFLD are diagnosed after they are found to have hepatomegaly, or more commonly, unexplained abnormalities of liver blood tests performed as part of routine health checks or during

drug monitoring (e.g., statin therapy). NAFLD is the commonest cause of incidental abnormal liver blood tests accounting for between 60% and 90% of such cases [39,40]. Importantly, the vast majority (around 80%) of patients with NAFLD have normal liver blood tests [2] and there is no difference in histological severity between those with and without abnormal tests [41]. Accordingly, NAFLD should be suspected and sought in all patients with established risk factors, including PCOS and OSA, regardless of liver blood tests. The history should concentrate on determining the presence/absence of conditions commonly associated with “primary” NAFLD – metabolic syndrome components, cardiovascular disease and OSA – and on excluding alternative causes of steatosis including excessive alcohol intake, previous abdominal surgery (leading to bacterial overgrowth) and drugs causing NAFLD such as amiodarone and tamoxifen. On examination, most patients are centrally obese and dorsocervical lipohypertrophy (a “buffalo hump”) appears to be a particular feature of the fat distribution in patients with advanced NAFLD [8]. Features of PCOS (hyperandrogenism) should be sought in young women with suspected NAFLD [35] and clinical evidence of lipodystrophy should be sought in young, non-obese patients in view of its association with NAFLD [42].

7. Investigation

In the absence of advanced disease routine liver blood tests are either normal or typically show mild elevations of transaminases, alkaline phosphatase and gamma glutamyl transpeptidase (GGT) 1.5–3 × the upper limit of normal. The ALT/AST ratio is greater than 1 unless there is advanced fibrotic NAFLD or the patient is a covert heavy drinker. Other blood tests are aimed at detecting associated conditions, such as dyslipidaemia, and excluding alternative causes of abnormal liver blood tests. Regarding lipids, it is worth measuring serum levels of apolipoprotein B (Apo-B) in patients either with no obvious risk factors for NAFLD or with low levels of LDL and HDL cholesterol, looking for evidence of hypobetalipoproteinemia a rare, familial cause of NAFLD [43]. Serum ferritin is often raised in NAFLD patients [44] and has been associated with advanced fibrosis [45]. *HFE* genotyping should be carried out when hyperferritinemia is accompanied by raised transferrin saturation. Autoantibodies associated with autoimmune hepatitis (AIH), including ANA and SMA, are often present at low titres in patients with NAFLD and have been associated with more advanced disease in some, but not all, studies [46,47]. Around 1 in 10 of these patients have histological features of autoimmune hepatitis on biopsy and fulfil diagnostic criteria for probable/definite AIH [46]. Currently available imaging

modalities including ultrasound, CT and routine MR imaging are all excellent at detecting steatosis (once more than around a third of the liver is affected) but none can reliably detect NASH or fibrosis [48]. Newer imaging techniques including proton magnetic resonance spectroscopy [49] and transient elastography [50] show promise but require further study prior to routine use for disease staging.

7.1. The role of liver biopsy

Undoubtedly the most important and controversial issue to consider in the investigation of patients with suspected NAFLD is whether or not to perform a liver biopsy. For diagnosis, biopsy is not required in a “typical” patient with abnormal liver blood tests, classical risk factors for NAFLD (obesity, T2DM, dyslipidemia) and an ultrasound showing steatosis, however, a high ferritin with *HFE* mutations, positive autoantibodies (ANA, SMA) or the use of medications associated with drug-induced liver injury all may justify a biopsy to exclude alternative/additional diagnoses. The main indication to perform a biopsy is, however, the accurate staging of the disease since (a) different stages have different prognoses and therefore require different management strategies, and (b) no currently available imaging techniques can perform this role [48].

7.2. Non-invasive markers for staging NAFLD

The current reliance on liver biopsy for disease staging has prompted many studies aimed at defining clinical or laboratory-based variables capable of acting as surrogate markers of disease stage [51]. Various clinical and laboratory markers have been shown to be associated with advanced fibrosis (bridging fibrosis or cirrhosis) in patients with NAFLD, notably advanced age (>45 years), BMI > 30 kg/m², T2DM (or raised fasting blood glucose), the severity of OSA [38] an AST:ALT ratio greater than 1, hyperferritinemia [45] and positive autoantibodies [46]. At present, it would therefore seem reasonable to restrict liver biopsy to patients with at least some, if not all, of these risk factors. Some of these markers (age, BMI, T2DM, AST/ALT ratio) have recently been combined together with platelet count and serum albumin concentration, into a NAFLD fibrosis “score” that accurately predicts the presence or absence of advanced fibrosis in the majority of patients with NAFLD [52]. This score has recently been combined with the European Liver Fibrosis (ELF) panel of serum fibrosis markers [53] and shown to have an accuracy of over 90% in differentiating different fibrosis stages in NAFLD [54]. With respect to the non-invasive diagnosis of NASH rather than fibrosis stage, serum levels of a caspase cleavage product of the hepatocyte protein cytokeratin-18 (a putative marker of hepatocyte

apoptosis) have recently been shown to accurately predict the presence of NASH in a small pilot study [55]. Clearly this and other tests and scoring systems require further validation before they can be used in routine clinical practice but they do appear, at last, to offer real potential to replace the need for liver biopsy in the majority of patients with NAFLD.

8. Overall management strategy for NAFLD

Almost no large randomised controlled trials (RCTs) have been published on which to establish evidence-based treatment recommendations for NAFLD. Accordingly, current management strategies are directed at treating, where present, the individual components of the metabolic syndrome since this will reduce the risk of cardiovascular disease and may also be beneficial for the liver. Alcohol intake should not exceed “sensible” limits, but there is no need to advise complete abstinence as an emerging body of data suggest that light to moderate intake may actually reduce the risk of NAFLD [25,26]. In view of their largely benign prognosis these strategies are all that is required for patients with simple steatosis who can be managed by general or primary-care physicians with no requirement for formal hepatological follow-up. In contrast, patients with more advanced NAFLD require long-term follow-up by hepatologists in light of their increased propensity for disease progression and the resulting need for surveillance for complications including esophageal varices and HCC. These patients will also be candidates either for emerging “second-line” therapies currently being evaluated in large RCTs or for entry into these trials. The rationale for NAFLD therapies is based on a growing understanding of disease pathogenesis with a particular focus on reducing insulin resistance, hepatic free fatty acid (FFA) levels, oxidative, endoplasmic reticulum and cytokine-mediated stress and influencing the balance and effects of profibrotic, pro-inflammatory and anti-fibrotic, anti-inflammatory adipokines released from adipose tissue [56]. Current and emerging therapies for NAFLD can be divided into those directed at the metabolic syndrome components with potential liver effects and those directed primarily at the liver.

9. Treatments directed at components of the metabolic syndrome

9.1. Obesity

Obesity is a rational target for NAFLD therapy since weight loss should reduce many of the putative mediators of liver injury including insulin resistance, hepatic FFA supply and pro-inflammatory, profibrotic adipokines.

9.1.1. Diet and exercise

Several small, largely uncontrolled, studies have shown an improvement in either ALT or steatosis following diet (with or without exercise)-induced weight loss. There is very little evidence that necroinflammation or fibrosis can be improved by weight loss alone although a few small case series have shown some improvement in these parameters with drastic weight loss (reviewed in [57]). To date, almost all studies of diet-induced weight loss have employed simple calorie restriction, with very few attempting to manipulate specific dietary components. This area seems worthy of study, since intake of both saturated fat and fibre are known to influence insulin resistance and diets high in saturated fat, soft drinks and meat and low in omega 3-containing fish appear to be associated with both NAFLD and NASH [23]. Dietary fat intake has also been shown to correlate with liver fat content and insulin resistance in short-term studies of obese, non-diabetic women – independently of changes in total-body, subcutaneous or abdominal fat [58]. The value of exercise in achieving and maintaining weight loss and improving insulin resistance is well established and thus far the only *controlled* study of weight loss that has reported histological improvement (steatosis) combined calorie restriction with increased exercise [59].

9.1.2. Pharmacological anti-obesity agents

Encouraging improvements in liver histology have been reported from pilot studies of the intestinal lipase inhibitor orlistat in patients with NASH [60,61], however there is no evidence as yet that this improvement is over and above what would be expected from the resulting weight loss. Nonetheless, data from currently ongoing large RCTs of orlistat are awaited with interest. The cannabinoid receptor 1 (CB₁) antagonist rimonabant has been shown to be effective in reducing weight and waist circumference, with improvements in several metabolic parameters including insulin resistance [62]. Its effects on the liver in patients with NAFLD are, as yet, unknown however, animal data demonstrating that CB₁ blockade is both anti-steatotic [63] and anti-fibrotic [64] provide strong rationale for forthcoming clinical trials of drugs directed at the CB₁ receptor in NAFLD.

9.1.3. Bariatric surgery

Various surgical procedures are currently in use for the treatment of obesity. Biliopancreatic diversion appears to carry a significant risk of liver failure and worsening fibrosis, and should therefore be avoided in patients with NAFLD, however, more encouraging results have been reported for gastric bypass and gastric banding surgery [65,66]. To date, all studies have shown improvements in metabolic parameters and steatosis with some, but not all, reporting improvements in necroinflammation and fibrosis [65].

9.2. Type 2 diabetes mellitus and insulin resistance

Evidence that insulin resistance may contribute to both inflammation and fibrosis in NAFLD has led to several pilot studies of metformin and other insulin-sensitizing agents in patients with NAFLD with and without diabetes. There is as yet no direct evidence that hyperinsulinaemia *per se* adversely affects the liver, however, evidence from animal studies that insulin is a direct cause of both hepatic steatosis and fibrosis [67] might suggest that insulin or sulphonylureas should be avoided if possible. It is of interest, therefore, that a recent pilot study in patients with T2DM has shown that long-term high dose insulin therapy results in a reduction of transaminases and hepatic steatosis presumably reflecting the beneficial effects of insulin on blood glucose and adipose tissue lipolysis [68]. Whether or not long-term insulin therapy increases fibrosis in patients with NAFLD is, however, as yet unknown.

9.2.1. Metformin

Pilot studies of metformin in diabetic and non-diabetic patients with NAFLD have shown inconsistent effects on liver blood tests and steatosis (determined by MRI or MR proton spectroscopy). However, the largest RCT to date, in non-diabetic NAFLD patients, has been more encouraging. In this 12-month, randomised open-label trial, metformin treatment (2 g/day) was associated with significantly higher rates of normalised aminotransferase levels and with significant decreases in liver fat, necroinflammation and fibrosis, compared with either vitamin E treatment or a weight-reducing diet treated patients [69]. The low number of patients who agreed to a second biopsy does, however, limit the strength of the conclusions that can be drawn from this study.

9.2.2. Thiazolidinediones (TZDs)

TZDs act as agonists for the peroxisome proliferator-activated receptor γ (PPAR γ). They improve insulin sensitivity, at least in part, via anti-steatotic effects in the liver and muscle which may in turn result from an increase in the secretion of the anti-inflammatory, anti-fibrotic adipokine, adiponectin by adipocytes. Moreover, their potential as a therapy for NAFLD is further increased by evidence from animal models that they may also exert direct anti-fibrotic effects in the liver [70]. Pilot studies of the second-generation TZDs, pioglitazone and rosiglitazone, have consistently reported encouraging improvements in insulin sensitivity, liver blood tests and liver histology and several large RCTs are currently in progress. The first placebo-controlled RCT of pioglitazone in the treatment of patients with NASH has recently reported significant improvements in steatosis, inflammation and ballooning necrosis associated with

a non-significant decrease in fibrosis [71]. A note of caution over the use of TZDs in the treatment of NASH has arisen recently as a result of several meta-analyses of trials of TZDs in T2DM patients that have consistently shown that rosiglitazone increases the incidence of myocardial infarction and heart failure [72]. The risk of heart failure is also increased by pioglitazone but it is associated with a lower risk of myocardial infarction and stroke compared to placebo-treated patients [73]. This is reassuring since a recent study suggests that pioglitazone treatment for NASH has to be continued long-term since stopping it led to a worsening of steatosis and inflammation [74].

9.3. Dyslipidaemia

Hypertriglyceridaemia affects 20–80% of patients with NAFLD. As with anti-obesity and insulin-sensitising drugs, there are sound scientific reasons to support the use of fibrates – the conventional triglyceride-lowering agents – in patients with NAFLD. Fibrates are agonists for the PPAR α receptor, a transcription factor that up-regulates the transcription of genes encoding various proteins that would be expected to reduce hepatic FFA levels and also exerts anti-inflammatory effects. As with many other potential therapies for NAFLD, studies of PPAR α agonists in animal models of NASH have been encouraging [75], however, the only controlled study in patients with histological follow-up reported that one year of clofibrate had no effect on liver biochemistry or histology [76]. There is less rationale for using HMG CoA reductase inhibitors (statins) to treat NAFLD, however, they can be safely prescribed for “conventional” indications, including T2DM and high cardiovascular risk. Importantly, there is no evidence that patients with pre-existing NAFLD are at increased risk of statin-induced idiosyncratic hepatotoxicity, or that statins are associated with a higher frequency of hepatic steatosis or serum ALT abnormalities in these subjects [77].

9.4. Hypertension

No RCTs have specifically examined the effect of different anti-hypertensive agents on the liver in hypertensive patients with NAFLD. However, a growing body of evidence from animal models of hepatic fibrosis and NASH suggests that therapy directed at the renin-angiotensin system and α -blockers may be beneficial for the liver [78,79]. As yet only one pilot study has examined the use of angiotensin II receptor blockade in patients with NASH and showed a reduction in serum markers of fibrosis [80]. Newer angiotensin II receptor blockers with insulin sensitising effects seem worthy of study in NAFLD [81].

10. Treatments directed at the liver

An increased understanding of the mechanisms of progressive liver damage in NAFLD has stimulated the search for therapies specifically targeting the liver rather than at the individual components of the metabolic syndrome that may have beneficial effects.

10.1. Anti-oxidants

Several encouraging pilot studies of various agents indicate potential beneficial effects which may be related to their anti-oxidant effects. These include probucol [82], betaine [83], iron depletion through venesection [84] and vitamin E [85]. However, a recent RCT of vitamin E combined with vitamin C in patients with NASH found no overall improvement in hepatic fibrosis score compared with placebo [86].

10.2. Anti-cytokine agents

Beneficial effects of anti-TNF α therapies have been demonstrated in animal models of NASH, and two pilot studies in patients with NAFLD have reported improvements in aminotransferase levels [87] and histology [88]. Given the emerging importance of pro-inflammatory cytokines in both liver pathology and insulin resistance in obesity, it seems likely that cytokines and their regulatory molecules, including NF- κ B, will become major therapeutic targets in both NAFLD and T2DM in the near future.

10.3. Ursodeoxycholic acid (UDCA)

Given its long history as a hepatoprotectant and recent evidence that bile acids may act as molecular chaperones capable of reducing ER stress implicated in NASH pathogenesis [56,89] it is hardly surprising that UDCA has been considered as a potential treatment for NASH. To date, however, the only large, placebo-controlled RCT in patients with NASH showed no benefit of UDCA (13–15 mg/kg/day) on liver histology after 2 years' treatment [90]. More encouraging results have recently been reported from a study combining UDCA with vitamin E [91].

10.4. Liver transplantation for patients with NAFLD

Patients with NAFLD who progress to decompensated cirrhosis or who develop HCC are candidates for liver transplantation. A favourable outcome depends on removing the factors that originally caused liver damage. Perhaps unsurprisingly, steatosis recurs in most patients within 4 years, with 50% developing NASH and fibrosis; cases of recurrent cirrhosis are also reported [92,93]. Risk factors for recurrence are the presence of

insulin resistance or T2DM pre- and posttransplantation, weight gain following transplantation, and a high cumulative steroid dose. These findings highlight the importance of ensuring weight and metabolic control in reducing the risk of disease recurrence, in a group of patients who will undoubtedly contribute increasing numbers to transplant programmes in the future.

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