Treatment of Non-Alcoholic Fatty Liver Disease

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Key Words

Non-alcoholic fatty liver disease · Non-alcoholic steatohepatitis · Metabolic syndrome · Treatment · Management

Abstract

Non-alcoholic fatty liver disease (NAFLD) is now the commonest cause of chronic liver disease in developed countries. Treatment depends on the stage of disease, and non-invasive methods for risk stratification are urgently needed. Lifestyle modification (aimed at weight loss and increasing physical activity) and management of the features of metabolic syndrome are vital for all patients with NAFLD. Metformin is the first-line therapy for diabetic patients with NAFLD and also reduces the risk of hepatocellular carcinoma. Clinicians should have a low threshold for introducing a statin for the management of dyslipidaemia. Antihypertensive agents that target the renin-angiotensin system should be first-line in NAFLD for the management of hypertension. For patients with progressive disease, liver-directed pharmacotherapy with vitamin E should be considered. Non-alcoholic steatohepatitis cirrhosis is an increasingly common indication for liver transplantation.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) affects up to a third of the population in developed countries, making it the commonest cause of chronic liver disease [1, 2]. The treatment of NAFLD depends on the stage of disease, emphasising the importance of careful risk stratification [3]. Between 70 and 90% of patients have simple steatosis which carries a benign liver-related prognosis and can potentially be managed in a primary care setting [4–7].

However, approximately a third of patients have non-alcoholic steatohepatitis (NASH) that can progress to fibrosis and cirrhosis, putting them at risk of liver-related complications and mortality [5, 8, 9]. Patients with NASH are also at an increased risk of cardiovascular mortality as a result of the metabolic risk factors that are common to both NAFLD and cardiovascular disease [10, 11].

Diagnosis and Staging

The diagnosis of NAFLD currently relies on clinical features, liver function tests (LFTs) and imaging. NAFLD is considered to be the hepatic manifestation of the metabolic syndrome. Recognising individuals with features of the metabolic syndrome [12] (central obesity, impaired

fasting glucose, dyslipidaemia, hypertension) is key to identifying patients with NAFLD given that most are asymptomatic. Patients are often identified following an incidental finding of abnormal LFTs or fatty liver on imaging. Other causes of liver disease must also be excluded [13]. Liver biopsy remains the gold standard for staging disease but is invasive and not an appropriate tool for risk stratification in a third of the population. There are a number of non-invasive methods (e.g. AST/ALT ratio, NAFLD fibrosis score, FibroScan) that can help identify patients at high risk of progressive disease for whom a liver biopsy is indicated to help prognosticate and guide treatment decisions [14–20]. However, validated and clinically useful tools with a positive predictive value >90% are urgently needed for diagnosing NASH/fibrosis.

Management of NAFLD

There are two strategies in the management of patients with NAFLD: first, therapies directed at managing obesity and the features of the metabolic syndrome with potential secondary ‘liver effects’; second, specific ‘liver-directed’ therapies for patients with advanced disease for whom other strategies have failed.

Lifestyle Modification

Lifestyle modification, aimed at weight loss and increasing physical activity, is vital for all patients with NAFLD. Patients should be encouraged to lose >10% of their body weight. Weight loss (by changes in diet and exercise) improves patients’ cardiovascular risk profile, improves steatosis [21] and probably reduces hepatic inflammation and hepatocellular injury (only with >7–9% weight loss) [22, 23]. To date, there is no evidence of improvement in fibrosis. Promrat et al. [22] found that patients who received dietary advice and undertook 200 min moderate physical activity per week for 48 weeks had an overall 9.3% reduction in body weight (vs. 0.2% in the control arm) with reduced steatosis and inflammation on liver biopsy.

Exercise

Aerobic exercise increases skeletal muscle insulin sensitivity, thereby reversing insulin resistance, which is one of the key pathophysiological mechanisms causing

NAFLD [24, 25]. Studies examining moderate intensity training, high-intensity training and resistance exercise have shown improved liver enzymes and reduced steatosis, independent of weight loss [26–28]. Hallsworth et al. [27] showed that 8 weeks of resistance exercise in sedentary adults with NAFLD resulted in a 13% relative reduction in liver lipid (14.0 ± 9.1 vs. 12.2 ± 9.0 ; $p < 0.05$) and an improvement in insulin resistance (5.9 ± 5.9 to 4.6 ± 4.6 vs. 4.7 ± 2.1 to 5.1 ± 2.5 ; $p < 0.05$). Bacchi et al. [29] conducted a randomised controlled trial of 31 sedentary adults with type 2 diabetes and NAFLD comparing the effects of 4 months of aerobic and resistance training on insulin sensitivity and hepatic steatosis. Hepatic fat content, hepatic steatosis and insulin sensitivity were reduced in both intervention groups.

All patients with NAFLD should be advised to increase physical activity and undertake regular exercise. One approach is to recommend 30 min of moderate exercise 5 times per week [30]. Many patients with NAFLD find it difficult to comply with these recommendations and using pedometers (aiming for >10,000 steps/day) can be useful. Individuals with NAFLD are less active than healthy controls [31, 32], and there is evidence to suggest that they lack the confidence to exercise and have reduced readiness to make lifestyle changes [33, 34]. This suggests that behavioural counselling may also have a place in the management of these patients.

Diet

Patients should be advised to follow a calorie-restricted diet (600 kcal less than a person needs to remain at the same weight), aiming to lose 0.5–1 kg per week until they achieve their target weight [30]. General dietary advice should include avoiding simple carbohydrates, saturated fats, and sweetened drinks [35, 36]. Ryan et al. [37] compared a Mediterranean diet (high in monounsaturated fatty acids) with a diet low in fat and high in carbohydrate (LF/HCD) in non-diabetic subjects with biopsy-proven NAFLD. Mean weight loss was not different between the two diets ($p = 0.22$), but there was a significant relative reduction in hepatic steatosis ($p = 0.012$) and improvement in insulin sensitivity with the Mediterranean diet ($p = 0.03$).

There has been recent interest in the role of dietary ω -3 polyunsaturated fatty acids (n-3 PUFAs). Patients with NAFLD consume less n-3 PUFAs than controls [38, 39]. A systematic review and meta-analysis showed that supplementation with n-3 PUFA decreases liver fat but

does not have a statistically significant effect on ALT levels [40]. Dietary fish oil supplementation may offer a simple therapeutic option for patients with NAFLD, but further studies are needed. Dietician input is also valuable in this patient group. Dietician-led lifestyle interventions (over 12 months) were more effective than standard care in terms of weight loss (5.6 vs. 0.6 kg) and achieving remission of NAFLD (64 vs. 20%) [41].

Bariatric Surgery

Bariatric surgery is becoming increasingly important in the management of obese patients with NAFLD. There are restrictive procedures (gastric band, gastric balloon, sleeve gastrectomy) which result in early satiety and malabsorptive procedures (gastric bypass). The weight loss that results from bariatric surgery improves insulin sensitivity and has specific effects on liver histology [42]. Dixon et al. [43] examined the effect of weight loss following gastric band placement on NAFLD with paired biopsies. There were major improvements in steatosis, necroinflammatory changes, and fibrosis at the second biopsy ($p < 0.001$ for all). Weight loss following gastric bypass has also been found to reduce hepatic steatosis and decrease the hepatic expression of factors involved in the progression of liver inflammation and fibrosis [44]. The majority of the histological benefits occur within the first year post-surgery but seem to be sustained 5 years later [45].

Bariatric surgery is not a primary treatment for NAFLD due to the lack of long-term outcome data [46]. However, recent guidelines state that NASH is not a contraindication to surgery in patients who are otherwise eligible [13]. In adults with a BMI >50 , surgery may need to be considered first-line [30]. Patients with cirrhosis and portal hypertension are at risk of hepatic decompensation with rapid weight loss and should not undergo bariatric surgery.

Management of Type 2 Diabetes Mellitus in NAFLD

Patients with NAFLD require screening for impaired glucose tolerance given that almost all have evidence of insulin resistance and up to 50% have type 2 diabetes mellitus (T2DM) [15, 47]. Dietary change is the initial appropriate management, but treatment should be escalated if the HbA_{1c} is $>6.5\%$. Metformin is the first-line pharmacological treatment for T2DM. Although it has not been shown to improve liver histology, it aids weight loss and

reduces the risk of any diabetes-related end-point, microvascular disease, myocardial infarction (large vessel disease) and all-cause mortality [48–50].

Importantly, there is emerging evidence that metformin reduces the risk of hepatocellular cancer (HCC) in diabetic patients in a dose-dependent manner [51]. In patients with NASH cirrhosis, the yearly cumulative incidence of HCC is 2.6% per year [52]. Metformin acts via an LKB1/AMPK-mediated mechanism to inhibit hepatic glucose production. Aberrant genes, including in the LKB1/AMPK pathway, are emerging as therapeutic targets in cancer treatment [53]. Metformin treatment in diabetic patients is associated with a statistically significant reduction in HCC risk (OR 0.33, 95% CI 0.1–0.7, $p = 0.006$) [54]. Chen et al. [55] confirmed a 7% risk reduction per year for HCC in diabetics treated with metformin in a Taiwanese nationwide case-control study (adjusted OR 0.93, 95% CI 0.91–0.94, $p < 0.0001$). A meta-analysis by Zhang et al. [56] found metformin was associated with a 62% reduction in the risk of liver cancer among patients with T2DM (OR 0.38, 95% CI 0.24–0.59; $p < 0.001$).

Treatment should be escalated further if the HbA_{1c} remains $>6.5\%$. Guidelines most usually recommend a sulphonylurea (such as gliclazide) as second-line therapy [48]. However, sulphonylureas may be injurious in NAFLD due to increasing insulin secretion and weight gain. Instead, insulin sensitisers, such as pioglitazone, should be used second-line in patients with NAFLD. Pioglitazone improves insulin sensitivity and reduces hepatic steatosis and inflammation (but not fibrosis) in subjects with NASH with and without T2DM [57–59]. Treatment with pioglitazone 30 mg/day for a year reduced hepatocellular injury and fibrosis compared with placebo [59]. The PIVENS trial showed resolution of steatohepatitis in 47% with pioglitazone (vs. 21% with placebo, $p = 0.001$), although it failed to meet the strict primary end-point (improvement in NAS ≥ 2 with at least 1 point improvement in ballooning without increase in fibrosis score) [58]. A meta-analysis showed that pioglitazone in NASH significantly improves steatosis, inflammation and to a lesser degree fibrosis [60] and a further meta-analysis of 16,390 patients with T2DM treated with pioglitazone demonstrated an 18% reduction in death, myocardial infarction and stroke [61]. There are, however, some concerns about the long-term safety of pioglitazone due to possible increased risks of congestive cardiac failure [62], bladder cancer [63], and reduced bone density [64]. In view of this, the use of pioglitazone should be reserved for patients with more aggressive NASH who have failed lifestyle interventions [65].

For obese patients who still have an $\text{HbA}_{1c} > 7.5\%$, GLP-1 analogues (such as liraglutide or exenatide) should be considered as a third-line agent. GLP-1 is secreted by ileal L-cells in response to food entering the small intestine. It increases insulin sensitivity, inhibits gastric emptying and increases satiety [66]. A meta-analysis of the phase 3 studies of liraglutide for the treatment of T2DM ($n = 4,442$) showed improvement in ALT and reduced steatosis measured by computed tomography (CT) [67]. These benefits are dependent on associated weight loss and improved glycaemic control. The effect of GLP-1 analogues on liver histology is yet to be determined. Caution must be used with agents though as there is an increased risk of pancreatitis (particularly if very high triglycerides) and potentially an increased risk of pancreatic cancer [66].

Dyslipidaemia

Treatment of lipid profile abnormalities is important in NAFLD to reduce patients' cardiovascular risk profile and associated mortality. Primary prevention should be given to individuals with a $\geq 20\%$ 10-year risk of developing cardiovascular disease (using a risk calculator such as the Framingham risk calculator) [68]. Fibrates activate transcription factors belonging to the peroxisome proliferator-activated receptor- α family, which regulate lipid and glucose metabolism as well as inflammation. Theoretically these agents should be beneficial in the management of NAFLD, but studies have not confirmed this [69, 70].

Simvastatin is recommended as first-line therapy for the primary prevention of cardiovascular disease [68]. In secondary prevention, we should aim for a total cholesterol < 4 mmol/l. Statin therapy reduces the 5-year incidence of all-cause mortality, major coronary events, coronary revascularisation, and stroke by about 20% per mmol/l reduction in LDL cholesterol [71]. Clinicians are often concerned about raised transaminases in patients taking statins. However, statins are safe in patients with liver disease and a large study actually demonstrated that statins improve liver enzymes and cardiovascular outcomes in patients with raised LFTs due to NAFLD [72]. Statins may also reduce the risk of HCC. El-Serag et al. [73] found an adjusted OR for HCC with statin use of 0.74 (95% CI 0.64–0.87) in diabetic patients. This was confirmed in a Taiwanese study of HCC in patients receiving statins (OR 0.62, 95% CI 0.42–0.91) [74]. A systematic review and meta-analysis found that patients on statins were less likely to develop HCC than those not taking statins (adjusted OR 0.63, 95% CI 0.52–0.76) [75].

Hypertension

Over 70% of patients with NAFLD have hypertension [76, 77], so all patients should have their blood pressure checked regularly. Antihypertensive therapy should be instituted if the blood pressure is $> 140/90$ mm Hg. Hypertension guidelines [78] recommend angiotensin-converting enzyme inhibitors or angiotensin receptor blockers first-line for patients less than 55 years of age, but calcium channel blockers in those over 55 years and of Afro-Caribbean origin. Targeting the renin-angiotensin system (RAS) is probably beneficial in all patients with NAFLD. Hepatic stellate cells (HSC) are implicated in fibrogenesis and have a RAS that prevents apoptosis, so drugs that induce HSC apoptosis will stimulate fibrosis reversion despite ongoing liver injury. Blocking the RAS reduces fibrosis in experimental models of hepatic fibrosis [79, 80]. Georgescu et al. [81] found that telmisartan and valsartan improve transaminase levels and insulin sensitivity, and telmisartan also significantly decreased the NASH activity score and fibrosis. Losartan has been shown in a small study to decrease markers of fibrosis, improve transaminases and improve histology [82]. Larger studies are needed and there is a multicentre randomised controlled trial ongoing in the UK. These agents also have the benefit of reducing the incidence of new onset diabetes (meta-analysis showed 20% reduction) [83].

Tested 'Liver-Directed' Therapies

For patients with biopsy-proven NASH, where lifestyle intervention has failed, liver-directed therapies can be considered.

Antioxidants: Vitamin E

Vitamin E is an antioxidant that has beneficial effects on liver histology in non-diabetic patients with NASH. It has not been evaluated in cirrhotic or diabetic patients. The PIVENS trial compared high-dose vitamin E (800 IU/day) or pioglitazone with placebo in 247 non-diabetic adults with NASH. Patients underwent liver biopsy after 96 weeks of treatment. Both agents improved steatosis and inflammation, but only patients on vitamin E reached the primary study end-point [58]. The TONIC trial also found reduced steatohepatitis with vitamin E in a study of childhood NASH [84]. Vitamin E therefore appears to have beneficial effects on histology, but there are some safety concerns. High doses may increase the risk of haemorrhagic stroke (although reduced risk of embolic

stroke) [85] and prostate cancer [86]. A meta-analysis also showed a small overall increase in all-cause mortality at doses >400 IU/day [87]. Currently, the use of vitamin E should be restricted to selected patients who have not responded to lifestyle interventions and who have more advanced pre-cirrhotic NASH [65].

Pentoxifylline

Pentoxifylline (PTX) inhibits pro-inflammatory cytokines including TNF- α and in vitro studies on HSC have suggested it has antifibrogenic effects [88, 89]. Zein et al. [90] showed that after a year of treatment with PTX, 38.5% of patients had a decrease of ≥ 2 points in the NAFLD activity score (vs 13.8% with placebo, $p = 0.036$). PTX also resulted in significant improvements in steatosis ($p < 0.001$), inflammation ($p = 0.02$) and fibrosis ($p = 0.038$).

Other Potential Therapies

Apoptosis of hepatocytes is known to be important in the pathophysiology of NASH. A phase 2 study of GS-9450, a selective caspase inhibitor, in biopsy-proven NASH showed significant improvements in ALT. Cyto-keratin-18 (a serum marker of apoptosis) levels were reduced, but the change was not statistically significant. This treatment option requires further investigation [91]. The interaction between bile acid transport and signalling and hepatic lipid metabolism is of particular interest currently. The farnesoid X receptor (FXR) is central in the regulation of enterohepatic circulation and lipid homeostasis. Zhang et al. [92] found that WAY-362450, an FXR agonist, decreased transaminases and reduced hepatic inflammation and fibrosis in mice. Obeticholic acid (OCA, a semisynthetic bile acid) is an FXR agonist. A proof-of-concept study in patients with NAFLD and T2DM showed OCA increases insulin sensitivity, reduces transaminases and reduces markers of liver fibrosis [93]. Other treatments which merit further investigation based on encouraging data from small pilot studies include resveratrol (a calorie-restriction mimetic) [94] and combination therapy with ursodeoxycholic acid and vitamin E [95].

Untested 'Liver-Directed' Therapies

There are many potential therapeutic options for NAFLD that have shown promising results in animal studies and are awaiting investigation in patients. Autophagy is a catabolic mechanism involving cell degradation of unnecessary or dysfunctional cellular compo-

nents, including lipid droplets. There has been interest in whether modulating autophagy could be an effective therapy for NAFLD. Initial work suggests that drugs enhancing autophagy (carbamazepine or rapamycin) reduce steatosis and improve insulin sensitivity [96].

Liver Transplantation

With the increasing prevalence of NAFLD, NASH cirrhosis is becoming an increasingly common indication for liver transplantation, and accounted for 12% of patients listed in the UK in 2009 [97]. Patient and graft survival in liver transplantation for NASH are comparable to other indications [97, 98]. Contos et al. [99] in study of patients transplanted for cryptogenic cirrhosis found that although all grafts have evidence of steatosis at 5 years post-transplant (vs. 25% in age- and sex-matched controls with primary biliary cirrhosis and primary sclerosing cholangitis), only 11% developed steatohepatitis and none progressed to cirrhosis. Another study analysing 98 patients undergoing liver transplantation for NASH cirrhosis found recurrent steatosis in 70% and NASH in 25%, but no patients developed graft failure or required re-transplantation at 3 years [100]. It is vital to manage cardiovascular risk factors post-transplant to reduce the risk of cardiovascular-related mortality [101].

Conclusion

Lifestyle modifications (exercise and diet change) to achieve weight loss are essential for all patients with NAFLD. For diabetic patients with NASH, treatment should be with metformin first-line and pioglitazone if glycaemic control is not achieved. Angiotensin receptor blockers are the antihypertensive agent of choice for hypertensive patients with NASH. If lifestyle changes and management of the metabolic syndrome are unsuccessful in preventing disease progression, vitamin E should be considered. Given the associated cardiovascular-related mortality and potential reduction in HCC risk, clinicians should have a low threshold for statin use. In non-diabetic patients with advanced NASH, vitamin E should be considered as first-line pharmacological therapy.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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