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Treatment of Non-Alcoholic Fatty Liver Disease

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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.

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

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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 endpoint (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 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 ≥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. Cytokeratin-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 components, 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.

References

1 Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, et al: Prevalence of hepatic steatosis in an urban population in the United States: Impact of ethnicity. Hepatology 2004;40:1387–1395.

2 Wong VW, Chu WC, Wong GL, Chan RS, Chim AM, Ong A, et al: Prevalence of non-alcoholic fatty liver disease and advanced fibrosis in Hong Kong Chinese: a population study using proton-magnetic resonance spectroscopy and transient elastography. Gut 2012;61:409–415.

3 Anstee QM, McPherson S, Day CP: How big a problem is non-alcoholic fatty liver disease? BMJ 2011;343:d3897.

4 Teli MR, James OF, Burt AD, Bennett MK, Day CP. The natural history of non-alcoholic fatty liver: a follow-up study. Hepatology 1995;22:1714–1719.

5 Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ: Non-alcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology 1999;116:1413–1419.

6 Dam-Larsen S, Franzmann M, Andersen IB, Christoffersen P, Jensen LB, Sorensen TI, et al: Long-term prognosis of fatty liver: risk of chronic liver disease and death. Gut 2004;53:750–755.

7 Ekstedt M, Franzen LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, et al: Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology 2006;44:865–873.

8 Wanless IR, Lentz JS: Fatty liver hepatitis (steatohepatitis) and obesity: an autopsy study with analysis of risk factors. Hepatology 1990;12:1106–1110.

9 Williams CD, Stengel J, Asike MI, Torres DM, Shaw J, Contreras M, et al: Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. Gastroenterology 2011;140:124–131.

10 Ekstedt M, Franzen LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, et al: Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology 2006;44:865–873.

11 Anstee QM, Targher G, Day CP: Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. Nat Rev Gastroenterol Hepatol 2013;10:330–344.

12 Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al: Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640–1645.

13 Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al: The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology 2012;55:2005–2023.

14 Dyson JK, McPherson S, Anstee QM: Non-alcoholic fatty liver disease: non-invasive investigation and risk stratification. J Clin Pathol 2013;66:1033–1045.

15 McPherson S, Stewart SF, Henderson E, Burt AD, Day CP: Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. Gut 2010;59:1265–1269.

16 Angulo P, Hui J, Marchesini G, Bugianesi E, George J, Farrell GC, et al: The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology 2007;45:847–854.

17 Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F, et al: Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound Med Biol 2003;29:1705–1713.

18 Wong VW, Vergniol J, Wong GL, Foucher J, Chan HL, Le Bail B, et al: Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. Hepatology 2010;51:454–462.

19 Castera L, Foucher J, Bernard PH, Carvalho F, Allaix D, Merrouche W, et al: Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. Hepatology 2010;51:828–835.

20 Myers RP, Pomier-Layrargues G, Kirsch R, Pollett A, Beaton M, Levstik M, et al: Discordance in fibrosis staging between liver biopsy and transient elastography using the FibroScan XL probe. J Hepatol 2012;56:564–570.

21 Sullivan S, Kirk EP, Mittendorfer B, Patterson BW, Klein S: Randomized trial of exercise effect on intrahepatic triglyceride content and lipid kinetics in nonalcoholic fatty liver disease. Hepatology 2012;55:1738–1745.

22 Promrat K, Kleiner DE, Niemeier HM, Jackvony E, Kearns M, Wands JR, et al: Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology 2010;51:121–129.

23 Harrison SA, Fecht W, Brunt EM, Neuschwander-Tetri BA: Orlistat for overweight subjects with nonalcoholic steatohepatitis: a randomized, prospective trial. Hepatology 2009;49:80–86.

24 Kirwan JP, Solomon TP, Wojta DM, Staten MA, Holloszy JO: Effects of 7 days of exercise training on insulin sensitivity and responsiveness in type 2 diabetes mellitus. Am J Physiol Endocrinol Metab 2009;297:E151–E156.

25 Van Der Heijden GJ, Wang ZJ, Chu Z, Toffolo G, Manesso E, Sauer PJ, et al: Strength exercise improves muscle mass and hepatic insulin sensitivity in obese youth. Med Sci Sports Exerc 2010;42:1973–1980.

26 Thoma C, Day CP, Trenell MI: Lifestyle interventions for the treatment of non-alcoholic fatty liver disease in adults: a systematic review. J Hepatol 2012;56:255–266.

27 Hallsworth K, Fattakhova G, Hollingsworth KG, Thoma C, Moore S, Taylor R, et al: Resistance exercise reduces liver fat and its mediators in non-alcoholic fatty liver disease independent of weight loss. Gut 2011;60:1278–1283.

28 Little JP, Gillen JB, Percival ME, Safdar A, Tarnopolsky MA, Punthakee Z, et al: Low-volume high-intensity interval training reduces hyperglycemia and increases muscle mitochondrial capacity in patients with type 2 diabetes. J Appl Physiol 2011;111:1554–1560.

29 Bacchi E, Negri C, Targher G, Faccioli N, Lanza M, Zoppini G, et al: Both resistance training and aerobic training reduce hepatic fat content in type 2 diabetic subjects with nonalcoholic fatty liver disease (the RAED2 randomized trial). Hepatology 2013;58:1287–1295.

30 NICE: NICE Clinical guidelines. CG43 Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children; in Care NIfHaCEaNCCfP, ed, 2006.

31 Zelber-Sagi S, Nitzan-Kaluski D, Goldsmith R, Webb M, Zvibel I, Goldiner I, et al: Role of leisure-time physical activity in nonalcoholic fatty liver disease: a population-based study. Hepatology 2008;48:1791–1798.

32 Hsieh SD, Yoshinaga H, Muto T, Sakurai Y: Regular physical activity and coronary risk factors in Japanese men. Circulation 1998;97:661–665.

33 Frith J, Day CP, Robinson L, Elliott C, Jones DE, Newton JL: Potential strategies to improve uptake of exercise interventions in non-alcoholic fatty liver disease. J Hepatol 2010;52:112–116.

34 Centis E, Marzocchi R, Suppini A, Dalle Grave R, Villanova N, Hickman IJ, et al: The role of lifestyle change in the prevention and treatment of NAFLD. Curr Pharm Des 2013;19:5270–5279.

35 Zivkovic AM, German JB, Sanyal AJ: Comparative review of diets for the metabolic syndrome: implications for nonalcoholic fatty liver disease. Am J Clin Nutr 2007;86:285–300.

36 Musso G, Gambino R, Pacini G, De Michieli F, Cassader M: Prolonged saturated fat-induced, glucose-dependent insulinotropic polypeptide elevation is associated with adipokine imbalance and liver injury in nonalcoholic steatohepatitis: dysregulated enteroadipocyte axis as a novel feature of fatty liver. Am J Clin Nutr 2009;89:558–567.

37 Ryan MC, Itsiopoulos C, Thodis T, Ward G, Trost N, Hofferberth S, et al: The Mediterranean diet improves hepatic steatosis and insulin sensitivity in individuals with non-alcoholic fatty liver disease. J Hepatol 2013;59:138–143.

38 Araya J, Rodrigo R, Videla LA, Thielemann L, Orellana M, Pettinelli P, et al: Increase in long-chain polyunsaturated fatty acid n–6/n–3 ratio in relation to hepatic steatosis in patients with non-alcoholic fatty liver disease. Clin Sci 2004;106:635–643.

39 Elizondo A, Araya J, Rodrigo R, Poniachik J, Csendes A, Maluenda F, et al: Polyunsaturated fatty acid pattern in liver and erythrocyte phospholipids from obese patients. Obesity 2007;15:24–31.

40 Parker HM, Johnson NA, Burdon CA, Cohn JS, O'Connor HT, George J: Omega-3 supplementation and non-alcoholic fatty liver disease: a systematic review and meta-analysis. J Hepatol 2012;56:944–951.

41 Wong VW, Chan RS, Wong GL, Cheung BH, Chu WC, Yeung DK, et al: Community-based lifestyle modification programme for non-alcoholic fatty liver disease: a randomized controlled trial. J Hepatol 2013;59:536–542.

42 Mummadi RR, Kasturi KS, Chennareddygari S, Sood GK: Effect of bariatric surgery on nonalcoholic fatty liver disease: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2008;6:1396–1402.

43 Dixon JB, Bhathal PS, Hughes NR, O'Brien PE: Nonalcoholic fatty liver disease: improvement in liver histological analysis with weight loss. Hepatology 2004;39:1647–1654.

44 Klein S, Mittendorfer B, Eagon JC, Patterson B, Grant L, Feirt N, et al: Gastric bypass surgery improves metabolic and hepatic abnormalities associated with nonalcoholic fatty liver disease. Gastroenterology 2006;130:1564–1572.

45 Mathurin P, Hollebecque A, Arnalsteen L, Buob D, Leteurtre E, Caiazzo R, et al: Prospective study of the long-term effects of bariatric surgery on liver injury in patients without advanced disease. Gastroenterology 2009;137:532–540.

46 Chavez-Tapia NC, Tellez-Avila FI, Barrientos-Gutierrez T, Mendez-Sanchez N, Lizardi-Cervera J, Uribe M: Bariatric surgery for non-alcoholic steatohepatitis in obese patients. Cochrane Syst Rev 2010;1:CD007340.

47 McPherson S, Anstee QM, Henderson E, Day CP, Burt AD: Are simple noninvasive scoring systems for fibrosis reliable in patients with NAFLD and normal ALT levels? Eur J Gastroenterol Hepatol 2013;25:652–658.

48 NICE: NICE clinical guidelines. CG87 type 2 diabetes: the management of type 2 diabetes. In NICE, ed, 2010.

49 Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–412.

50 UK Prospective Diabetes Study (UKPDS) Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854–865.

51 Bo S, Benso A, Durazzo M, Ghigo E: Does use of metformin protect against cancer in type 2 diabetes mellitus? J Endocrinol Invest 2012;35:231–235.

52 Ascha MS, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN: The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. Hepatology 2010;51:1972–1978.

53 Pollak M: Energy metabolism, cancer risk, and cancer prevention. Recent Results Cancer Res 2009;181:51–54.

54 Donadon V, Balbi M, Ghersetti M, Grazioli S, Perciaccante A, Della Valentina G, et al: Antidiabetic therapy and increased risk of hepatocellular carcinoma in chronic liver disease. World J Gastroenterol 2009;15:2506–2511.

55 Chen HP, Shieh JJ, Chang CC, Chen TT, Lin JT, Wu MS, et al: Metformin decreases hepatocellular carcinoma risk in a dose-dependent manner: population-based and in vitro studies. Gut 2013;62:606–615.

56 Zhang ZJ, Zheng ZJ, Shi R, Su Q, Jiang Q, Kip KE: Metformin for liver cancer prevention in patients with type 2 diabetes: a systematic review and meta-analysis. J Clin Endocrinol Metab 2012;97:2347–2353.

57 Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, et al: A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med 2006;355:2297–2307.

58 Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, et al: Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med 2010;362:1675–1685.

59 Aithal GP, Thomas JA, Kaye PV, Lawson A, Ryder SD, Spendlove I, et al: Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. Gastroenterology 2008;135:1176–1184.

60 Boettcher E, Csako G, Pucino F, Wesley R, Loomba R: Meta-analysis: pioglitazone improves liver histology and fibrosis in patients with non-alcoholic steatohepatitis. Aliment Pharmacol Ther 2012;35:66–75.

61 Lincoff AM, Wolski K, Nicholls SJ, Nissen SE: Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA 2007;298:1180–1188.

62 Lago RM, Singh PP, Nesto RW: Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. Lancet 2007;370:1129–1136.

63 Piccinni C, Motola D, Marchesini G, Poluzzi E: Assessing the association of pioglitazone use and bladder cancer through drug adverse event reporting. Diabetes Care 2011;34:1369–1371.

64 Lecka-Czernik B: Bone loss in diabetes: use of antidiabetic thiazolidinediones and secondary osteoporosis. Curr Osteoporos Rep 2010;8:178–184.

65 Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al: The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology 2012;142:1592–1609.

66 Nauck MA: A critical analysis of the clinical use of incretin-based therapies: the benefits by far outweigh the potential risks. Diabetes Care 2013;36:2126–2132.

67 Armstrong MJ, Houlihan DD, Rowe IA, Clausen WH, Elbrond B, Gough SC, et al: Safety and efficacy of liraglutide in patients with type 2 diabetes and elevated liver enzymes: individual patient data meta-analysis of the LEAD program. Aliment Pharmacol Ther 2013;37:234–242.

68 NICE: NICE clinical guidelines. CG67 Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. In NICE, ed, 2010.

69 Basaranoglu M, Acbay O, Sonsuz A: A controlled trial of gemfibrozil in the treatment of patients with nonalcoholic steatohepatitis. J Hepatol 1999;31:384.

70 Fernandez-Miranda C, Perez-Carreras M, Colina F, Lopez-Alonso G, Vargas C, Solis-Herruzo JA: A pilot trial of fenofibrate for the treatment of non-alcoholic fatty liver disease. Dig Liver Dis 2008;40:200–205.

71 Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al: Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267–1278.

72 Athyros VG, Tziomalos K, Gossios TD, Griva T, Anagnostis P, Kargiotis K, et al: Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post hoc analysis. Lancet 2010;376:1916–1922.

73 El-Serag HB, Johnson ML, Hachem C, Morgana RO: Statins are associated with a reduced risk of hepatocellular carcinoma in a large cohort of patients with diabetes. Gastroenterology 2009;136:1601–1608.

74 Chiu HF, Ho SC, Chen CC, Yang CY: Statin use and the risk of liver cancer: a population-based case-control study. Am J Gastroenterol 2011;106:894–898.

75 Singh S, Singh PP, Singh AG, Murad MH, Sanchez W: Statins are associated with a reduced risk of hepatocellular cancer: a systematic review and meta-analysis. Gastroenterology 2013;144:323–332.
76 Marchesini G, Bugianesi E, Forlani G, Cerrelli F, Lenzi M, Manini R, et al: Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. Hepatology 2003;37:917–923.
77 Dixon JB, Bhathal PS, O'Brien PE: Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. Gastroenterology 2001;121:91–100.
78 NICE: NICE clinical guidelines. CG127 hypertension: clinical management of primary hypertension in adults. In NICE, ed, 2011.
79 Bataller R, Sancho-Bru P, Gines P, Lora JM, Al-Garawi A, Sole M, et al: Activated human hepatic stellate cells express the renin-angiotensin system and synthesize angiotensin II. Gastroenterology 2003;125:117–125.
80 Paschos P, Tziomalos K: Nonalcoholic fatty liver disease and the renin-angiotensin system: implications for treatment. World J Hepatol 2012;4:327–331.
81 Georgescu EF, Ionescu R, Niculescu M, Mogoanta L, Vancica L: Angiotensin-receptor blockers as therapy for mild-to-moderate hypertension-associated non-alcoholic steatohepatitis. World J Gastroenterol 2009;15:942–954.
82 Yokohama S, Yoneda M, Haneda M, Okamoto S, Okada M, Aso K, et al: Therapeutic efficacy of an angiotensin II receptor antagonist in patients with nonalcoholic steatohepatitis. Hepatology 2004;40:1222–1225.
83 Al-Mallah M, Khawaja O, Sinno M, Alzohaili O, Samra AB: Do angiotensin-converting enzyme inhibitors or angiotensin receptor blockers prevent diabetes mellitus? A meta-analysis. Cardiol J 2010;17:448–456.
84 Lavine JE, Schwimmer JB, Van Natta ML, Molleston JP, Murray KF, Rosenthal P, et al: Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. JAMA 2011;305:1659–1668.
85 Schurks M, Glynn RJ, Rist PM, Tzourio C, Kurth T: Effects of vitamin E on stroke subtypes: meta-analysis of randomised controlled trials. BMJ 2010;341:c5702.
86 Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, Ford LG, et al: Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 2009;301:39–51.
87 Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E: Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med 2005;142:37–46.
88 Romanelli RG, Caligiuri A, Carloni V, DeFranco R, Montalto P, Ceni E, et al: Effect of pentoxifylline on the degradation of procollagen type I produced by human hepatic stellate cells in response to transforming growth factor-β_1. Br J Pharmacol 1997;122:1047–1054.
89 Preaux AM, Mallat A, Rosenbaum J, Zafrani ES, Mavier P: Pentoxifylline inhibits growth and collagen synthesis of cultured human hepatic myofibroblast-like cells. Hepatology 1997;26:315–322.
90 Zein CO, Yerian LM, Gogate P, Lopez R, Kirwan JP, Feldstein AE, et al: Pentoxifylline improves nonalcoholic steatohepatitis: a randomized placebo-controlled trial. Hepatology 2011;54:1610–1619.
91 Ratziu V, Sheikh MY, Sanyal AJ, Lim JK, Conjeevaram H, Chalasani N, et al: A phase 2, randomized, double-blind, placebo-controlled study of GS-9450 in subjects with nonalcoholic steatohepatitis. Hepatology 2012;55:419–428.
92 Zhang S, Wang J, Liu Q, Harnish DC: Farnesoid X receptor agonist WAY-362450 attenuates liver inflammation and fibrosis in murine model of non-alcoholic steatohepatitis. J Hepatol 2009;51:380–388.
93 Mudaliar S, Henry RR, Sanyal AJ, Morrow L, Marschall HU, Kipnes M, et al: Efficacy and safety of the farnesoid X receptor agonist obeticholic acid in patients with type 2 diabetes and nonalcoholic fatty liver disease. Gastroenterology 2013;145:574–582.e1.
94 Timmers S, Konings E, Bilet L, Houtkooper RH, van de Weijer T, Goossens GH, et al: Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. Cell Metab 2011;14:612–622.
95 Dufour JF, Oneta CM, Gonvers JJ, Bihl F, Cerny A, Cereda JM, et al: Randomized placebo-controlled trial of ursodeoxycholic acid with vitamin E in nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol 2006;4:1537–1543.
96 Lin CW, Zhang H, Li M, Xiong X, Chen X, Chen X, et al: Pharmacological promotion of autophagy alleviates steatosis and injury in alcoholic and non-alcoholic fatty liver conditions in mice. J Hepatol 2013;58:993–999.
97 Charlton MR, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA: Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. Gastroenterology 2011;141:1249–1253.
98 Ratziu V, Bellentani S, Cortez-Pinto H, Day C, Marchesini G: A position statement on NAFLD/NASH based on the EASL 2009 special conference. J Hepatol 2010;53:372–384.
99 Contos MJ, Cales W, Sterling RK, Luketic VA, Shiffman ML, Mills AS, et al: Development of nonalcoholic fatty liver disease after orthotopic liver transplantation for cryptogenic cirrhosis. Liver Transplant 2001;7:363–373.
100 Malik SM, Devera ME, Fontes P, Shaikh O, Sasatomi E, Ahmad J: Recurrent disease following liver transplantation for nonalcoholic steatohepatitis cirrhosis. Liver Transplant 2009;15:1843–1851.
101 Newsome PN, Allison ME, Andrews PA, Auzinger G, Day CP, Ferguson JW, et al: Guidelines for liver transplantation for patients with non-alcoholic steatohepatitis. Gut 2012;61:484–500.