



REVIEW ARTICLE

Nonalcoholic fatty liver disease, association with cardiovascular disease and treatment (II). The treatment of nonalcoholic fatty liver disease[☆]



Ángel Brea^{a,*}, Xavier Pintó^b, Juan F. Ascaso^c, Mariano Blasco^d, Ángel Díaz^e, Pedro González-Santos^f, Antonio Hernández-Mijares^g, Teresa Mantilla^h, Jesús Millánⁱ, Juan Pedro-Botet^j, Working Group on Atherogenic Dyslipemia of the Spanish Society of Arteriosclerosis

^a Unidad de Lípidos, Servicio de Medicina Interna, Hospital San Pedro, Logroño, Spain

^b Unidad de Lípidos y Riesgo Vascular, Servicio de Medicina Interna, Hospital Universitario de Bellvitge, Idibell, CiberObn, L'Hospitalet de Llobregat, Barcelona, Spain

^c Servicio de Endocrinología, Hospital Clínico, Valencia, Spain

^d Área Sanitaria de Delicias, Atención Primaria, Zaragoza, Spain

^e Centro de Salud de Bembibre, Bembibre, León, Spain

^f Departamento de Medicina, Universidad de Málaga, Málaga, Spain

^g Servicio de Endocrinología, Hospital Universitario Dr. Peset, Universitat de València, Valencia, Spain

^h Centro de Salud de Prosperidad, Atención Primaria, Madrid, Spain

ⁱ Unidad de Lípidos, Servicio de Medicina Interna, Hospital General Universitario Gregorio Marañón, Universidad Complutense, Madrid, Spain

^j Unidad de Lípidos y Riesgo Vascular, Servicio de Endocrinología y Nutrición, Hospital del Mar, Universitat Autònoma de Barcelona, Barcelona, Spain

Received 24 June 2016; accepted 28 June 2016

Available online 23 June 2017

KEYWORDS

Nonalcoholic fatty liver disease;
Nonalcoholic steatohepatitis;

Abstract Disease nonalcoholic fatty liver disease (NAFLD) comprises a series of histologically similar to those induced by alcohol consumption in people with very little or no liver damage same. The importance of NAFLD is its high prevalence in our Western societies, from the point of view liver in its progressive evolution from steatosis to steatohepatitis, cirrhosis and liver cancer. During the last decade it has been observed that NAFLD leads to an increased cardiovascular risk with accelerated atherosclerosis and cardiovascular events, the leading cause of

[☆] Please cite this article as: Brea Á, Pintó X, Ascaso JF, Blasco M, Díaz Á, González-Santos P, et al. Enfermedad del hígado graso no alcohólico, asociación con la enfermedad cardiovascular y tratamiento (II). Tratamiento de la enfermedad del hígado graso no alcohólico. Clin Invest Arterioscler. 2017;29:185–200.

* Corresponding author.

E-mail address: abrea@riojasalud.es (Á. Brea).

Cardiovascular risk;
Cardiovascular
diseases;
Arteriosclerosis;
Treatment

PALABRAS CLAVE

Enfermedad del
hígado graso no
alcohólica;
Esteatohepatitis no
alcohólica;
Riesgo
cardiovascular;
Enfermedades
cardiovasculares;
Arteriosclerosis;
Tratamiento

morbidity and mortality. This updated January 2016 revision consists of two parts. In this second part, the treatment of NAFLD and its influence on cardiovascular disease and drugs used in the control of cardiovascular risk factors showing a beneficial effect on the liver disease will be reviewed.

© 2017 Published by Elsevier España, S.L.U. on behalf of Sociedad Española de Arteriosclerosis.

Enfermedad del hígado graso no alcohólico, asociación con la enfermedad cardiovascular y tratamiento (II). Tratamiento de la enfermedad del hígado graso no alcohólico

Resumen La enfermedad del hígado graso no alcohólico (EHGNA) comprende una serie de lesiones hepáticas histológicamente similares a las inducidas por el alcohol en personas con un consumo del mismo muy escaso o nulo. La importancia de la EHGNA radica en su alta prevalencia en nuestras sociedades occidentales y, desde el punto de vista hepático, en su progresiva evolución desde esteatosis a esteatohepatitis, cirrosis y cáncer de hígado. Durante la última década se ha observado que la EHGNA da lugar a un incremento del riesgo cardiovascular con aceleración de la arteriosclerosis y de los episodios cardiovasculares, principal causa de su morbilidad. Esta revisión actualizada a enero de 2016 consta de 2 partes. En esta segunda parte se revisarán el tratamiento de la EHGNA y su influencia sobre la enfermedad cardiovascular, así como los fármacos empleados en el control de los factores de riesgo cardiovascular que muestran un efecto beneficioso sobre esta hepatopatía.

© 2017 Publicado por Elsevier España, S.L.U. en nombre de Sociedad Española de Arteriosclerosis.

In the first part of this review,¹ the association of nonalcoholic fatty liver disease (NAFLD) with cardiovascular disease (CVD) was analysed. The second part reviews the treatment of NAFLD, its influence on CVD and the drugs used in the control of risk factors that show a beneficial effect on this liver disease.

Introduction

Given that non-alcoholic fatty liver disease (NAFLD) comprises both progressive liver disease and the onset of cardiovascular disease (CVD), treatment objectives must seek to improve both complications. Measures taken to meet these objectives include improving the histological abnormalities of the liver with a subsequent fall in cardiovascular risk. This paper primarily focuses on tried and tested treatments to reverse the histological changes inherent in this disease, as well as their impact on treating the associated cardiovascular risk factors (CVRF) to reduce the accelerated atherosclerotic burden caused by the onset of this liver disease. In addition, the influence of those drugs that have been shown to be effective in controlling CVRF or CVD, which have also been found to have a positive effect on the clinical or histological characteristics of NAFLD, will also be examined.

Lifestyle changes to treat non-alcoholic fatty liver disease

The basic treatment for NAFLD is diet, exercise and weight loss. By adopting an appropriate lifestyle that includes these

three components, the advance of liver disease may be slowed and cardiovascular risk is extremely likely to fall as an additional benefit.

Weight loss

Numerous studies have clearly shown how even modest weight loss improves insulin resistance (IR), transaminase levels (ALT), fat infiltration and inflammatory phenomena.²⁻⁵ In morbidly obese patients who followed extremely low calorie diets, the amount of liver fat, as measured by magnetic resonance imaging, fell by up to 40% after losing 9 kg in 6 weeks.⁶⁻⁸ Other studies achieved similar results by reducing daily intake to 500 kcal for 6 months.^{7,9} From a histological point of view, it has been conclusively proven that weight loss improves steatosis, inflammation, ballooning and the histological severity of the disease, as assessed by the NAFLD activity score (NAS).¹⁰ However, whether or not it improves fibrosis remains open to debate.^{11,12}

A meta-analysis of weight loss studies has shown that weight loss of 7% or more improves steatosis, ballooning and inflammation, but not fibrosis. However, this meta-analysis found that less than 50% of patients achieved weight loss of more than 7%, and that losing between 5% and 7% of body weight improves liver fat content.¹³ Another meta-analysis, which investigated the effects of lifestyle change in obese patients, showed that only 3.5% weight loss was achieved on average over a 2-3 period, which is below the optimum figure required to achieve histological change.¹⁴ Two recent

studies that assessed the histological impact of weight loss found that the greater the weight loss, the greater the benefit, both in terms of the NAS and non-alcoholic steatohepatitis (NASH). Fibrosis also improved with weight loss in excess of 10%, regardless of the patient's starting weight.^{15,16} Although the rs738409[G]/I148 M polymorphism of the patatin-like phospholipase domain-containing protein 3 (PNPLA3) causes an increased risk of developing steatosis, the response of carriers of this polymorphism is three times greater than the general population in terms of reduced intrahepatic fat content after lifestyle change.¹⁷ One evidence-based review concluded that dietary recommendations for patients with non-alcoholic fatty liver disease should include a reduction of 600–800 calories per day or a calorie intake limited to 25–30 kcal/kg/day of ideal body weight.¹⁸ The combined Practice Guideline by the American Association for the Study of Liver Diseases, the American College of Gastroenterology, and the American Gastroenterological Association (AASLD/AGA/ACG) recommends weight loss of at least 3–5% to improve steatosis, and more than 10% to have an impact on necrosis and inflammation.¹⁹

In terms of cardiovascular effects, a meta-analysis¹³ confirmed that weight loss largely reduces cardiovascular risk because it improves the obesity-related risk factors deriving from glucose and lipid metabolism. It should be noted that the influence of weight loss on cardiovascular prognosis in patients with ischaemic heart disease was only confirmed after a meta-analysis, which showed that intentional weight loss improved survival and reduced the risk of cardiovascular events by 33%. Unintentional weight loss, on the other hand, led to an increase in cardiovascular events.²⁰

Diet

The optimum diet to treat NAFLD has yet to be definitively established.⁸ Nevertheless, it is believed that a low-fat diet reduces hepatic lipid deposition,²¹ although a meta-analysis of three small controlled and randomised clinical trials that compared the effects of calorie-control with a low-carbohydrate diet *versus* a low-fat diet concluded that both diets yielded similar weight loss, similar liver fat content, as assessed by spectroscopic magnetic resonance imaging, and similar ALT serum levels, as well as similar improvements in insulin sensitivity as estimated by the Homeostasis Model Assessment (HOMA), plasma triglycerides and adiponectin levels. However, the low-carbohydrate diet led to a greater reduction in waist circumference and blood glucose compared to a low-fat diet, which more consistently improved the lipid profile.¹³ A recent review concluded that data on the effect of macronutrients in NAFLD are scarce, particularly in human models. A higher consumption of simple carbohydrates, sugary drinks and saturated fatty acids may exacerbate NAFLD and cause increased fat accumulation in the liver, while a higher intake of fibre and low-glycaemic index carbohydrates, monounsaturated fatty acids, omega-3, soya and whey protein tend to improve NASH. Furthermore, it is believed that a low-carbohydrate, low-fat and high-protein diet is of benefit to NAFLD patients.²² Whatever the diet, it seems that replacing saturated fat with polyunsaturated and monounsaturated fats improves both cardiovascular risk and NAFLD.²³

Mediterranean diet

The Mediterranean diet deserves special mention for its beneficial effects on both the liver and CVD. Notwithstanding the fact that adhering to a diet of this type prevents or improves metabolic syndrome (MetS),²⁴ its impact on reducing NAFLD severity has also been demonstrated. In this regard, a case-control study found that good adherence to the Mediterranean diet is associated with lower insulin resistance, lower ALT levels and a reduced risk of developing steatohepatitis.²⁵ A study of NAFLD patients diagnosed by biopsy compared the Mediterranean diet with another high-carbohydrate, low-fat diet, and found that the Mediterranean diet significantly reduced steatosis as measured by MRI (39% *versus* 7%), despite no difference in weight loss between the two groups. There were also improvements to IR, as measured by HOMA, as well as blood pressure. This study suggests that the Mediterranean diet may benefit NAFLD patients to a much greater extent than just dyslipidaemia management.²⁶

In terms of its cardiovascular effects, the Mediterranean diet has been shown to be useful in both primary prevention (PREDIMED study)²⁷ and secondary prevention (LYON study).²⁸ A systematic review confirmed that adherence to this diet reduces cardiovascular morbidity and mortality by 38%. According to the scoring system used, a two-point increase in adherence to the Mediterranean diet was associated with a 13% reduction in CVD risk.²⁹

Fructose

Fructose, which is widely used as a sweetener in soft drinks, has been independently associated with the risk of onset of NAFLD and its severity in both population studies and a randomised trial.¹³ However, a meta-analysis of fructose studies found no direct correlation between fructose intake and NAFLD, apart from in terms of excess calorie intake that its consumption may involve. The meta-analysis also found that fructose intake contributed to increased intrahepatic fat, as measured by magnetic resonance imaging, as well as to higher transaminase levels.³⁰

Alcohol

Data concerning whether or not alcohol may be consumed in NAFLD are conflicting. While some argue that alcohol consumption in small amounts may protect against development of the disease,^{31,32} others advise against its consumption once the disease has been diagnosed.^{33,34} A Japanese 10-year follow-up study found that 40–280 g of alcohol per week protect from steatosis.³⁵ Another study showed that moderate alcohol consumption in NAFLD reduces the likelihood of developing carotid plaques or stenosis.³⁶ A recent meta-analysis of more than 40,000 subjects found that moderate alcohol consumption (<40 g/day) has a protective effect on NAFLD irrespective of the body mass index (BMI), reducing its prevalence by 31% and with greater benefit to women (53% reduction) than to men (30%). An extremely surprising finding was that NASH progression fell by almost 50% with alcohol consumption.³⁷ The AASLD/AGA/ACG guideline recommends a maximum alcohol consumption of four drinks per day for men and two for women.¹⁹ Nevertheless, recent

data from large prospective cohort studies suggest that the combined effects of alcohol and obesity may synergistically increase the risk of liver damage, liver disease-related death and the onset of liver cancer. As such, this is an area that requires more clinical research.^{38–40}

In terms of cardiovascular effects, very moderate consumption may be more beneficial than abstinence. In this regard, daily consumption of 1–2 drinks was found to reduce cardiovascular mortality by 25%, myocardial infarction by 29%, coronary mortality by 25% and total mortality by 13%.⁴¹

Exercise

We will first consider how exercise may prevent NAFLD, and then how it may play a part in its treatment.

Exercise and NAFLD prevention

A number of epidemiological studies have confirmed an inverse correlation between NAFLD and physical activity.⁴² The National Health and Nutrition Examination Survey (NHANES) 2003–2006⁴³ showed that NAFLD patients tend to be less physically active, both in terms of time invested and actual activity as measured by an accelerometer. In another cross-sectional study of 72,359 healthy Korean adults, those who exercised regularly had a 28–53% lower risk of NAFLD across almost all the BMI deciles.⁴⁴ Numerous studies have found an inverse correlation between different types of physical activity and NAFLD prevalence, proportional to exercise intensity and irrespective of visceral obesity, IR and MetS.^{45,46} Doing regular exercise in one's free time prevents the onset of steatosis fundamentally by reducing abdominal fat, with anaerobic exercise appearing to have a more pronounced effect.⁴⁷ Daily individual lifestyle has a significant impact on fat accumulation in the liver. It has been proven that sitting for a long time is a risk factor for NAFLD, regardless of total daily physical activity.⁴⁸ Time spent watching television is also associated with NAFLD, irrespective of other parameters such as exercise, although this appears to be attenuated if BMI is taken into account.⁴⁹

Exercise and benefits to the liver in non-alcoholic fatty liver disease

A significant number of research studies have shown that exercise reduces liver fat and potentially transaminase levels in patients with NAFLD, with or without weight loss. One study found that three 30–45-min weekly sessions on a bike led to a significant fall in liver triglyceride levels and visceral adipose tissue in patients with NAFLD, with no changes to body weight.⁵⁰ Similarly, doing 30–60 min of exercise five times a week for 16 weeks reduced liver fat by 10% without changes to body weight, but had no effect on liver triglyceride secretion, unless the patient also experienced weight loss.⁵¹ In another study, 60 min of aerobic exercise a week was found to reduce liver triglyceride content and ALT levels in NAFLD patients.⁵² A meta-analysis of controlled trials – excluding exercise and diet *versus* diet alone – concluded that exercise reduces liver fat content by 37%, but in no case improves transaminase levels. This benefit was still seen with minimal or no weight loss and with an exercise level below the current recommendations for obesity treatment.⁵³ The AASLD/AGA/ACG guideline suggests that

in adults with NAFLD, exercise may only reduce hepatic steatosis, while its capacity to improve other aspects of liver histology remains unknown.¹⁹ The effect of exercise on falling liver triglyceride levels is supported by the first randomised and controlled study to investigate these aspects, which found that any type of aerobic exercise, regardless of frequency, intensity or duration, reduced liver fat without significant weight loss.⁵⁴ Although scarce data are available on histological improvements as a result of exercise, a systematic review found a trend towards reduced inflammation, while its effect on fibrosis was inconclusive.⁸ In NAFLD diagnosed by biopsy, it would appear that only intense exercise reduces the likelihood of developing NASH by 35% and fibrosis by 47%, with mild or moderate exercise having no preventive effect.⁵⁵ Resistance training also improves steatosis, as measured by MRI, regardless of weight loss.⁵⁶ A randomised and controlled study also found that 3 months of resistance training improved fat content as quantified by the hepatorenal-ultrasound index.⁵⁷ However, it has yet to be established whether aerobic exercise or resistance training offers greater benefits. One study found that both forms of exercise reduced liver fat in NAFLD patients in equal measure.⁵⁸

All of the studies referred to above suggest that doctors should actively recommend regular exercise to their NAFLD patients. This is particularly applicable to non-obese patients, in whom it is not feasible to prescribe slimming diets.⁵⁹ Although there is still no clear consensus on the frequency, duration or intensity of exercise, or indeed on the combination of anaerobic exercise with resistance training or the need to follow a calorie-controlled diet,⁶⁰ overall lifestyle change should encompass these elements. When faced with the question of how much exercise to recommend, it is probably safe to say as much as possible and the more the better. Some experts recommend 150–300 min of exercise per week spread over at least 3 days.⁶¹ A recent review extols the hepatic physiopathological benefits of exercise.⁶²

In terms of cardiometabolic effects, there is substantial evidence to suggest that exercise improves vascular and metabolic comorbidity associated with NASH, including IR, dyslipidaemia, inflammation, hypertension⁶³ and endothelial dysfunction,⁶⁴ thereby reducing the risk of coronary, cardiovascular and hepatic morbidity and mortality.⁶⁵ A dose-response relationship concerning these preventive effects of exercise has been identified.⁶⁶ In fact, an improvement of one metabolic equivalent in cardiorespiratory fitness (3.5 ml/kg/min) was associated with a 13% reduction in all-cause mortality and a 15% fall in the risk of cardiovascular events, respectively.^{66,67} Conversely, time spent sitting is correlated to total mortality.⁶⁸

Bariatric surgery

Non-randomised studies have shown that bariatric surgery improves the components of metabolic syndrome (MetS), with a drastic reduction in hepatic steatosis, as well as reduced ballooning and inflammation that may manifest with NAFLD, while its effect on fibrosis remains unclear.^{69,70} Nevertheless, steatohepatitis and fibrosis may be exacerbated if the surgery leads to excessively rapid weight loss of

more than 1.6 kg per week.⁷¹ A meta-analysis of 15 studies that investigated the influence of bariatric surgery on NAFLD found improved steatosis, steatohepatitis and fibrosis, as well as a fall in BMI.⁷² A review conducted by Cochrane on bariatric surgery as a treatment for NASH did not identify any randomised clinical trials or quasi-randomised controlled trials but examined 21 cohort studies. Although consistent improvements in steatosis and inflammation scores were found, four studies reported fibrosis deterioration 5 years after surgery.⁷³ The American guidelines¹⁹ specify that: (1) bariatric surgery is not contraindicated in obese subjects with NAFLD and NASH with no established cirrhosis; (2) the safest, most effective and best form of bariatric surgery in NASH-induced cirrhosis has not yet been established, and (3) it is premature to consider surgery as a specifically established option in the treatment of NASH. Another more recent systematic review identified significant improvements in steatosis (50%), ballooning (68%), inflammation (50%), fibrosis (12%) and a fall in liver enzyme levels: ALT (11 U/l), AST (4 U/l), GGT (18 U/l). Concerning point 2 of the aforementioned guidelines, surgery does not appear to exacerbate cirrhosis. As with the reviews cited above, the high heterogeneity between the studies must be taken into account as this prevents definitive conclusions from being drawn.⁷⁴ In terms of type of surgery, the Roux-en-Y gastric bypass seems to be more effective than the gastric band in achieving a better NAFLD activity score as it improves all NAFLD-related parameters.⁷⁵ Although the most influential factor was greater weight loss, this does not fully explain the benefits achieved.

In terms of cardiovascular effects, the metabolic changes resulting from bariatric surgery that may lead to reduced cardiovascular risk are multiple and complex. IR tends to improve instantly, and, if it fails to do so, NAFLD usually persists.⁷⁶ Bariatric surgery results in diabetes remission in 80% of patients,⁷⁷ a 65% improvement in dyslipidaemia—defined as HDL cholesterol <40 mg/dl, or LDL cholesterol >160 mg/dl, or TG >200 mg/dl—,⁷⁸ and a 25% fall in oxidised LDLs.⁷⁹ Blood pressure has been reported to drop by up to 38%, with an 8 mmHg fall in systolic blood pressure and a 5 mmHg fall in diastolic blood pressure. However, other authors have not found any differences in blood pressure before and after surgery, leading some to conclude that the role of bariatric surgery on hypertension has yet to be determined.⁸⁰ On the other hand, it has been found to improve left ventricular hypertrophy and diastolic dysfunction.⁸¹ A meta-analysis on observational studies showed that weight loss surgery reduces total mortality by 50%, CVD by 46%, myocardial infarction by 54% and stroke by 51%.⁸² Another 10-year follow-up case-control study of more than 800 patients found that gastric bypass surgery reduces mortality by 52%.⁸³ The pathophysiological explanation for the beneficial effects of bariatric surgery on the cardiovascular system was examined in a recent publication.⁸⁰

Pharmacological treatment of non-alcoholic fatty liver disease

A multitude of drugs to treat NAFLD that act on different levels of the sequence of pathophysiological pathways,

ranging from simple steatosis to advanced disease, have been investigated in the last 10 years. However, none of which to date has been found to completely reverse liver damage or to reduce associated morbidity and mortality. This review shall present the results of randomised clinical trials assessing the effects of five drugs on hepatic histology in NAFLD: thiazolidinediones, vitamin E, pentoxifylline, obeticholic acid and liraglutide (Table 1). It will also review a small group of drugs administered to control CVRFs, which in turn have a beneficial effect on NAFLD.

Thiazolidinediones

They act as peroxisome proliferator-activated receptor gamma (PPAR- γ) agonists to improve insulin sensitivity, increase the peripheral uptake and the oxidation of free fatty acids (FFA) and decrease their intrahepatic synthesis. They also increase adiponectin levels. An analytical and histological improvement was found in short-term studies with thiazolidinediones,^{84,85} particularly with pioglitazone, which may even improve fibrosis.^{86,87} In a 1-year follow-up study, rosiglitazone reduced ALT levels and steatosis, but had no effect on inflammation or fibrosis.⁸⁸ Extending the treatment to 2 years did not lead to a greater improvement than that seen in the first year in the majority of patients in this series.⁸⁹ The largest meta-analysis of studies assessing the effects of thiazolidinediones in patients with NAFLD incorporated 11 randomised trials and 862 participants (38% diabetic). Findings included an improvement in steatosis, hepatocyte ballooning and necroinflammation, as well as delayed liver fibrosis progression. The insulin resistance of adipose and muscle tissue also improved.¹⁴ Two further meta-analyses corroborate these results⁹⁰ and also found that pioglitazone leads to an improvement in fibrosis.⁹¹ The effects of thiazolidinediones tend to subside shortly after they are withdrawn.⁹² The AASLD/AGA/ACG guideline only permits pioglitazone administration to treat patients with biopsy-proven steatohepatitis. Nevertheless, the guideline also expresses concerns about its long-term safety and efficacy due to the increased risk of coronary events with rosiglitazone and pioglitazone's association with bladder cancer, loss of bone mass, weight gain, painful swelling of the legs and congestive heart failure.¹⁹ Pioglitazone reduces arteriosclerosis progression, as measured both by changes to the carotid artery intima-media thickness (IMT),⁹² as well as by analysis of the atheromatous plaque by intravascular ultrasound of the coronary arteries.⁹³ The *post hoc* analyses of the Prospective pioglitazone clinical trial in macrovascular events (PROACTIVE) found the cardiovascular preventive effect of pioglitazone to be most pronounced in secondary prevention.⁹⁴ This trial found that patients treated with pioglitazone who had previously had a myocardial infarction had a 28% lower risk of infarction, a 39% lower risk of acute coronary syndrome (ACS), a 19% fall in the combined objective comprising infarction, coronary revascularisation, ACS and cardiac death, as well as a 47% reduction in the risk of suffering a stroke.⁹⁵ It was also found that pioglitazone reduced the likelihood of experiencing another cerebrovascular accident by 47% in patients who had already suffered a stroke.⁹⁶ Furthermore, pioglitazone reduced the likelihood of death, infarction and stroke by 16%

Table 1 Primary drugs that histologically improve non-alcoholic fatty liver disease.

Drug	Mechanism of action	Histological effect	Disadvantages
Glitazones (pioglitazone)	PPAR agonist γ	Improves steatosis, necroinflammation and fibrosis	Weight gain. Bladder cancer. Loss of bone mass. Heart failure
Vitamin E	Decreases oxidative stress	Improves steatosis and inflammation	Long-term safety not proven. Lack of experience in diabetics and patients with cirrhosis
Pentoxifylline	Inhibits TNF α and decreases oxidative stress	Improves steatosis, inflammation and fibrosis	Lack of data from large randomised clinical trials
Obeticholic acid	FXR agonist. Reduces insulin resistance. Immunomodulatory and anti-inflammatory action	Improves steatosis, necroinflammation and fibrosis	Pruritus reduces the HDL-C/LDL-C ratio
Liraglutide	GLP-1 agonist. Improves resistance	Improves steatosis, necroinflammation and steatohepatitis	Gastrointestinal effects. Subcutaneous insulin administration

FXR: farnesoid X nuclear receptor; GLP-1: glucagon-like peptide 1; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; PPAR γ : peroxisome proliferator-activated receptor gamma; TNF α : tumour necrosis factor- α .

in high-risk diabetic patients.⁹⁴ Finally, a meta-analysis of 19 randomised controlled trials confirmed that patients treated with pioglitazone were at a significantly lower risk of death, infarction and stroke.⁹⁷ In addition, the publication on the 6-year follow-up of the patients enrolled in the PROACTIVE study reported that pioglitazone reduced the number of cardiovascular events compared to patients who did not receive the drug, irrespective of duration of treatment.⁹⁸

Vitamin E

As an antioxidant, a series of preliminary *in vitro* and *in vivo* studies indicated that vitamin E (α -tocopherol) may be useful in improving certain aspects of NAFLD. The following were the two most significant clinical trials. In the Pioglitazone *versus* Vitamin E *versus* Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis (PIVENS) study, which recruited 247 biopsied patients with NASH, it was shown that a dose of 800 IU/day improves ALT levels, steatosis and inflammation, but not fibrosis.⁹⁹ The Treatment of NAFLD in Children (TONIC) study found that only ballooning reduced in children treated with 800 IU/day of vitamin E *versus* placebo, with no improvements in other histological parameters or transaminase levels. However, the NAFLD Activity Score (NAS) improved, as did the percentage of resolved NASH cases.¹⁰⁰ Given that numerous meta-analyses and systematic reviews have found that administration of vitamin E increases total mortality (39 deaths per 10,000 patients who take 400 IU/day^{13,101,102}), raises the risk of haemorrhagic stroke¹⁰³ and increases the likelihood of developing prostate cancer in patients over the age of 50,¹⁰⁴ some authors advise against its use. Despite this, the AASLD/AGA/ACG guideline argues that 800 IU/day of vitamin E improves hepatic histology in non-diabetic adults with steatohepatitis diagnosed by biopsy, and as such it should be considered a first-line pharmacological treatment for this patient population. Having said that, pending new data, its use is advised against for the treatment of NASH in diabetic patients, NAFLD without a liver biopsy, cirrhosis or

cryptogenic NASH or cirrhosis.¹⁹ A recent meta-analysis of five studies and 401 patients indicated that administering 400 IU/day of vitamin E improves NASH histology (steatosis, inflammation and ballooning) and fibrosis, while also improving transaminase and alkaline phosphatase concentrations. The authors of the meta-analysis observed that these findings should improve the grading quality of evidence currently laid out by the guidelines.¹⁰⁵ Another smaller meta-analysis of three articles produced similar results.¹⁰⁶

In terms of the cardiovascular system, vitamin E offers no preventive or therapeutic effect.^{107,108}

Pentoxifylline

Pentoxifylline inhibits multiple pro-inflammatory cytokines, such as tumour necrosis factor- α (TNF α), and acts as an antioxidant, limiting the production of oxygen free radicals and increasing liver glutathione synthesis.¹⁰⁹ The *in vitro* studies conducted also suggest that pentoxifylline has an antifibrogenic effect on hepatic stellate cells activated by the degradation of extracellular collagen, while also reducing fibrogenic cytokine levels.^{109,110} However, evidence supporting the use of pentoxifylline is only of moderate quality. A meta-analysis on five small randomised, double-blind and placebo-controlled studies of 145 patients with NAFLD found that pentoxifylline improves weight, transaminase and TNF α levels, the NAS and lobular inflammation, but has no effect on ballooning or fibrosis.¹¹¹ Another meta-analysis of these same studies confirmed most of these results, finding that pentoxifylline may reduce transaminase activity and the NAS while improving certain histological parameters—steatosis, inflammation and fibrosis. It was also found to reduce BMI and baseline blood glucose, but not TNF α levels. Further well-designed, randomised placebo-controlled studies with a significant sample size should be conducted to confirm these results.¹¹²

In terms of its application in the cardiovascular setting, a meta-analysis of six studies with 221 patients with a

systolic ejection fraction below 40% found that mortality due to heart failure reduced by 71% in the cohort of patients that took 1200 mg/day of pentoxifylline for 6 months.¹¹³ A Cochrane review¹¹⁴ concluded that a lack of data prevents any definitive conclusion being reached on whether or not pentoxifylline improves intermittent claudication, which is the primary cardiovascular treatment objective for which this drug is prescribed in Spain.

Obeticholic acid

This is a derivative of chenodeoxycholic acid, a natural FXR agonist, which is a farnesoid X nuclear receptor that regulates glucose and lipid metabolism. In animal models, obeticholic acid (OCA) reduces gluconeogenesis, glycogenolysis and IR,^{115,116} controls lipid homeostasis and leads to a fall in hepatic steatosis by reducing *de novo* lipogenesis.^{117,118} It has been shown that OCA possesses immunomodulatory and anti-inflammatory properties, inhibiting nuclear factor $\kappa\beta$ (NF- $\kappa\beta$).¹¹⁹ In an initial phase 2, double-blind, controlled trial, 25 and 50 mg/day of OCA was administered to patients with type 2 diabetes and NAFLD for 6 weeks. The drug was well tolerated, insulin sensitivity increased while liver enzyme levels, inflammatory markers and fibrosis all fell.¹²⁰ A phase IIb multicentre, randomised, double-blind study sponsored by the US administration (FLINT),¹²¹ which treated 147 NASH patients with OCA for 72 weeks *versus* 142 patients treated with placebo, has recently been conducted. Although the study was suspended prematurely, an interim analysis planned in advance found that more patients in the OCA treatment arm achieved the primary objective of a two-point histological improvement on the NAFLD activity score without worsening of fibrosis (45% *versus* 21%; relative risk: 1.9; 95% CI: 1.3–2.8). Treatment with OCA doubled the likelihood of histological improvement – steatosis, ballooning and inflammation –, as well as improved fibrosis. In terms of its side effects, OCA led to a fall in the HDL/LDL cholesterol ratio and the onset of pruritus in more than 20% of patients. Although these resolved upon withdrawal of the drug, its discontinuation also led to increased transaminase levels. Given that it was a single study, other larger and longer studies are required to confirm its long-term benefits and safety. This is particularly pertinent given that the FLINT study found that OCA improves the NAS more than histological parameters, with a significant non-responder rate, and that its effect is severely curtailed in non-diabetic patients.^{122–125}

No data are available concerning the effect of OCA on cardiovascular risk.

Liraglutide

Incretins, such as glucagon-like peptide 1 (GLP-1), are hormones released by the gastrointestinal tract after meals in response to the activation of the G protein-coupled receptor by bile acids (TGR5). GLP-1 improves insulin sensitivity, promotes fatty acid oxidation and inhibits the release of fibroblast growth factor 21, which is secreted by the liver to regulate the glucose and lipid metabolism.¹²⁶ Secretion of GLP-1 and hepatic GLP-1 receptors falls in NAFLD and NASH patients, while serum activity and the hepatic expression

of dipeptidyl peptidase-4 (DPP-4) increases in NAFLD.¹²⁷ Liraglutide is a GLP-1 receptor agonist indicated for the treatment of type 2 diabetes and obesity. In experimental trials, liraglutide was found to reduce liver fat content and the inflammatory component of steatohepatitis.^{128,129}

In human studies, a meta-analysis of the LEAD programme, which investigated the effect of liraglutide on 4422 diabetic patients administered 1.8 mg/week for 26 weeks, found that this drug improves transaminase levels, liver fat content, as measured by computed axial tomography, and the NAS.¹³⁰ These findings led to the conduct of a prospective, randomised, placebo-controlled study (LEAN)¹³¹ that recruited 52 patients with biopsy-diagnosed NASH, 30% of which were diabetic, who were administered 1.8 mg of liraglutide per week for 48 weeks. The drug achieved significant histological resolution of NASH with reduced steatosis and ballooning (39% in the liraglutide group *versus* 9% in the control group; $p=0.019$). Improved fibrosis was also observed, although this was not statistically significant. A LEAN substudy,¹³² which adopted a sophisticated methodology, demonstrated that liraglutide's action in NAFLD is based on: the reduction of *de novo* hepatic triglyceride synthesis; improved insulin action with reduced adipose tissue lipolysis irrespective of weight loss; reduced adipocytokine levels (leptin, resistin and monocyte chemoattractant protein-1 [MCP1]); increased adiponectin concentrations, which could explain the improvement in NASH and reduced fibrosis due to a reduction in proinflammatory factors; and finally, the fall in hepatic glucose production during fasting and fasting hyperglycaemia by improving insulin sensitivity. Liraglutide's gastrointestinal side effects, particularly nausea, and its subcutaneous route of administration, constitute the drug's main drawbacks.

In terms of its cardiometabolic effects, as well as improving glycaemic control and inducing weight loss, liraglutide may reduce LDL cholesterol and triglyceride concentrations,¹³³ in addition to waist circumference and the percentage of patients with metabolic syndrome.¹³⁴ Although its clinical significance is unknown, it has been reported that liraglutide may increase heart rate.¹³⁵ This is being investigated in the trial entitled Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long-Term Evaluation (LEADER),¹³⁶ which was completed in December 2015 and the results of which are due to be published.

Effect of cardiovascular preventive drugs on non-alcoholic fatty liver disease

This section assesses the few drugs that, as well as having demonstrated reduced cardiovascular risk or CVRF control, exert some beneficial effect on the clinical or histological characteristics of NAFLD.

Lipid-lowering drugs

Statins

HMG-CoA reductase inhibitors play a well-established role in both dyslipidaemia treatment¹³⁶ and cardiovascular disease prevention by reducing total and cardiovascular morbidity and mortality.^{137,138}

Despite potential hepatotoxicity, it has been known for some time that statins pose no hepatic risk to NAFLD patients, even with discretely elevated baseline transaminases.^{139,140}

In terms of hepatic benefits, statins may reduce transaminase and TNF α concentrations in patients with NAFLD, as well as the level of radiologically-determined steatosis.¹⁴¹ They also improve the histological degree of inflammation, but not fibrosis.¹⁴² These effects are irrespective of their lipid-lowering characteristics. Two meta-analyses found no evidence supporting the efficacy of statins in improving "hard" hepatic histological endpoints,^{143,144} although the findings of a recent study suggest that statins may improve NASH and fibrosis.¹⁴⁵ Statins have been shown to reduce the likelihood of developing hepatocellular carcinoma in various observational studies and in two meta-analyses of observational studies.^{146,147} Given that the design of the studies and the origins of the populations are heterogeneous, more specific studies are required to be able to extrapolate these results.

In terms of cardiovascular effects, a *post hoc* analysis of the GREACE study¹⁴⁸ not only showed that statins are safe in subjects with abnormal liver function, presumably due to NAFLD, but also that patients with steatosis who received atorvastatin at a mean dose of 24 mg/day for 3 years experienced a significant reduction in cardiovascular events *versus* those who were not administered the drug (10% *versus* 30%; $p < 0.0001$), as well as a 36% fall in transaminase levels. The study found that statins were more effective in patients with NAFLD than in patients without this condition. Subjects with ischaemic heart disease, suspected NAFLD and elevated ALT levels experienced a 39% fall in cardiovascular events compared to those with normal transaminase levels. Just five patients needed to be treated to identify this benefit. The *post hoc* analysis of a further two studies—Treatment Effect in Metabolic Syndrome Without Perceptible Diabetes (ATTEMPT)¹⁴⁹ and Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL)¹⁵⁰—which administered various doses of atorvastatin in primary and secondary prevention, respectively, demonstrated improved transaminase levels in patients with elevated baseline transaminases. The ATTEMPT study also identified steatosis resolution as determined by ultrasound, while in the IDEAL study, the administration of 80 mg/day of atorvastatin *versus* 20–40 mg/day of simvastatin to patients with elevated ALT, probably caused by NAFLD, significantly reduced the rate of cardiovascular events by 44%. In light of the above, it would appear that moderately abnormal transaminase levels not only improve when higher statin doses are administered, but they could also be a useful marker for identifying subjects at particularly high cardiovascular risk who specifically need aggressive pharmaceutical treatment¹⁵¹.

Fibrates

Fibrates act on the PPAR α , regulating the intrahepatic metabolism of lipids, reducing IR and improving the lipid profile. Despite this, neither clobefibrate nor fenofibrate were found to improve NAFLD-related analytical or histological abnormalities in preliminary studies.¹⁵² However, a prospective randomised study in non-diabetic patients with MetS

and NAFLD, established due to the combination of elevated ALT levels and ultrasonographic evidence, found that 42% of patients treated with fenofibrate and 70% with the combination fenofibrate plus atorvastatin no longer presented these two NAFLD markers at the end of the trial.¹⁵³ A meta-analysis of 145 patients¹³ found that fibrates do not improve transaminase levels, steatosis or histological parameters. However, as shown by two meta-analyses of trials that investigated these drugs,^{154,155} it must be remembered that fibrates reduce cardiovascular morbidity and mortality in patients with atherogenic dyslipidaemia, the most typical lipid abnormality associated with NAFLD, characterised by hypertriglyceridaemia and low HDL cholesterol. Because of its inferior myopathic potential, fenofibrate may be prescribed concomitantly with statins to improve atherogenic dyslipidaemia, especially in patients with metabolic syndrome or type 2 diabetes.^{156,157} Collectively, although it has not been proven that fibrates improve the histology of NAFLD, they are a safe and effective treatment for patients with dyslipidaemia and hepatic steatosis.¹⁵⁸

Ezetimibe

Ezetimibe reduces plasma cholesterol by inhibiting its intestinal absorption by means of the NPC1L1 receptor. It has been shown to reduce cardiovascular morbidity in secondary prevention in combination with statins.¹⁵⁹

In terms of hepatic physiopathology, the presence of free cholesterol influences progression from simple steatosis to NASH. Ezetimibe blocks the NPC1L1 receptor in the liver, thereby improving insulin sensitivity and intrahepatic fat in obese mice.¹⁶⁰ Two in-human studies suggest that ezetimibe leads to an improvement in liver enzymes. Although one did not find relevant ultrasonographic changes,¹⁶¹ the other reported an improvement in inflammatory phenomena.¹⁶² The addition of ezetimibe to a weight-loss diet reduces liver fat content, as determined by magnetic resonance spectroscopy, by 18%.¹⁶³ Data concerning hepatic histology are conflicting. One study¹⁶⁴ that investigated the administration of ezetimibe 10 mg/day for 24 months to 45 patients with biopsy-diagnosed NASH found that IR, the lipid profile, liver damage markers and inflammation all improved. Fibrosis progressed in 9% of patients, was unchanged in 88% and regressed in 3%. Another study administered ezetimibe to 32 patients with NAFLD for 6 months. Cholesterol levels fell, while ballooning and fibrosis improved.¹⁶⁵ Other authors have observed improved fibrosis and ballooning but no improvement in steatosis, inflammation or the NAS.¹⁶⁶

ω 3 polyunsaturated fatty acids

According to several meta-analyses of controlled and randomised trials, omega-3 (ω 3) polyunsaturated fatty acid supplements reduced the risk of fatal coronary heart disease and sudden death by 10% in patients with a history of CVD, although the fall in the risk of sudden death was not significant.¹⁶⁷ As well as sudden death, long-term cardiac mortality and myocardial infarction also appeared to fall with the use of these supplements in secondary prevention patients.¹⁶⁸ Other potential beneficial cardiovascular effects of ω 3 polyunsaturated fatty acids include reduced triglyceridaemia and improved vascular and cardiac haemodynamics, endothelial function, inflammation, thrombosis

and arrhythmia, as well as autonomic control.¹⁶⁹ Its role in primary prevention is less clear.¹⁷⁰ Several studies^{171–174} and a meta-analysis¹⁷⁵ have confirmed that the effect of ω 3 polyunsaturated fatty acids on the liver is clear whether consumed through the diet or as supplements, as they improve transaminase levels and liver fat content in patients with steatosis, albeit with little effect on histological parameters. The AASLD/AGA/ACG guideline¹⁹ finds it premature to recommend ω 3 in NAFLD but advocates their use in patients with steatosis if they have hypertriglyceridaemia. The main dietary ω 3 polyunsaturated fatty acids from fish are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). However, their role in NAFLD treatment as purified agents is far from being well established. DHA seems to reduce liver fat content^{176,177} but does not improve transaminase levels in either the adult or the paediatric population.^{178,179} Data concerning the use of purified EPA also appear to be contradictory, with one study finding that it improves steatosis, inflammation and fibrosis,¹⁸⁰ while another study found no beneficial effect from its administration in steatohepatitis.¹⁸¹

Antidiabetic drugs

Metformin

This biguanide has proven to be effective both in treating diabetes and in slowing the development of carbohydrate intolerance.¹⁸² The UKPDS 34 study also found that it reduced total mortality by 36%.¹⁸³ Metformin may also exert a cardioprotective effect by reducing arterial stiffness and improving endothelial function markers.^{184,185}

Numerous studies conducted in patients with biopsy-diagnosed NAFLD initially asserted that the administration of metformin is associated with reduced transaminase levels and liver volume, as determined by ultrasound, as well as improved fatty infiltration and necroinflammatory phenomena.^{186,187} However, both the largest randomised trial conducted in children (TONIC¹⁰⁰), as well as two systematic reviews^{188,189} concluded that, irrespective of the dose or the presence of diabetes, metformin does not improve transaminase levels or liver histology any more than lifestyle change, although transaminase levels did fall in the review by Li et al.¹⁸⁹ On this basis, the AASLD/AGA/ACG guideline does not recommend metformin as a specific treatment for NAFLD or NASH, although it can be administered to diabetic patients with these liver diseases.¹⁹ In this regard, two separate meta-analyses found that metformin administered to diabetic patients was associated with a 62% fall in the risk of developing liver cancer¹⁹⁰ and that it improves survival in diabetic patients with cirrhosis.¹⁹¹ In fact, in the cirrhosis phase of diabetic patients with NAFLD, metformin reduces total mortality by 53% without causing lactic acidosis.¹⁹²

Dipeptidyl peptidase-4 inhibitors

According to a meta-analysis of small controlled and randomised trials, DPP-4 inhibitors do not appear to reduce the risk of cardiovascular events, but have also not been associated with a greater risk of their onset.¹⁹³ The administration of saxagliptin may increase hospital admissions due to heart failure.¹⁹⁴

DPP-4 activity has been found to increase by 30% in NASH,¹⁹⁵ with a correlation between this activity and the degree of steatohepatitis, thereby providing a rational basis for its clinical application. However, experience with these drugs is limited and broader studies need to be conducted. Even so, a small 4-month study in patients with NAFLD found that sitagliptin improved ALT levels, steatosis as determined by resonance, ballooning and the NAS.¹⁹⁶ A meta-analysis of two studies and very few patients showed that sitagliptin reduced transaminase levels.¹⁹⁷ In similar vein, linagliptin has been shown to improve insulin sensitivity and steatosis in obese patients.¹⁹⁸

Antihypertensive drugs

Angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers (ARBs) are important modulators of the renin-angiotensin-aldosterone system used to treat hypertension and proteinuria. They have been widely proven to reduce cardiovascular mortality, myocardial infarction and stroke and to improve clinical outcomes in chronic heart failure.¹⁹⁹ They also increase insulin sensitivity,²⁰⁰ which enhances their cardioprotective effect by reducing the likelihood of developing diabetes, as highlighted by two meta-analyses.^{201,202}

ARBs

In initial trials, ARBs appeared to reduce hepatic fibrosis.²⁰³ Later, a small study of seven patients found that losartan improved steatosis, inflammation and necrosis. However, a 12-month, open-label, randomised study found that losartan combined with rosiglitazone did not improve liver histological parameters.⁹¹ A small trial on 54 hypertensive patients with biopsy-diagnosed NASH compared the effect of telmisartan with valsartan after 20 months of treatment. The results for both drugs were similar, but plasma lipids, insulin sensitivity, hepatic steatosis, necroinflammation and fibrosis improved to a greater extent in the telmisartan group.²⁰⁴ Another study conducted in patients being treated with simvastatin concluded that losartan was superior to amlodipine in improving hepatic steatosis indices.²⁰⁵ Based on the above evidence, it is difficult to assess the actual efficacy of ARBs in treating NAFLD and NASH. Nevertheless, they are recommended by the latest guidelines issued by the Japanese Society of Gastroenterology for patients with steatosis and hypertension.²⁰⁶

Effect of improved non-alcoholic fatty liver disease on vascular risk

To date, it has not been shown that improved NAFLD severity improves associated cardiovascular risk. A pre-specified sub-study of the WELCOME trial¹⁷⁷ was the first to demonstrate that an improvement in NAFLD severity reduces carotid IMT, an indirect marker of CVD. This study, which administered 4g/day of a combination of DHA and EPA for 18 months, found that improved NAFLD severity, defined as a lower percentage of liver fat, as determined by magnetic resonance spectroscopy, and necroinflammation determined by cytokeratin 18 (CK-18), a highly sensitive and specific serum marker of hepatocyte apoptosis in NASH diagnosis, was

associated with slower IMT progression. ω 3 administration had no influence on IMT, although DHA tissue concentration was associated with a lower percentage of liver fat. Further studies must be conducted to ascertain whether an improvement in NAFLD severity has any cardiovascular benefit.

Conclusion

This review has assessed aspects of lifestyle and pharmacological treatments that may improve some of the phases of NAFLD. Despite the availability of five active substances that may offer some histological improvement, none is backed by sufficient clinical evidence to advocate its use in all patients with NAFLD. Numerous drugs are currently being trialled for potential use in NAFLD. For the time being, weight loss and exercise are the most appropriate and cost-effective strategies for this highly prevalent and far-reaching condition.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

Confidentiality of data. The authors declare that no patient data appears in this article.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

- Brea A, Pintó X, Ascaso J, Blasco M, Díaz A, González-Santos P, et al. Enfermedad del hígado graso no alcohólico, asociación con la enfermedad cardiovascular y tratamiento (I). Enfermedad del hígado graso no alcohólico y su asociación con la enfermedad cardiovascular. *Clin Invest Arterioscler*. 2016.
- Ueno T, Sugawara H, Sujaku K, Hashimoto O, Tsuji R, Tamaki S, et al. Therapeutic effects of restricted diet and exercise in obese patients with fatty liver. *J Hepatol*. 1997;27:103–7.
- Hickman IJ, Jonsson JR, Prins JB, Ash S, Purdie DM, Clouston AD, et al. Modest weight loss and physical activity in overweight patients with chronic liver disease results in sustained improvements in alanine aminotransferase, fasting insulin, and quality of life. *Gut*. 2004;53:413–9.
- Suzuki A, Lindor K, St Saver J, Lymp J, Mendes F, Muto A, et al. Effect of changes on body weight and lifestyle in nonalcoholic fatty liver disease. *J Hepatol*. 2005;43:1060–6.
- Huang MA, Greenon JK, Chao C, Anderson L, Peterman D, Jacobson J, et al. One-year intense nutritional counseling results in histological improvement in patients with non-alcoholic steatohepatitis: a pilot study. *Am J Gastroenterol*. 2005;100:1072–81.
- Lewis MC, Phillips ML, Slavotinek JP, Kow L, Thompson CH, Toouli J. Change in liver size and fat content after treatment with Optifast very low calorie diet. *Obes Surg*. 2006;16:697–701.
- Larson-Meyer DE, Newcomer BR, Heilbronn LK, Volaufova J, Smith SR, Alfonso AJ, et al. Effect of 6-month calorie restriction and exercise on serum and liver lipids and markers of liver function. *Obesity (Silver Spring)*. 2008;16:1355–62.
- 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;56:255–66.
- Shah K, Stufflebam A, Hilton TN, Sinacore DR, Klein S, Villareal DT. Diet and exercise interventions reduce intrahepatic fat content and improve insulin sensitivity in obese older adults. *Obesity (Silver Spring)*. 2009;17:2162–8.
- Kleiner DE, Brunt EM, van Natta M, Behling C, Contos MJ, Cummings OW, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology*. 2005;41:1313–21.
- 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;51:121–9.
- Tendler D, Lin S, Yancy WS, Mavropoulos J, Sylvestre P, Rockey DC, et al. The effect of a low-carbohydrate, ketogenic diet on nonalcoholic fatty liver disease: a pilot study. *Dig Dis Sci*. 2007;52:589–93.
- Musso G, Cassader M, Rosina F, Gambino R. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. *Diabetologia*. 2012;55:885–904.
- Douketis JD, Macie C, Thabane L, Williamson DF. Systematic review of long-term weight loss studies in obese adults: clinical significance and applicability to clinical practice. *Int J Obes (Lond)*. 2005;29:1153–67.
- Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight loss via lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. *Gastroenterology*. 2015;149:367–78.
- Glass LM, Dickson RC, Anderson JC, Suriawinata AA, Putra J, Berk BS, et al. Total body weight loss of $\geq 10\%$ is associated with improved hepatic fibrosis in patients with nonalcoholic steatohepatitis. *Dig Dis Sci*. 2015;60:1024–30.
- Shen J, Wong GL, Chan HL, Chan RS, Chan HY, Chu WC, et al. PNPLA3 gene polymorphism and response to lifestyle modification in patients with nonalcoholic fatty liver disease. *J Gastroenterol Hepatol*. 2015;30:139–46.
- Arab JP, Candia R, Zapata R, Muñoz C, Arancibia JP, Ponichik J, et al. Management of nonalcoholic fatty liver disease: an evidence-based clinical practice review. *World J Gastroenterol*. 2014;20:12182–201.
- 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;55:2005–23.
- Pack QR, Rodríguez-Escudero JP, Thomas RJ, Ades PA, West CP, Somers VK, et al. The prognostic importance of weight loss in coronary artery disease: a systematic review and meta-analysis. *Mayo Clin Proc*. 2014;89:1368–77.
- Westerbacka J, Lammi K, Häkkinen AM, Rissanen A, Salminen I, Aro A, et al. Dietary fat content modifies liver fat in overweight nondiabetic subjects. *J Clin Endocrinol Metab*. 2005;90:2804–9.
- Nseir W, Hellou E, Assy N. Role of diet and lifestyle changes in nonalcoholic fatty liver disease. *World J Gastroenterol*. 2014;20:9338–44.
- Conlon BA, Beasley JM, Aebersold K, Jhangiani SS, Wylie-Rosett J. Nutritional management of insulin resistance in nonalcoholic fatty liver disease (NAFLD). *Nutrients*. 2013;5:4093–114.

24. Kastorini CM, Milionis HJ, Esposito K, Giugliano D, Goudevenos JA, Panagiotakos DB. The effect of Mediterranean diet on metabolic syndrome and its components: a meta-analysis of 50 studies and 534,906 individuals. *J Am Coll Cardiol*. 2011;57:1299–313.
25. Kontogianni MD, Tileli N, Margariti A, Georgoulis M, Deutsch M, Tiniakos D, et al. Adherence to the Mediterranean diet is associated with the severity of non-alcoholic fatty liver disease. *Clin Nutr*. 2014;33:678–83.
26. 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;59:138–43.
27. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med*. 2013;368:1279–90.
28. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation*. 1999;99:779–85.
29. Martinez-Gonzalez MA, Bes-Rastrollo M. Dietary patterns, Mediterranean diet, and cardiovascular disease. *Curr Opin Lipidol*. 2014;25:20–6.
30. Chiu S, Sievenpiper JL, de Souza RJ, Cozma AI, Mirrahimi A, Carleton AJ, et al. Effect of fructose on markers of non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of controlled feeding trials. *Eur J Clin Nutr*. 2014;68:416–23.
31. Dunn W, Xu R, Schwimmer JB. Modest wine drinking and decreased prevalence of suspected nonalcoholic fatty liver disease. *Hepatology*. 2008;47:1947–54.
32. Moriya A, Iwasaki Y, Ohguchi S, Kayashima E, Mitsumune T, Taniguchi H, et al. Alcohol consumption appears to protect against non-alcoholic fatty liver disease. *Aliment Pharmacol Ther*. 2011;33:378–88.
33. Ekstedt M, Franzén LE, Holmqvist M, Bendtsen P, Mathiesen UL, Bodemar G, et al. Alcohol consumption is associated with progression of hepatic fibrosis in non-alcoholic fatty liver disease. *Scand J Gastroenterol*. 2009;44:366–74.
34. Seitz HK, Mueller S, Hellerbrand C, Liangpunsakul S. Effect of chronic alcohol consumption on the development and progression of non-alcoholic fatty liver disease (NAFLD). *Hepatobiliary Surg Nutr*. 2015;4:147–51.
35. Hashimoto Y, Hamaguchi M, Kojima T, Ohshima Y, Ohbora A, Kato T, et al. Modest alcohol consumption reduces the incidence of fatty liver in men: a population-based large-scale cohort study. *J Gastroenterol Hepatol*. 2015;30:546–52.
36. Sinn DH, Gwak GY, Cho J, Son HJ, Paik YH, Choi MS, et al. Modest alcohol consumption and carotid plaques or carotid artery stenosis in men with non-alcoholic fatty liver disease. *Atherosclerosis*. 2014;234:270–5.
37. Sookoian S, Castaño GO, Pirola CJ. Modest alcohol consumption decreases the risk of non-alcoholic fatty liver disease: a meta-analysis of 43 175 individuals. *Gut*. 2014;63:530–2.
38. Loomba R, Yang HI, Su J, Brenner D, Ilseje U, Chen CJ. Obesity and alcohol synergize to increase the risk of incident hepatocellular carcinoma in men. *Clin Gastroenterol Hepatol*. 2010;8:891–8, 898.e1–2.
39. Hart CL, Morrison DS, Batty GD, Mitchell RJ, Davey Smith G. Effect of body mass index and alcohol consumption on liver disease: analysis of data from two prospective cohort studies. *BMJ*. 2010;340:c1240.
40. Loomba R, Yang HI, Su J, Brenner D, Barrett-Connor E, Ilseje U, et al. Synergism between obesity and alcohol in increasing the risk of hepatocellular carcinoma: a prospective cohort study. *Am J Epidemiol*. 2013;177:333–42.
41. Ronksley PE, Brien SE, Turner BJ, Mukamal KJ, Ghali WA. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. *BMJ*. 2011;342:d671.
42. Johnson NA, George J. Fitness versus fatness: moving beyond weight loss in nonalcoholic fatty liver disease. *Hepatology*. 2010;52:370–81.
43. Gerber L, Otgonsuren M, Mishra A, Escheik C, Bircerdinc A, Stepanova M, et al. Non-alcoholic fatty liver disease (NAFLD) is associated with low level of physical activity: a population-based study. *Aliment Pharmacol Ther*. 2012;36:772–81.
44. Bae JC, Suh S, Park SE, Rhee EJ, Park CY, Oh KW, et al. Regular exercise is associated with a reduction in the risk of NAFLD and decreased liver enzymes in individuals with NAFLD independent of obesity in Korean adults. *PLoS ONE*. 2012;7:e46819.
45. Kwak MS, Kim D, Chung GE, Kim W, Kim YJ, Yoon JH. Role of physical activity in nonalcoholic fatty liver disease in terms of visceral obesity and insulin resistance. *Liver Int*. 2015;35:944–52.
46. Oni ET, Kalathiya R, Aneni EC, Martin SS, Blaha MJ, Feldman T, et al. Relation of physical activity to prevalence of nonalcoholic fatty liver disease independent of cardiometabolic risk. *Am J Cardiol*. 2015;115:34–9.
47. Zelber-Sagi S, Nitzan-Kaluski D, Goldsmith R, Webb M, Zivbel I, Goldiner I, et al. Role of leisure-time physical activity in nonalcoholic fatty liver disease: a population-based study. *Hepatology*. 2008;48:1791–8.
48. Trenell MI. Sedentary behaviour, physical activity, and NAFLD: curse of the chair. *J Hepatol*. 2015;63:1064–5.
49. Helajärvi H, Pakkala K, Heinonen OJ, Juonala M, Oikonen M, Tammelin T, et al. Television viewing and fatty liver in early midlife. The Cardiovascular Risk in Young Finns Study. *Ann. Med*. 2015:1–8.
50. Johnson NA, Sachinwalla T, Walton DW, Smith K, Armstrong A, Thompson MW, et al. Aerobic exercise training reduces hepatic and visceral lipids in obese individuals without weight loss. *Hepatology*. 2009;50:1105–12.
51. 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;55:1738–45.
52. St George A, Bauman A, Johnston A, Farrell G, Chey T, George J. Independent effects of physical activity in patients with nonalcoholic fatty liver disease. *Hepatology*. 2009;50:68–76.
53. Keating SE, Hackett DA, George J, Johnson NA. Exercise and non-alcoholic fatty liver disease: a systematic review and meta-analysis. *J Hepatol*. 2012;57:157–66.
54. Keating SE, Hackett DA, Parker HM, O'Connor HT, Gerofi JA, Sainsbury A, et al. Effect of aerobic exercise training dose on liver fat and visceral adiposity. *J Hepatol*. 2015;63:174–82.
55. Kistler KD, Brunt EM, Clark JM, Diehl AM, Sallis JF, Schwimmer JB, et al. Physical activity recommendations, exercise intensity, and histological severity of nonalcoholic fatty liver disease. *Am J Gastroenterol*. 2011;106:460–8, quiz 9.
56. 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;60:1278–83.
57. Zelber-Sagi S, Buch A, Yeshua H, Vaisman N, Webb M, Harari G, et al. Effect of resistance training on non-alcoholic fatty-liver disease: a randomized-clinical trial. *World J Gastroenterol*. 2014;20:4382–92.
58. 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 non-alcoholic fatty liver disease (the RAED2 Randomized Trial). *Hepatology*. 2013;58:1287–95.

59. Montesi L, Caselli C, Centis E, Nuccitelli C, Moscatello S, Supini A, et al. Physical activity support or weight loss counseling for nonalcoholic fatty liver disease? *World J. Gastroenterol.* 2014;20:10128–36.
60. Gerber LH, Weinstein A, Pawloski L. Role of exercise in optimizing the functional status of patients with nonalcoholic fatty liver disease. *Clin Liver Dis.* 2014;18:113–27.
61. Keating SE, George J, Johnson NA. The benefits of exercise for patients with non-alcoholic fatty liver disease. *Expert Rev Gastroenterol Hepatol.* 2015;9:1247–50.
62. Guo R, Liong EC, So KF, Fung ML, Tipoe GL. Beneficial mechanisms of aerobic exercise on hepatic lipid metabolism in non-alcoholic fatty liver disease. *Hepatobiliary Pancreat Dis Int.* 2015;14:139–44.
63. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al., American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc.* 2011;43:1334–59.
64. Pugh CJ, Cuthbertson DJ, Sprung VS, Kemp GJ, Richardson P, Umpleby AM, et al. Exercise training improves cutaneous microvascular function in nonalcoholic fatty liver disease. *Am J Physiol Endocrinol Metab.* 2013;305:E50–8.
65. Shiroma EJ, Lee IM. Physical activity and cardiovascular health: lessons learned from epidemiological studies across age, gender, and race/ethnicity. *Circulation.* 2010;122:743–52.
66. Sattelmair J, Pertman J, Ding EL, Kohl HW, Haskell W, Lee IM. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. *Circulation.* 2011;124:789–95.
67. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA.* 2009;301:2024–35.
68. Patel AV, Bernstein L, Deka A, Feigelson HS, Campbell PT, Gapstur SM, et al. Leisure time spent sitting in relation to total mortality in a prospective cohort of US adults. *Am J Epidemiol.* 2010;172:419–29.
69. Benaiges D, Goday A, Pedro-Botet J, Más A, Chillarón JJ, Flores-le Roux JA. Bariatric surgery: to whom and when? *Minerva Endocrinol.* 2015;40:119–28.
70. Verna EC, Berk PD. Role of fatty acids in the pathogenesis of obesity and fatty liver: impact of bariatric surgery. *Semin Liver Dis.* 2008;28:407–26.
71. Andersen T, Gluud C, Franzmann MB, Christoffersen P. Hepatic effects of dietary weight loss in morbidly obese subjects. *J Hepatol.* 1991;12:224–9.
72. Mummadi RR, Kasturi KS, Chennareddygar S, Sood GK. Effect of bariatric surgery on nonalcoholic fatty liver disease: systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2008;6:1396–402.
73. 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 Database Syst Rev.* 2010;CD007340.
74. Bower G, Toma T, Harling L, Jiao LR, Efthimiou E, Darzi A, et al. Bariatric surgery and non-alcoholic fatty liver disease: a systematic review of liver biochemistry and histology. *Obes Surg.* 2015;25:2280–9.
75. Caiazzo R, Lassailly G, Leteurtre E, Baud G, Verkindt H, Raverdy V, et al. Roux-en-Y gastric bypass versus adjustable gastric banding to reduce nonalcoholic fatty liver disease: a 5-year controlled longitudinal study. *Ann Surg.* 2014;260:893–9.
76. 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;137:532–40.
77. Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ, et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med.* 2009;122:248–56.e5.
78. Puzifferri N, Roshek TB, Mayo HG, Gallagher R, Belle SH, Livingston EH. Long-term follow-up after bariatric surgery: a systematic review. *JAMA.* 2014;312:934–42.
79. Julve J, Pardina E, Pérez-Cuellar M, Ferrer R, Rossell J, Baena-Fustegueras JA, et al. Bariatric surgery in morbidly obese patients improves the atherogenic qualitative properties of the plasma lipoproteins. *Atherosclerosis.* 2014;234:200–5.
80. Tailleux A, Rouskas K, Pattou F, Staels B. Bariatric surgery, lipoprotein metabolism and cardiovascular risk. *Curr Opin Lipidol.* 2015;26:317–24.
81. Vest AR, Heneghan HM, Agarwal S, Schauer PR, Young JB. Bariatric surgery and cardiovascular outcomes: a systematic review. *Heart.* 2012;98:1763–77.
82. Kwok CS, Pradhan A, Khan MA, Anderson SG, Keavney BD, Myint PK, et al. Bariatric surgery and its impact on cardiovascular disease and mortality: a systematic review and meta-analysis. *Int J Cardiol.* 2014;173:20–8.
83. Guidry CA, Davies SW, Sawyer RG, Schirmer BD, Hallowell PT. Gastric bypass improves survival compared with propensity-matched controls: a cohort study with over 10-year follow-up. *Am J Surg.* 2015;209:463–7.
84. Neuschwander-Tetri BA, Brunt EM, Wehmeier KR, Oliver D, Bacon BR. Improved nonalcoholic steatohepatitis after 48 weeks of treatment with the PPAR-gamma ligand rosiglitazone. *Hepatology.* 2003;38:1008–17.
85. 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;355:2297–307.
86. 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;135:1176–84.
87. Ratzliff V, Giral P, Jacqueminet S, Charlotte F, Hartemann-Heurtier A, Serfaty L, et al. Rosiglitazone for nonalcoholic steatohepatitis: one-year results of the randomized placebo-controlled Fatty Liver Improvement with Rosiglitazone Therapy (FLIRT) Trial. *Gastroenterology.* 2008;135:100–10.
88. Ratzliff V, Charlotte F, Bernhardt C, Giral P, Halbron M, Lenaour G, et al. Long-term efficacy of rosiglitazone in nonalcoholic steatohepatitis: results of the fatty liver improvement by rosiglitazone therapy (FLIRT 2) extension trial. *Hepatology.* 2010;51:445–53.
89. 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.
90. Mahady SE, Wong G, Craig JC, George J. Pioglitazone and vitamin E for nonalcoholic steatohepatitis: a cost utility analysis. *Hepatology.* 2012;56:2172–9.
91. Torres DM, Jones FJ, Shaw JC, Williams CD, Ward JA, Harrison SA. Rosiglitazone versus rosiglitazone and metformin versus rosiglitazone and losartan in the treatment of nonalcoholic steatohepatitis in humans: a 12-month randomized, prospective, open-label trial. *Hepatology.* 2011;54:1631–9.
92. Mazzone T, Meyer PM, Feinstein SB, Davidson MH, Kondos GT, d'Agostino RB, et al. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. *JAMA.* 2006;296:2572–81.
93. Nissen SE, Nicholls SJ, Wolski K, Nesto R, Kupfer S, Perez A, et al. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2

- diabetes: the PERISCOPE randomized controlled trial. *JAMA*. 2008;299:1561–73.
94. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet*. 2005;366:1279–89.
 95. Erdmann E, Dormandy JA, Charbonnel B, Massi-Benedetti M, Moules IK, Skene AM, et al. The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction: results from the PROactive (PROactive 05) Study. *J Am Coll Cardiol*. 2007;49:1772–80.
 96. Wilcox R, Bousser MG, Betteridge DJ, Scherthaner G, Pirags V, Kupfer S, et al. Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). *Stroke*. 2007;38:865–73.
 97. 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;298:1180–8.
 98. Erdmann E, Song E, Spanheimer R, van Troostenburg de Bruyn AR, Perez A. Observational follow-up of the PROactive study: a 6-year update. *Diabetes Obes Metab*. 2014;16:63–74.
 99. 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;362:1675–85.
 100. 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;305:1659–68.
 101. Miller ER, 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.
 102. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. *JAMA*. 2007;297:842–57.
 103. Schürks 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.
 104. Klein EA, Thompson IM, Tangen CM, Crowley JJ, Lucia MS, Goodman PJ, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA*. 2011;306:1549–56.
 105. Sato K, Goshima M, Yamamoto T, Kobayashi Y, Ishii N, Ohashi T, et al. Vitamin E has a beneficial effect on nonalcoholic fatty liver disease: a meta-analysis of randomized controlled trials. *Nutrition*. 2015;31:923–30.
 106. Xu R, Tao A, Zhang S, Deng Y, Chen G. Association between vitamin E and non-alcoholic steatohepatitis: a meta-analysis. *Int J Clin Exp Med*. 2015;8:3924–34.
 107. Ye Y, Li J, Yuan Z. Effect of antioxidant vitamin supplementation on cardiovascular outcomes: a meta-analysis of randomized controlled trials. *PLoS One*. 2013;8:e56803.
 108. Fortmann SP, Whitlock EP, Burda BU. Vitamin and mineral supplements in the primary prevention of cardiovascular disease and cancer. *Ann Intern Med*. 2014;160:656.
 109. Préaux AM, Mallat A, Rosenbaum J, Zafrani ES, Mavrier P. Pentoxifylline inhibits growth and collagen synthesis of cultured human hepatic myofibroblast-like cells. *Hepatology*. 1997;26:315–22.
 110. Raetsch C, Jia JD, Boigk G, Bauer M, Hahn EG, Riecken EO, et al. Pentoxifylline downregulates profibrogenic cytokines and procollagen I expression in rat secondary biliary fibrosis. *Gut*. 2002;50:241–7.
 111. Du J, Ma YY, Yu CH, Li YM. Effects of pentoxifylline on nonalcoholic fatty liver disease: a meta-analysis. *World J Gastroenterol*. 2014;20:569–77.
 112. Zeng T, Zhang CL, Zhao XL, Xie QK. Pentoxifylline for the treatment of nonalcoholic fatty liver disease: a meta-analysis of randomized double-blind, placebo-controlled studies. *Eur J Gastroenterol Hepatol*. 2014;26:646–53.
 113. Champion S, Lapidus N, Cherié G, Spagnoli V, Oliary J, Solal AC. Pentoxifylline in heart failure: a meta-analysis of clinical trials. *Cardiovasc Ther*. 2014;32:159–62.
 114. Salhiyyah K, Forster R, Senanayake E, Abdel-Hadi M, Booth A, Michaels JA. Pentoxifylline for intermittent claudication. *Cochrane Database Syst Rev*. 2015;9:CD005262.
 115. Ma K, Saha PK, Chan L, Moore DD. Farnesoid X receptor is essential for normal glucose homeostasis. *J Clin Invest*. 2006;116:1102–9.
 116. Zhang Y, Lee FY, Barrera G, Lee H, Vales C, Gonzalez FJ, et al. Activation of the nuclear receptor FXR improves hyperglycemia and hyperlipidemia in diabetic mice. *Proc Natl Acad Sci U S A*. 2006;103:1006–11.
 117. Lambert G, Amar MJ, Guo G, Brewer HB, Gonzalez FJ, Sinal CJ. The farnesoid X-receptor is an essential regulator of cholesterol homeostasis. *J Biol Chem*. 2003;278:2563–70.
 118. Wu W, Liu X, Peng X, Xue R, Ji L, Shen X, et al. Bile acids override steatosis in farnesoid X receptor deficient mice in a model of non-alcoholic steatohepatitis. *Biochem Biophys Res Commun*. 2014;448:50–5.
 119. Wang YD, Chen WD, Wang M, Yu D, Forman BM, Huang W. Farnesoid X receptor antagonizes nuclear factor kappaB in hepatic inflammatory response. *Hepatology*. 2008;48:1632–43.
 120. 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;145:574–82.e1.
 121. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, Lavine JE, van Natta ML, Abdelmalek MF, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. *Lancet*. 2015;385:956–65.
 122. Ratz V. Starting the battle to control non-alcoholic steatohepatitis. *Lancet*. 2015;385:922–4.
 123. Musso G, Cassader M, Gambino R. Trials of obeticholic acid for non-alcoholic steatohepatitis. *Lancet*. 2015;386:27.
 124. Wong VW, Wong GL, Chan FK. Is obeticholic acid the solution to nonalcoholic steatohepatitis? *Gastroenterology*. 2015;148:851–2.
 125. Musso G. Obeticholic acid and resveratrol in nonalcoholic fatty liver disease: all that is gold does not glitter, not all those who wander are lost. *Hepatology*. 2015;61:2104–6.
 126. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology*. 2007;132:2131–57.
 127. Bernsmeier C, Meyer-Gerspach AC, Blaser LS, Jeker L, Steinert RE, Heim MH, et al. Glucose-induced glucagon-like peptide 1 secretion is deficient in patients with non-alcoholic fatty liver disease. *PLoS One*. 2014;9:e87488.
 128. Sharma S, Mells JE, Fu PP, Saxena NK, Anania FA. GLP-1 analogs reduce hepatocyte steatosis and improve survival by enhancing the unfolded protein response and promoting macroautophagy. *PLoS ONE*. 2011;6:e25269.
 129. Trevaskis JL, Griffin PS, Wittmer C, Neuschwander-Tetri BA, Brunt EM, Dolman CS, et al. Glucagon-like peptide-1 receptor agonism improves metabolic, biochemical, and histopathological indices of nonalcoholic steatohepatitis in mice. *Am J Physiol Gastrointest Liver Physiol*. 2012;302:G762–72.

130. Armstrong MJ, Houlihan DD, Rowe IA, Clausen WH, Elbrønd 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;37:234–42.
131. Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet.* 2016;387:679–90.
132. Armstrong MJ, Hull D, Guo K, Barton D, Hazlehurst JM, Gathercole LL, et al. Glucagon-like peptide 1 decreases lipotoxicity in non-alcoholic steatohepatitis. *J Hepatol.* 2016;64:399–408.
133. Astrup A, Carraro A, Finer N, Harper A, Kunesova M, Lean ME, et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. *Int J Obes (Lond).* 2012;36:843–54.
134. Wadden TA, Hollander P, Klein S, Niswender K, Woo V, Hale PM, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. *Int J Obes (Lond).* 2013;37:1443–51.
135. Marso SP, Poulter NR, Nissen SE, Nauck MA, Zinman B, Daniels GH, et al. Design of the liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results (LEADER) trial. *Am Heart J.* 2013;166:823–30.e5.
136. Reiner Z, Catapano AL, de Backer G, Graham I, Taskinen MR, Wiklund O, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J.* 2011;32:1769–818.
137. 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;366:1267–78.
138. Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, Mihaylova B, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet.* 2015;385:1397–405.
139. Chalasani N, Aljadhey H, Kesterson J, Murray MD, Hall SD. Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity. *Gastroenterology.* 2004;126:1287–92.
140. Cohen DE, Anania FA, Chalasani N, Panel NLASSTFLE. An assessment of statin safety by hepatologists. *Am J Cardiol.* 2006;97:77C–81C.
141. Foster T, Budoff MJ, Saab S, Ahmadi N, Gordon C, Guerri AD. Atorvastatin and antioxidants for the treatment of nonalcoholic fatty liver disease: the St Francis Heart Study randomized clinical trial. *Am J Gastroenterol.* 2011;106:71–7.
142. Ekstedt M, Franzén LE, Mathiesen UL, Holmqvist M, Bodemar G, Kechagias S. Statins in non-alcoholic fatty liver disease and chronically elevated liver enzymes: a histopathological follow-up study. *J Hepatol.* 2007;47:135–41.
143. Younossi ZM, Reyes MJ, Mishra A, Mehta R, Henry L. Systematic review with meta-analysis: non-alcoholic steatohepatitis – a case for personalised treatment based on pathogenic targets. *Aliment Pharmacol Ther.* 2014;39:3–14.
144. Musso G, Gambino R, Cassader M, Pagano G. A meta-analysis of randomized trials for the treatment of nonalcoholic fatty liver disease. *Hepatology.* 2010;52:79–104.
145. Dongiovanni P, Petta S, Mannisto V, Mancina RM, Pipitone R, Karja V, et al. Statin use and non-alcoholic steatohepatitis in at risk individuals. *J Hepatol.* 2015;63:705–12.
146. 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;144:323–32.
147. Pradelli D, Soranna D, Scotti L, Zamboni A, Catapano A, Mancina G, et al. Statins and primary liver cancer: a meta-analysis of observational studies. *Eur J Cancer Prev.* 2013;22:229–34.
148. 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;376:1916–22.
149. Athyros VG, Gioulema O, Ganotakis ES, Elisaf M, Tziomalos K, Vassiliadis T, et al. Safety and impact on cardiovascular events of long-term multifactorial treatment in patients with metabolic syndrome and abnormal liver function tests: a post hoc analysis of the randomised ATTEMPT study. *Arch Med Sci.* 2011;7:796–805.
150. Tikkanen MJ, Fayyad R, Faergeman O, Olsson AG, Wu CC, Laskey R, et al. Effect of intensive lipid lowering with atorvastatin on cardiovascular outcomes in coronary heart disease patients with mild-to-moderate baseline elevations in alanine aminotransferase levels. *Int J Cardiol.* 2013;168:3846–52.
151. Lonnard A, Ballestri S, Targher G, Loria P. Diagnosis and management of cardiovascular risk in nonalcoholic fatty liver disease. *Expert Rev Gastroenterol Hepatol.* 2015;9:629–50.
152. Fernández-Miranda C, Pérez-Carreras M, Colina F, López-Alonso G, Vargas C, Solís-Herruzo JA. A pilot trial of fenofibrate for the treatment of non-alcoholic fatty liver disease. *Dig Liver Dis.* 2008;40:200–5.
153. Athyros VG, Mikhailidis DP, Didangelos TP, Gioulema OI, Liberopoulos EN, Karagiannis A, et al. Effect of multifactorial treatment on non-alcoholic fatty liver disease in metabolic syndrome: a randomised study. *Curr Med Res Opin.* 2006;22:873–83.
154. Sacks FM, Carey VJ, Fruchart JC. Combination lipid therapy in type 2 diabetes. *N Engl J Med.* 2010;363:692–4.
155. Lee M, Saver JL, Towfighi A, Chow J, Ovbiagele B. Efficacy of fibrates for cardiovascular risk reduction in persons with atherogenic dyslipidemia: a meta-analysis. *Atherosclerosis.* 2011;217:492–8.
156. Catapano AL, Reiner Z, de Backer G, Graham I, Taskinen MR, Wiklund O, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Atherosclerosis.* 2011;217 Suppl. 1:S1–44.
157. Millán Núñez-Cortés J, Pedro-Botet J, Brea-Hernando A, Díaz-Rodríguez A, González-Santos P, Hernández-Mijares A, et al. Use of expert consensus to improve atherogenic dyslipidemia management. *Rev Esp Cardiol (Engl Ed).* 2014;67:36–44.
158. Brea A, Puzo J. Non-alcoholic fatty liver disease and cardiovascular risk. *Int J Cardiol.* 2013;167:1109–17.
159. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med.* 2015;372:2387–97.
160. Ushio M, Nishio Y, Sekine O, Nagai Y, Maeno Y, Ugi S, et al. Ezetimibe prevents hepatic steatosis induced by a high-fat but not a high-fructose diet. *Am J Physiol Endocrinol Metab.* 2013;305:E293–304.
161. Enjoji M, Machida K, Kohjima M, Kato M, Kotoh K, Matsunaga K, et al. NPC1L1 inhibitor ezetimibe is a reliable therapeutic agent for non-obese patients with nonalcoholic fatty liver disease. *Lipids Health Dis.* 2010;9:29.
162. Yoneda M, Fujita K, Nozaki Y, Endo H, Takahashi H, Hosono K, et al. Efficacy of ezetimibe for the treatment of non-alcoholic steatohepatitis: an open-label, pilot study. *Hepatol Res.* 2010;40:566–73.

163. Chan DC, Watts GF, Gan SK, Ooi EM, Barrett PH. Effect of ezetimibe on hepatic fat, inflammatory markers, and apolipoprotein B-100 kinetics in insulin-resistant obese subjects on a weight loss diet. *Diabetes Care*. 2010;33:1134–9.
164. Park H, Shima T, Yamaguchi K, Mitsuyoshi H, Minami M, Yasui K, et al. Efficacy of long-term ezetimibe therapy in patients with nonalcoholic fatty liver disease. *J Gastroenterol*. 2011;46:101–7.
165. Takeshita Y, Takamura T, Honda M, Kita Y, Zen Y, Kato K, et al. The effects of ezetimibe on non-alcoholic fatty liver disease and glucose metabolism: a randomised controlled trial. *Diabetologia*. 2014;57:878–90.
166. Musso G. Ezetimibe in the balance: can cholesterol-lowering drugs alone be an effective therapy for NAFLD? *Diabetologia*. 2014;57:850–5.
167. Kromhout D, de Goede J. Update on cardiometabolic health effects of ω -3 fatty acids. *Curr Opin Lipidol*. 2014;25:85–90.
168. Casula M, Soranna D, Catapano AL, Corrao G. Long-term effect of high dose omega-3 fatty acid supplementation for secondary prevention of cardiovascular outcomes: a meta-analysis of randomized, placebo controlled trials [corrected]. *Atheroscler Suppl*. 2013;14:243–51.
169. Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. *J Am Coll Cardiol*. 2011;58:2047–67.
170. Roncaglioni MC, Tombesi M, Silletta MG. n-3 fatty acids in patients with cardiac risk factors. *N Engl J Med*. 2013;369:781–2.
171. Spadaro L, Magliocco O, Spampinato D, Piro S, Oliveri C, Alagona C, et al. Effects of n-3 polyunsaturated fatty acids in subjects with nonalcoholic fatty liver disease. *Dig Liver Dis*. 2008;40:194–9.
172. Sofi F, Giangrandi I, Cesari F, Corsani I, Abbate R, Gensini GF, et al. Effects of a 1-year dietary intervention with n-3 polyunsaturated fatty acid-enriched olive oil on non-alcoholic fatty liver disease patients: a preliminary study. *Int J Food Sci Nutr*. 2010;61:792–802.
173. Zhu FS, Liu S, Chen XM, Huang ZG, Zhang DW. Effects of n-3 polyunsaturated fatty acids from seal oils on nonalcoholic fatty liver disease associated with hyperlipidemia. *World J Gastroenterol*. 2008;14:6395–400.
174. Oya J, Nakagami T, Sasaki S, Jimba S, Murakami K, Kasa-hara T, et al. Intake of n-3 polyunsaturated fatty acids and non-alcoholic fatty liver disease: a cross-sectional study in Japanese men and women. *Eur J Clin Nutr*. 2010;64:1179–85.
175. 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;56:944–51.
176. Scorletti E, Bhatia L, McCormick KG, Clough GF, Nash K, Hodson L, et al. Effects of purified eicosapentaenoic and docosahexaenoic acids in non-alcoholic fatty liver disease: results from the Welcome* study. *Hepatology*. 2014;60:1211–21.
177. Bhatia L, Scorletti E, Curzen N, Clough GF, Calder PC, Byrne CD. Improvement in non-alcoholic fatty liver disease severity is associated with a reduction in carotid intima-media thickness progression. *Atherosclerosis*. 2015;246:13–20.
178. Nobili V, Bedogni G, Alisi A, Pietrobattista A, Risé P, Galli C, et al. Docosahexaenoic acid supplementation decreases liver fat content in children with non-alcoholic fatty liver disease: double-blind randomised controlled clinical trial. *Arch Dis Child*. 2011;96:350–3.
179. Pacifico L, Bonci E, di Martino M, Versacci P, Andreoli G, Silvestri LM, et al. A double-blind, placebo-controlled randomized trial to evaluate the efficacy of docosahexaenoic acid supplementation on hepatic fat and associated cardiovascular risk factors in overweight children with nonalcoholic fatty liver disease. *Nutr Metab Cardiovasc Dis*. 2015;25:734–41.
180. Tanaka N, Sano K, Horiuchi A, Tanaka E, Kiyosawa K, Aoyama T. Highly purified eicosapentaenoic acid treatment improves nonalcoholic steatohepatitis. *J Clin Gastroenterol*. 2008;42:413–8.
181. Sanyal AJ, Abdelmalek MF, Suzuki A, Cummings OW, Chojkier M, Group E-AS. No significant effects of ethyl-eicosapentaenoic acid on histologic features of nonalcoholic steatohepatitis in a phase 2 trial. *Gastroenterology*. 2014;147:377–84.e1.
182. Lily M, Lilly M, Godwin M. Treating prediabetes with metformin: systematic review and meta-analysis. *Can Fam Physician*. 2009;55:363–9.
183. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:854–65.
184. Sofer E, Boaz M, Matas Z, Mashavi M, Shargorodsky M. Treatment with insulin sensitizer metformin improves arterial properties, metabolic parameters, and liver function in patients with nonalcoholic fatty liver disease: a randomized, placebo-controlled trial. *Metabolism*. 2011;60:1278–84.
185. de Jager J, Kooy A, Schalkwijk C, van der Kolk J, Leher P, Bets D, et al. Long-term effects of metformin on endothelial function in type 2 diabetes: a randomized controlled trial. *J Intern Med*. 2014;275:59–70.
186. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Zoli M, Melchionda N. Metformin in non-alcoholic steatohepatitis. *Lancet*. 2001;358:893–4.
187. Loomba R, Lutchman G, Kleiner DE, Ricks M, Feld JJ, Borg BB, et al. Clinical trial: pilot study of metformin for the treatment of non-alcoholic steatohepatitis. *Aliment Pharmacol Ther*. 2009;29:172–82.
188. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther*. 2011;34:274–85.
189. Li Y, Liu L, Wang B, Wang J, Chen D. Metformin in non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Biomed Rep*. 2013;1:57–64.
190. 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;97:2347–53.
191. Singh S, Singh PP, Singh AG, Murad MH, Sanchez W. Anti-diabetic medications and the risk of hepatocellular cancer: a systematic review and meta-analysis. *Am J Gastroenterol*. 2013;108:881–91.
192. Zhang X, Harmsen WS, Mettler TA, Kim WR, Roberts RO, Therneau TM, et al. Continuation of metformin use after a diagnosis of cirrhosis significantly improves survival of patients with diabetes. *Hepatology*. 2014;60:2008–16.
193. Petrie JR. The cardiovascular safety of incretin-based therapies: a review of the evidence. *Cardiovasc Diabetol*. 2013;12:130.
194. Scirica BM, Braunwald E, Bhatt DL. Saxagliptin, alogliptin, and cardiovascular outcomes. *N Engl J Med*. 2014;370:483–4.
195. Balaban YH, Korkusuz P, Simsek H, Gokcan H, Gedikoglu G, Pinar A, et al. Dipeptidyl peptidase IV (DDP IV) in NASH patients. *Ann Hepatol*. 2007;6:242–50.
196. Yilmaz Y, Yonal O, Deyneli O, Celikel CA, Kalayci C, Duman DG. Effects of sitagliptin in diabetic patients with nonalcoholic steatohepatitis. *Acta Gastroenterol Belg*. 2012;75:240–4.
197. Carbone LJ, Angus PW, Yeomans ND. Incretin-based therapies for the treatment of nonalcoholic fatty liver disease: a systematic review and meta-analysis. *J Gastroenterol Hepatol*. 2016;31:23–531.
198. Kern M, Klöting N, Niessen HG, Thomas L, Stiller D, Mark M, et al. Linagliptin improves insulin sensitivity and hepatic steatosis in diet-induced obesity. *PLoS ONE*. 2012;7:e38744.

199. Hypertension EETFFtMoA. 2013 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC): ESH/ESC Task Force for the Management of Arterial Hypertension. *J Hypertens.* 2013;31:1925–38.
200. Paschos P, Tziomalos K. Nonalcoholic fatty liver disease and the renin-angiotensin system: implications for treatment. *World J Hepatol.* 2012;4:327–31.
201. Andraws R, Brown DL. Effect of inhibition of the renin-angiotensin system on development of type 2 diabetes mellitus (meta-analysis of randomized trials). *Am J Cardiol.* 2007;99:1006–12.
202. 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;17:448–56.
203. 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;40:1222–5.
204. 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;15:942–54.
205. Fogari R, Maffioli P, Mugellini A, Zoppi A, Lazzari P, Derosa G. Effects of losartan and amlodipine alone or combined with simvastatin in hypertensive patients with nonalcoholic hepatic steatosis. *Eur J Gastroenterol Hepatol.* 2012;24:164–71.
206. Watanabe S, Hashimoto E, Ikejima K, Uto H, Ono M, Sumida Y, et al. Evidence-based clinical practice guidelines for non-alcoholic fatty liver disease/nonalcoholic steatohepatitis. *J Gastroenterol.* 2015;50:364–77.