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Treatment of NAFLD with diet, physical activity and exercise

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Summary

Lifestyle intervention can be effective when treating non-alcoholic fatty liver diseases (NAFLD) patients. Weight loss decreases cardiovascular and diabetes risk and can also regress liver disease. Weight reductions of $\geqslant 10\%$ can induce a near universal non-alcoholic steatohepatitis resolution and fibrosis improvement by at least one stage. However, modest weight loss (>5%) can also produce important benefits on the components of the NAFLD activity score (NAS). Additionally, we need to explore the role of total calories and type of weight loss diet, micro- and macronutrients, evidence-based benefits of physical activity and exercise and finally support these modifications through established behavioural change models and techniques for long-term maintenance of lifestyle modifications.

Following a Mediterranean diet can reduce liver fat even without weight loss and is the most recommended dietary pattern for NAFLD. The Mediterranean diet is characterised by reduced carbohydrate intake, especially sugars and refined carbohydrates (40% of the calories vs. 50–60% in a typical low fat diet), and increased monounsaturated and omega-3 fatty acid intake (40% of the calories as fat vs. up-to 30% in a typical low fat diet). Both TV sitting (a reliable marker of overall sedentary behaviour) and physical activity are associated with cardio-metabolic health, NAFLD and overall mortality. A 'triple hit behavioural phenotype' of: i) sedentary behaviour, ii) low physical activity, and iii) poor diet have been defined. Clinical evidence strongly supports the role of lifestyle modification as a primary therapy for the management of NAFLD and NASH. This should be accompanied by the implementation of strategies to avoid relapse and weight regain.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a major health problem because of its high prevalence and the associated risk of progression to liver cirrhosis, liver cancer and also, increased cardiovascular and solid neoplasm risk. NAFLD comprises a wide pathological spectrum ranging from simple steatosis to steatohepatitis (NASH) with variable degrees of fibrosis and cirrhosis.[1] The strongest predictor of fibrosis progression in NAFLD is the presence of steatohepatitis.[2] The risk of detrimental outcomes is increased in patients with significant fibrosis, or steatohepatitis, whilst it is lower in patients with simple steatosis. Liver biopsy remains the gold standard for histological evaluation of the disease. Non-invasive methods combining imaging and biochemical tests are warranted to pre-empt the need for liver biopsies.

The prevalence of NAFLD varies largely from 20% to 30% and increases with age,[3] with an annual incidence of around two new cases/100 patients/year. Since NASH is becoming one of the most frequent causes of cirrhosis and liver transplantation worldwide,[4,5] it is crucial to identify patients at risk of NAFLD progression in order to implement therapeutic interventions that can lead to prevention or reversal of the deleterious consequences of advanced NASH.

Patients with NAFLD are frequently obese and/or have diabetes, and insulin resistance is a key pathogenic trigger. Four phenotypes of patients with NAFLD have been defined: i) obese, ii) type 2 diabetes, iii) metabolic syndrome and iv) lean patients. PNPLA3 is the genetic hallmark of NAFLD. Patients bearing genotype GG were at three times greater risk of NAFLD. This increased risk is more evident in patients without metabolic syndrome.[6] Indeed, TM6SF2 mutation has an additive effect on NAFLD risk.[7]

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Review

Role of macro- and micronutrients in NAFLD

Role of energy restriction

Excess caloric consumption leading to obesity and related comorbidities is a leading risk factor for NAFLD.[8] Furthermore, weight gain by itself, even only a modest 3–5 kg, predicts the development of NAFLD, regardless of baseline body mass index (BMI).[9] Interestingly, not only excess caloric consumption, but also the way food consumption is distributed throughout the day, affects liver fat accumulation. In a 6-week randomised **controlled** trial (RCT), high fat high sugar, or high sugar hyper-caloric diets were consumed either together with main meals or between them as snacks. Only the latter increased liver fat (measured by magnetic resonance spectrometry [MRS]) and abdominal fat (measured by magnetic resonance imaging [MRI]), suggesting that snacking, a common feature in the Western diet, independently contributes to hepatic steatosis.[10] There is a consensus that gradual weight reduction achieved by caloric restriction, with or without increased physical activity,[11] leads to an improvement in serum liver enzymes, liver fat, degree of hepatic inflammation and fibrosis.[12]

Role of dietary composition

Fat type and the Mediterranean dietary pattern

Experimental studies have shown that diets enriched with omega-3 polyunsaturated fatty acids (PUFA) increase insulin sensitivity,[13] reduce intra-hepatic triglyceride content and ameliorate steatohepatitis.[14,15] In epidemiological studies, the diet of normal weight NASH patients compared to age, gender and BMI matched controls, is richer in saturated fat and cholesterol and poorer in PUFA.[16,17] Within the PUFAs, there is superiority for the omega-3 PUFAs and its sub-types; eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (both abundant in fish oil) over the omega-6 PUFAs. Epidemiological studies implicate a lower consumption of omega-3 PUFA and a higher n-6/n-3 ratio among NAFLD and NASH patients compared to controls.[18,19]

In fact, overfeeding with PUFA and saturated FAs (SFAs) has distinct effects on liver and visceral fat accumulation in humans. In a 7-week RCT overeating SFAs or omega 6-PUFAs led to a similar weight gain, but the SFAs markedly increased liver fat compared with PUFAs and caused a twofold increase in visceral fat compared to PUFAs.[20] Similarly, a 10-week RCT of isocaloric diets demonstrated that intake of omega 6-PUFAs reduced liver fat compared to increased liver fat with the high saturated fat diet.[21] A meta-analysis of small or uncontrolled trials, using omega-3 supplements with varying types and dosages indicated a potentially beneficial effect on reducing liver fat.[22] In another meta-analysis of 10 RCTs, omega-3 treatment was beneficial in terms of decreasing the amount of liver fat and improved gamma-glutamyl transferase (GGT) levels, but it was not significantly efficient in reducing alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels.[23] Recent RCTs, which also include liver histology analysis, offer further insight into the effects of omega-3 treatment on NASH and fibrosis, but results are conflicting, indicating a beneficial effect for liver fat reduction (for DHA containing supplements, not for EPA alone), but not for improving NASH or fibrosis.[24–26] Furthermore, in contrast to experimental findings, there was no consistent significant effect on insulin resistance.[25,26] In summary, consumption of different types of fats have different effects on NAFLD and NASH, therefore, a reduction in total fat intake is not the simple solution.

The traditional Mediterranean diet is characterised by a high intake of olive oil, which is rich in monounsaturated-fat [MUFA], nuts, fruits and legumes, vegetables, and fish and a low intake of red meat, processed meats, and sweets (wine in moderation). In contrast to the low fat diet, which contains up-to 30% fat, 40% of the calories in the Mediterranean diet are derived from fats, mostly MUFA and omega-3 PUFA. MUFA has a favourable effect on lipid profile.[27,28] Moreover, the Mediterranean diet plays a beneficial role in metabolic profile[29] and has been shown to reduce the risk of cardiovascular disease[30] and diabetes,[31] two outcomes highly relevant in NAFLD patients.

Interestingly, one of the principles of the Mediterranean diet is to minimise processed and high sugar food. A reduction in processed[32–34] and high fructose food[35] may also lead to reduced intake of advanced glycation end products (AGEs). These are a heterogeneous class of non-enzymatic products derived from protein, lipid and nucleic acid glycation,[36] produced endogenously but also introduced through the diet. AGEs are related to the aetiology of diabetes and other metabolic alterations.[34,37,38] They have been shown to be elevated in NASH patients compared to simple steatosis and controls, and to be positively correlated with insulin resistance and negatively with adiponectin.[39] Furthermore, the soluble receptor of AGEs (sRAGE) that prevents the binding of extracellular AGEs to the cell-surface RAGE, thus exerting protective effects,[40] was shown to be inversely correlated with the level of liver fat, and more interestingly, sRAGE levels were increased by lifestyle changes.[41]

It has been suggested in a single-arm trial that adherence to the Mediterranean dietary pattern leads to a significant decrease in liver fat among overweight patients with NAFLD.[42] This was supported by two short-term randomised trials in NAFLD patients with or without type 2 diabetes. In both studies, patients were assigned to two isocaloric diets; either a low fat high carbohydrate diet or an 8-week high-MUFA diet in one study and in the

> **Key point**
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other study the low fat high carbohydrate diet or a 6-week Mediterranean diet. Liver fat content decreased more in the MUFA or the Mediterranean diet (about −35%) than in the low fat high carbohydrate diet (about −5%), despite a stable weight in both groups.[43,44] Importantly, the Mediterranean diet is also characterised by reduced carbohydrate intake (40% of the calories *vs.* 50–60% in a typical low fat diet), especially reduced sugars and refined carbohydrates, which may partially account for its beneficial effect in NAFLD. Longer-term trials testing the effects of a Mediterranean diet are warranted.

It should be noted that although the Mediterranean diet advocates consumption of wine in moderation, it is unclear whether NAFLD patients should adopt this recommendation. NASH patients with cirrhosis should avoid alcohol, as any regular alcohol consumption puts them at a greater risk of developing hepatocellular carcinoma (HCC).[45] However, uncertainty remains regarding moderate alcohol consumption (up-to two drinks per day) in patients without cirrhosis. Several studies have shown a protective association of moderate alcohol consumption with NAFLD[46–50] and NASH.[51] The protective effect may be specific to wine, as it was found in a national cross-sectional survey that modest wine drinking of up-to 10 g of alcohol per day, but not other types of alcoholic beverages, was associated with a lower prevalence of unexplained elevated ALT compared to non-drinking.[47]

Currently, the Mediterranean diet is the dietary pattern recommended for NAFLD patients by the recent EASL–EASD–EASO Clinical Practice Guidelines (Grade: B1)[11] (Fig. 1).

Added sugars

Added sugar refers to refined sugars (sucrose, fructose and high fructose corn syrup) added to sugared sweetened beverages (SSB) and incorporated into food, fruit drinks, and other beverages.[52] Epidemiological studies show convincing evidence that there is an association between added sugars and NAFLD. The association is more prominent with SSB.[19,53–55] A sucrose or fructose-rich diet increases the hepatic synthesis of triglycerides.[56,57] Furthermore, in animal studies fructose intake is associated with alterations in intestinal microflora, increased gut permeability, endotoxemia, increased hepatic tumour necrosis factor production, lipid peroxidation and hepatic steatosis.[58,59] There is a growing body of evidence to support the role of fructose in increased gut permeability and endotoxin in human NAFLD.[60] Fructose also promotes uric acid production,[61] which may cause oxidative stress and insulin resistance. Indeed, in epidemiological studies, serum uric acid was shown to be associated with the development of cirrhosis[62] and NAFLD,[63] and had a positive dose-response association with elevated serum ALT levels regard-

less of BMI.[64] In addition, cola soft drinks contain caramel colouring, which is rich in AGEs, may increase insulin resistance, inflammation and exacerbate liver injury, steatohepatitis, and liver fibrosis.[39,65]

Indeed, the Framingham Heart Study cohort, which included cross-sectional analysis of fat infiltration in the liver by computed tomography in 2,634 people and ALT measurements in 5,908 participants, showed a dose-response association between soft drinks and fatty liver disease, with a 61% increased risk of fatty liver disease in daily consumers of SSB compared to non-consumers. In addition, sugared soft drink consumption was positively associated with ALT levels. In contrast, there was no significant association between diet soda intake and either liver fat or ALT levels.[66] Similarly, in a 6-month RCT, one litre per day of regular cola, but not isocaloric semi skimmed milk or aspartame-sweetened diet cola, led to increased liver fat.[67] In an observational study, fructose-containing soft drinks were also demonstrated to be associated with more severe fibrosis in NAFLD patients if consumed on a daily basis.[68] Taken together, these findings imply that, like alcohol, questions regarding SSB consumption should be part of the patient's medical history assessment.

Role of dietary composition in NASH to HCC transition risk reduction

Little is known about the association between dietary composition and HCC in humans. Evidence for a potential association is provided from three large prospective studies. In a population-based prospective cohort study of 90,296 Japanese subjects, consuming n-3 PUFA-rich fish and individual types of n-3 PUFAs was inversely associated with HCC.[69] In a prospective cohort of 9,221 American participants of the first National Health and Nutrition Examination Survey, high cholesterol intake, but not total fat consumption, was associated with a higher risk of cirrhosis or liver cancer.[70] Among 477,206 participants of the European Prospective Investigation into Cancer and Nutrition cohort, the risk of liver cancer was increased by 43% per 50 g/day of total sugar, and was reduced by 30% per 10 g/day of total dietary fibre.[71] Accordingly, in a meta-analysis of observational studies the intake of vegetables, but not fruit, was associated with a lower risk of HCC, which decreased by 8% for every 100 g/day increase in vegetable intake.[72] Interestingly, in a case-control study the Mediterranean diet pattern, which is based on high consumption of fish, vegetables and fibre with low consumption of sugars, was shown to be associated with lower odds of liver cancer.[73]

Coffee drinking can also reduce the risk of HCC. The hepatoprotective effects of coffee may be linked not only to caffeine, but also to its polyphenolic fraction.[74,75] According to animal studies, coffee exerts its effects by reducing hepatic fat accumulation, sys-

> **Key point**
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> Fructose consumption is associated with alterations in gut microbiota, increased intestinal permeability, endotoxemia, increased hepatic TNF production and lipid peroxidation, promoting hepatic steatosis and NAFLD.

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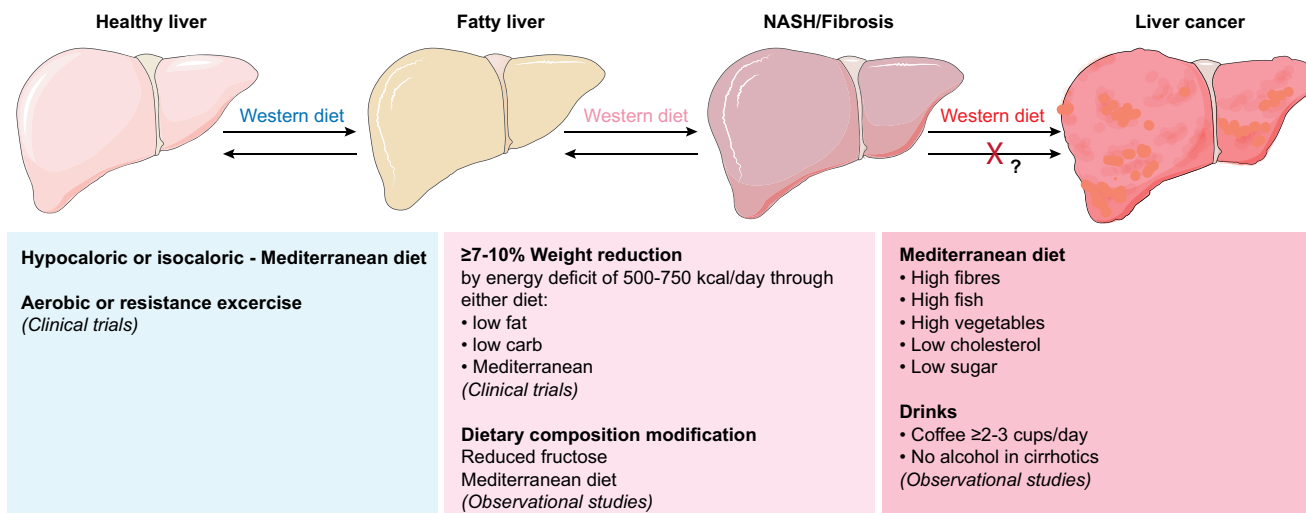> Drinking coffee reduces HCC risk. The hepatoprotective effects of coffee may be linked not only to caffeine but also to its polyphenolic fraction.

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Fig. 1. A summary of the nutritional treatment options (based on clinical trials or observational studies) through the course of NAFLD. Remission of steatosis can occur with weight reduction achieved by several types of diet or with isocaloric Mediterranean diet (which induces metabolic and anti-inflammatory benefits), as indicated by clinical trials. For remission of NASH or fibrosis, there is no evidence from clinical trials for a benefit of merely improving dietary composition, while there is evidence that at least 7% weight reduction is needed. For prevention of progression to liver cancer, the evidence regarding certain foods and nutrients is derived only from large observational studies and needs further confirmation.

temic and liver oxidative stress, liver inflammation, and expression and concentrations of proteins and cytokines related to inflammation.[74] Furthermore, it was demonstrated that chlorogenic acid, a main coffee polyphenol, inhibits hepatic stellate cells activation *in vitro*.[76]

In epidemiological studies, coffee consumption is associated with a lower risk of metabolic syndrome,[77] and caffeinated and decaffeinated coffee is associated with reduced diabetes risk in a dose-response manner.[78] Epidemiological studies in NAFLD patients indicate an inverse association between coffee consumption and liver fibrosis.[79–82] However, with regard to steatosis the results are conflicting and mostly indicate a lack of association[79,80,82–84] (Table 1). Epidemiological studies, including prospective cohorts, repeatedly suggested a protective effect against HCC.[85,86] In a US multi-ethnic prospective cohort of 162,022 participants, those who drank 2-3 cups of coffee per day had a 38% risk reduction for HCC compared with non-coffee drinker. Those who drank ≥4 cups per day had a 41% reduction in HCC risk. Furthermore, compared with non-coffee drinkers, participants who consumed 2-3 cups of coffee per day had a 46% risk reduction of death from chronic liver disease and those who drank ≥4 cups per day had a 71% reduction. The inverse associations were significant regardless of the participants' ethnicity, sex, BMI, smoking status, alcohol intake or diabetes status.[85]

Although the association between diet and liver cancer seems to be important, the results of these observational studies should be confirmed in additional prospective studies specific for NAFLD patients, controlling carefully for other dietary and lifestyle-related potential confounders.

Role of micronutrients

In spite of the evidence supporting the association of oxidative stress with NASH and the usefulness of antioxidants in animal models, the efficacy of antioxidant therapy in humans has not been shown or properly tested,[87] with the exception of vitamin E in a high dose supplement form.[88] A study in 3,471 subjects tested the cross-sectional association between ultrasound diagnosed NAFLD and dietary vitamin C intake. It found a significant inverse, energy-adjusted association among men and normal weight subgroups.[89] Supporting this finding, another cross-sectional study also showed a significant positive association between low vitamin C intake and NAFLD in the male population.[90] In contrast, other smaller studies did not find such an association.[91,92] In a large cross-sectional population-based study in Hong Kong using MRS-diagnosed NAFLD, an inverse association was seen between the intake of vitamin C, vegetables, legumes and fruits and NAFLD prevalence. In this context, the high Dietary Quality Index, created from the joint consumption of these foods, indicated a reduced likelihood of NAFLD, regardless of BMI and other risk factors.[93]

Choline is an essential component of cell membranes and is required for the synthesis of phospholipids. In a cross-sectional analysis, postmenopausal women with deficient choline intake had worse fibrosis.[94] Choline is particularly abundant in egg yolks and animal sources of protein.

Table 1. Summary of epidemiological studies testing the association between coffee or caffeine consumption and NAFLD.

Author	Type of coffee	Sample size	Improvement in steatosis	Improvement in fibrosis
Zelber-Sagi 2015 [80]	All caffeinated coffee types	347	No	Yes (Fibrotest)
Bambha 2013 [82]	Caffeinated and decaffeinated	782	No	Yes
Anty 2012 [81]	Regular coffee, not espresso	195	NE	Yes
Birerdinc 2012 [84]	Caffeine intake	41,658	Yes	NE
Molloy 2012 [79]	Regular coffee	306	No	Yes
Catalano 2010 [83]	Only espresso coffee	245	Yes	NE

NE, not evaluated.

Vitamin D has several favourable metabolic effects and according to experimental data it acts as an anti-inflammatory and anti-fibrotic agent.[95,96] Emerging evidence suggests that vitamin D deficiency may play a role in the pathogenesis of human NAFLD. In support of that, a meta-analysis of observational studies demonstrated that compared to controls, NAFLD patients were more likely to be vitamin D deficient.[97] However, a study carefully adjusting for adiposity (evaluated by dual energy X-ray absorptiometry) suggests that there is no relationship between vitamin D levels and insulin resistance, the amount of liver fat (by MRS and liver biopsy), or the severity of NASH.[98] In contrast, in a large study using the NASH CRN cohort, vitamin D deficiency was, independently of BMI and metabolic syndrome, associated with histologic features of NAFLD; definitive NASH, increased lobular inflammation, more ballooning and the presence of fibrosis, but not with grade of steatosis or insulin resistance.[99] Therefore, the role of vitamin D in human NAFLD is still unclear. Deficient nutritional intake of vitamin D is very common, intake in Europe from food alone is on average 190 IU/day for men and 130 IU/day for women, the lowest in Spain (44 IU/day, in women) and the highest in Finland (330 IU/day, in men),[100] whereas the Dietary Reference Intakes for adults is 600 IU/day. However, there is no clear evidence from RCTs that a high dose vitamin D supplement benefits NAFLD in terms of hepatic steatosis, liver enzymes or insulin resistance.[101,102]

Physical activity in NAFLD

Our body is programmed to move. As such, it is not surprising that physical movement, or lack of, plays an important role in the development and management of NAFLD and NASH.

a) Sedentary behaviour, also referred to as physical inactivity, holds strong epidemiological, physiological and molecular relationships with the development of over thirty long-term conditions.[103] Both TV sitting (a reliable marker of overall sedentary behaviour) and physical activity are associated with cardio-metabolic health when viewed separately[104,105] or in combination.[106] Beyond cardio-metabolic health, ⩽3 h of daily sitting is linked to all-cause mortality (RR 1.30; 95% CI, 1.06–1.56).[104] Increasing sedentary behaviour is becoming a growing problem in the general population, and low levels of physical activity are compounded by an increase in physical inactivity. Sedentary behaviour is reported to be higher in people predisposed to the metabolic syndrome, excessive adiposity and type 2 diabetes.[107] In addition, prospective studies show that a change in TV viewing over 5 years was associated with waist circumference and clustered cardio-metabolic risk score, independent of physical activity.[108] Not only is the total duration of sedentary time important for metabolic risk, but also the breaks in sedentary time, independent of total sedentary time. Increased breaks in sedentary times were beneficial for obesity control, glucose and triglyceride metabolism.[109] Consequently, increases in sedentary time could play a potential role in the development of, or predisposition towards NAFLD, independent of physical activity/exercise, and need to be considered when introducing lifestyle interventions. Targeting a reversal of sedentary behaviour may also provide an additional therapeutic avenue to complement physical activity and exercise guidelines. There is limited but promising evidence from prospective cohort studies identifying sedentary behaviour as an independent risk factor for NAFLD.[110] At this point it is important to highlight that physical activity and sedentary behaviour have independent effects on cardio-metabolic health. Microarray studies exploring the molecular effects of sedentary behaviour and exercise show that they downregulate and upregulate different pathways,[111] demonstrating that they are not just the reciprocal of each other. The confusion comes as they tend to be interrelated behaviourally; those who sit most also tend to move least. Worse still, sitting is also associated with more snacking and an unhealthy diet.[112] Combined, these create a 'triple hit behavioural phenotype' of: i) sedentary behaviour, ii) low physical activity, and iii) poor diet.

b) Physical activity, we have known for some time that everyday physical activity, not exercise, is associated with health. In a seminal report in 1953 Professor Jerry Morris[113] reported that London (UK) bus drivers, who spend most of their day sitting, were three times as likely to have a coronary heart disease than bus conductors, who spend most of the day physically active collecting tickets on double-decker buses. Cross-sectional studies suggest that people with NAFLD have lower levels of physical

Key point

Sedentary behaviour and physical activity are not just the reciprocal of each other. Increases in sedentary time could play a potential role in the development of, or predisposition towards NAFLD, independent of physical activity.

Key point

A '*triple hit behavioural phenotype*' of i) sedentary behaviour, ii) low physical activity, and iii) poor diet have been defined.

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activity than those without,[114–116] and are also more prone to fatigue.[117] However, activity levels in people with NAFLD have only been measured and described using physical activity questionnaires. Importantly, questionnaires have significant limitations and are subject to recall and social desirability bias, and are inaccurate in determining frequency, duration and intensity of physical activity.[118,119] A poor association between objective and subjective reports highlight the importance of objectively assessing physical activity in clinical practice. Physical activity is a key determinant of metabolic control and is commonly recommended for people with NAFLD, usually alongside weight loss and dietary change. Even though physical activity and exercise are recommended as part of the treatment for NAFLD, there have been no large-scale studies with adequate statistical power to guide healthcare practitioners in prescribing exercise programmes, or for generating physical activity guidelines for the management of these patients. Evidence for the benefit of physical activity comes from prospective studies showing that individuals who maintain a physically active lifestyle are less likely to develop insulin resistance, impaired glucose tolerance, or type 2 diabetes.[118,119] To date, no prospective studies have reported the effect of reducing sedentary behaviour or increasing physical activity on NAFLD incidence or severity. However, given the weight of evidence, sedentary behaviour should be explored in NAFLD management, albeit as an adjunct to diet and exercise.

c) Exercise, unlike the usually unstructured and unplanned nature of physical activity, more deliberate physical activity is described as exercise. Exercise is one of the cornerstones of NAFLD and NASH management, although the evidence underpinning this is still in its infancy compared to other conditions (type 2 diabetes for example). This is likely the product of studies combining diet and exercise interventions until recently. Indeed, in 2012 two independent systematic reviews in the *Journal of Hepatology* could only identify a maximum of six studies that had undertaken RCT to explore the effects of exercise on liver fat in people with NAFLD.[120,121] A more recent systematic review in 2017 was able to identify 24 exercise studies, showing the rapid increase in work in this area.[122] These reviews reveal that exercise, without weight loss, produced a 20–30% relative reduction in intrahepatic lipid.

Different forms of exercise (aerobic exercise, resistance exercise, or high intensity intermittent exercise) appear to have similar effects on liver fat.[120–122] More vigorous aerobic exercise does not hold additional benefit for liver fat compared with aerobic exercise.[123,124] However, it should be noted that all exercise trials are still small and have a wide range of variability. The studies to date have been mainly relatively short, lasting in the majority

between 8 and 12 weeks. Longer-term studies are starting to be published and reveal that if patients continue to exercise for 12 months the benefits remain.[125] However, if patients do not continue to exercise, the benefits are lost.[126] As with many other conditions, if you do not use it, you lose it. Moreover, further studies should take into account genetic background of the patients and its influence on response to physical activity. Indeed, *PNPLA3* seems to influence response to lifestyle intervention. Patients bearing unfavourable genotype GG did respond better than patients with genotype CC or CG.[127]

The mechanisms underlying the change in liver fat following exercise in NAFLD reflect changes in energy balance, circulatory lipids and insulin sensitivity. Much of the early work looking at exercise in NAFLD has been debated, as exercise was either accompanied by dietary changes, or diet induced weight loss – leaving the question of whether there is an exercise only effect unanswered. More recently, better controlled studies are able to not only demonstrate that there is an exercise only effect on liver fat, but also begin to explore the underlying mechanisms. Exercise has little effect on hepatic insulin sensitivity, but does improve peripheral insulin sensitivity,[128] producing a net improvement in insulin action and consequently, reducing hepatic *de novo* lipogenesis. It should be noted that the direct benefits of exercise on glycaemic control are significant, but modest, even in people with impaired glucose control.[118] However, tracer studies also show that exercise has a direct effect on lipid flux, with an increase in very low density lipoproteins clearance contributing to the reduction in liver fat with exercise,[129] so not all of the changes in liver fat are attributable to insulin sensitivity alone.

Although not the liver itself, there is an important reduction in visceral adipose tissue with exercise. Visceral fat directly links with liver inflammation and fibrosis, independent of insulin resistance and hepatic steatosis.[130] The precise mechanism of how visceral fat applies its detrimental effects on liver metabolism, fibrotic and inflammatory consequences remain unclear, although influx of fatty acids and synthesis of cytokines and adipokines has been shown to promote liver lipid accumulation, insulin resistance and inflammation.[130] There is much that is not known in the field of exercise and NAFLD, including; the effect of exercise on inflammation (a key mediator in the progression of NAFLD), effect on gut microbiota, and appetite for a start. However, given that people with NAFLD are at nearly double the risk of developing cardiovascular disease than those without,[131] the beneficial effects of exercise on cardiovascular function[132] should be explored further. Indeed, it is possible that the major benefits for exercise in NAFLD are not in the liver, but in improving cardiovascular function. A schematic representation of the media-

tors of response to exercise in NAFLD can be seen in Fig. 2.

Data reporting the effects of exercise in people with NASH are limited. To date, only a few studies have reported the effects of exercise on NASH. One presents promising effects on liver lipid, but not on circulating markers of inflammation or fibrosis and a non-significant reduction in circulatory apoptosis marker,[133] while another presents a significant reduction in apoptosis marker.[134] The one study with liver histology, showed little effect on biopsy measures of liver disease in a small number of patients.[135]

Diet, sedentary behaviour, physical activity and exercise

Although exercise has a significant and clinically meaningful effect on liver lipid (20–30% relative reduction), its effects are modest in comparison to weight reduction, which can produce >80% reduction in liver fat.[120] This is important as, clinically, supporting people to manage their weight through diet approaches will produce greater changes in liver fat than exercise alone. However, completely disassociating exercise and diet may not be beneficial as data suggests that cardiorespiratory fitness is a determinant of response to dietary intervention in NAFLD, with those with a greater cardiorespiratory fitness having a greater response to dietary intervention.[136] This creates a difficult paradox where those with the lowest cardiorespiratory fitness, who find exercise most difficult, also have the lowest response to diet-induced lifestyle interventions. Additionally, high levels of physical activity (*i.e.*, 200–300 min/week) are crucial for weight loss maintenance,[137] and since physical activity has an independent effect in NAFLD treatment, it provides another treatment option for those who have difficulties in weight loss.

Weight loss as the first endpoint treating NASH

The primary approach to treat NAFLD focuses on the control of the underlying risk factors like diabetes, hyperlipidaemia, obesity and other comorbidities. Lifestyle changes through diet and physical activity modifications are well-established therapeutic strategies for conditions such as diabetes and cardiovascular disease.[138,139] To date, only a few studies have evaluated the impact of lifestyle modification on NAFLD (summarised in Table 2). Marked differences in the study design including various forms of lifestyle intervention with different diets and physical activity regimens, absence of standardised endpoints, diverse phenotypes of NAFLD, different following times together with a relatively small number of patients included in these earlier trials have led to inconclusive recommendations. Recent studies have reported that a comprehensive lifestyle modification based on reduced energy intake and increased physical activity during 6–12 months induces improvement in liver enzymes (AST/ALT and GGT levels) and metabolic (fasting glucose and insulin sensitivity) parameters, improved intrahepatic triacylglycerol concentrations (assessed by proton magnetic resonance spectroscopy[140,141]), and reduced steatosis and necroinflammation, including ballooning and fibrosis detected in paired liver biopsies.[142,143] Moreover, weight loss can also have a favourable impact on abdominal obesity,[144,145] cardiovascular disease[146] and extrahepatic malignancies.[147] Most studies conclude that at least 7–10% of weight loss is required to induce an improvement in NAFLD activity score (NAS) and its components (steatosis, lobular inflammation and ballooning).[148,149] However, lifestyle changes that produce even modest, sustained weight loss of about 5% of initial body weight, can reduce steatosis,[140] liver enzymes[150] and health benefits as clinically meaningful reductions in triglycerides, blood glucose, haemoglobin A1c, and the risk of developing type 2 diabetes.[137]

Promrat *et al.* conducted a small-randomised controlled trial to examine the effects of lifestyle intervention using a combination of diet, exercise, and behaviour modification, on histological parameters of NASH. The primary outcome measure was the change in NAS after 48 weeks of intervention. The lifestyle intervention group had significant improvements in histology at 48 weeks, with 67% improving their NAS. There was improvement in hepatic steatosis, lobular inflammation, and ballooning in the intervention group; but results showed no improvement in fibrosis in either group.[148] In another study on the effect of lifestyle changes in patients with NASH, those who lost 10% or more of total body weight exhibited significantly higher rates of fibrosis regression (63% *vs.* 9%).[151]

A prospective study by Vilar *et al.*[12] evaluated the impact on histological features of NASH in a large cohort of patients of a program of lifestyle changes through a hypocaloric diet combined with exercise. They followed these patients during routine clinical practice for 12 months. The study examined the relationship between the degree of weight reduction and the improvements in overall histological parameters. It reported that a dose-response relationship is evident among weight loss percentage and overall histological changes, with the greatest reduction observed in those with the greatest weight loss. Weight reductions of ⩾10% are required for inducing NASH resolution (reaching 90% of patients who achieved this weight reduction) or improving fibrosis by at least one stage (81%). However, more modest weight losses (7–10%) produce important benefits on NAS (88%) and its components (steatosis, 100%; lobular inflammation, 100%; and ballooning, 90% of patients who achieved this weight reduction) (Fig. 3). In a post-hoc analysis of this study, patients

Key point

Losing weight decreases cardiovascular and diabetes risk and also regresses liver disease.

Key point

Weight reductions of ⩾10% are required for inducing near universal NASH resolution or fibrosis improvement by at least one stage.

Key point

NASH resolution rate after lifestyle intervention appears to be reduced in older people, in patients suffering from type 2 diabetes and in patients showing higher histological activity in liver biopsy (NAS ⩾5); and increased in patients achieving normalisation of ALT (⩽19 in females or ⩽30 in males) and weight loss percentage ⩾10%.

Review

Benefits of exercise in NALFD

Changes in the liver

1. Peripheral insulin sensitivity ↑ = *de novo* lipogenesis ↓
2. Visceral fat ↓ = lipid supply to liver ↓
3. VLDL clearance ↑ = lipid storage ↓

Changes to cardiovascular system

1. Torsion ↓ = myocardial damage ↓
2. EDV ↑ = preload ↑
3. Ca^{2+} handing ↑ = SV ↑ + EF ↑
4. FMD ↑ = O² supply ↑
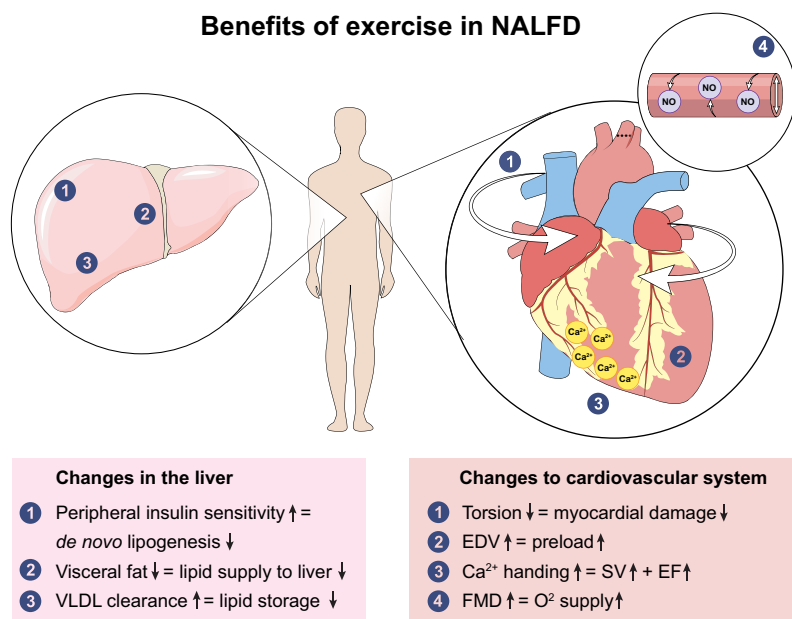
Fig. 2. Benefits of exercise and physical activity in NAFLD: changes in the liver and changes to cardiovascular system. EDV, end diastolic volume; SV, stroke volume; EF, ejection fraction; FMD, flow-modulated dilatation; VLDL, very low density lipoprotein.

with weight loss between 7 and 10% and "unfavourable" risk factors such as female sex, presence of diabetes, a BMI of >35 or many ballooned cells at baseline had lower rates of NASH resolution. However, higher rates of NASH resolution were seen in subjects with more significant weight losses (⩾10%) irrespective of the presence of "unfavourable" risk factors,[152] suggesting that a weight reduction >10% is required in the high risk group of patients.

Accordingly, the EASL–EASD–EASO Clinical Practice Guidelines recommend that in overweight/obese NAFLD patients, a 7–10% weight loss is the target of most lifestyle interventions, and results in an improvement of liver enzymes and histology (Grade B1).[11]

The impact of weight loss on histological improvement depends on the degree of weight reduction irrespective of the method used to reach it. Lifestyle intervention including hypocaloric diet and exercise, weight loss-induced by drugs like orlistat or weight loss after bariatric surgery seem to have the same positive impact on NASH resolution and fibrosis regression. For example, low carbohydrate diet may seem more effective in reducing liver fat, but only in the short-term.[153,154] In the long-term, reduction appears to be similar in both diets as long as a 7% weight loss is achieved.[155] In a 6-month RCT, both energy restricted diets of either reduced carbohydrate (<90 g carbohydrates and a minimum of 30% fat of total energy intake) or reduced fat (<20% fat of total energy intake) led to similar, significant reductions in intrahepatic lipid content and

ALT.[156] This equivalence of diets is also supported by a small meta-analysis.[149] These findings indicate that the diet of choice should be the one which individuals are able to adhere to for years, as long as it is generally healthy and leads to weight reduction.

NASH resolution rate after lifestyle intervention appears to be reduced in older people, in patients suffering from type 2 diabetes and in patients showing higher histological activity in liver biopsy (NAS ⩾5). Moreover, NASH resolution was demonstrated to be strongly related to the normalisation of ALT (⩽19 in females or ⩽30 in males) and weight loss percentage.[152] Taking into account all these five variables, a NASH resolution calculator ([NASHRES] available at http://www.aeeh.es/calculadora-nashres/) has been developed and could be useful in the management of patients undergoing focussed weight loss intervention. In a cohort of 261 patients treated with a lifestyle intervention during 52 weeks (140 in derivation set and 121 in the temporary validation set), the NASHRES calculator showed a high diagnostic accuracy (AUROC 0.96 in the estimation cohort and AUROC 0.95 in the validation cohort). A score lower than 46.15 showed a negative predictive value for NASH resolution of 92%, whereas a result higher than 69.72 showed a positive predictive value of 91%. Indeed, this tool was validated in the LEAN trial comparing liraglutide, a GLP-1 agonist, *vs.* placebo.[157] NASHRES calculator allowed the correct classification of patients with a diagnostic accuracy of 94% to detect lack of NASH resolution. Thus, it is a useful tool to detect futility impact of lifestyle intervention and could help to select patients requiring further therapeutic interventions.[158]

Behavioural aspects of lifestyle modification

There is no doubt that lifestyle modification and weight loss pose a great challenge to both the patients and caregivers. NAFLD patients may have a low level of readiness for change and motivation to adopt a healthier lifestyle.[159] Furthermore, NAFLD diagnosis is not necessarily associated with lower general health perception nor is it associated with higher health care utilisation.[160] It has been repeatedly demonstrated that weight loss achieved by diet is highest at 6-months follow-up and thereafter a weight regain occurs, with patients only reaching 3 to 4 kg weight reduction at 2-year follow-up.[137] Interestingly, even if there is weight regain after diet, there seems to be a long lasting beneficial effect on liver fat and insulin resistance. In a study with 2-year follow-up after six months dietary intervention, improvements in liver fat and insulin resistance were maintained despite regaining of weight, perhaps because the intervention elicited sustained favourable lifestyle changes.[161] In support of that, in overweight and obese adults with type 2 diabetes undergoing lifestyle intervention and followed for four years, despite partial weight regain

Table 2. Summary of the effect of lifestyle interventions on NAFLD and NASH.

Author, Year	Study design	Patients	Intervention (duration, type)	Outcomes			
				Liver histology	Liver fat by imaging (modality)	Liver enzymes	Insulin resistance[†]
Ueno, 1997 [135]	Controlled trial	25 obese NAFLD; 15 treated, 10 untreated	3 months, restricted low fat diet and exercise *vs.* no changes in lifestyle	Reduced steatosis, no significant change in inflammation or fibrosis	NE	Reduced	NE
Hickman, 2004 [172]	Single-arm trial	10 NAFLD (3 with follow-up biopsies)	15 months (3 months intensive visits), diet and exercise intervention	Steatosis reduced in the 3 repeated biopsies, fibrosis reduced in 2	NE	Reduced	Reduced
Petersen, 2005 [173]	Single-arm trial	8 obese patients with type 2 diabetes	7 weeks on average (3–12 weeks range), very low fat (3%) liquid diet, supplemented with raw fruits and vegetables	NE	Reduced (MRS)	Unchanged	Reduced
Huang, 2005 [174]	Single-arm trial	15 NASH	12 months, nutritional counselling	Reduced NASH score (not statistically significant), no change in steatosis and fibrosis	NE	Unchanged (reduced only in cases with improved histology)	Reduced
Zelber-Sagi, 2006 [175]	Randomised controlled trial (diet *vs.* diet and orlistat)	23 NAFLD (in the diet only arm), 11 had a repeat liver biopsy	6 months, low calorie, low fat (⩽30%) diet and physical activity 3–4 times a week	Reduced steatosis, not significant for necroinflammatory grade or fibrosis stage	Reduced (AUS)	Reduced	Unchanged
Benjaminov, 2007 [176]	Single-arm trial	14 candidates for bariatric surgery	4 weeks, low-carbohydrate diet <30 g/day, no limitation of calories	NE	Reduced (CT)	Unchanged	NE
Tendler, 2007[177]	Single-arm trial	5 obese NAFLD	6 months, low-carbohydrate <20 g/day, ketogenic diet	Reduced steatosis, necroinflammatory grade, not significant for stage of fibrosis	NE	Unchanged	Unchanged
Yamamoto, 2007 [178]	Controlled trial	12 NASH and simple steatosis treated and 6 untreated	6 months, low calorie, low fat (20%) and low iron (<6 mg/day) diet	NE	NE	Reduced only in the treated arm	NE
de Luis, 2008 [179]	Single-arm trial	142 obese non-diabetic (with and without elevated ALT)	3 months, hypocaloric low fat diet	NE	NE	Reduced	Reduced
Kantartzis, 2009 [136]	Single-arm trial	50 NAFLD	9 months, dietary counselling with up to 10 sessions with a dietician	NE	Reduced (MRS)	Reduced	Reduced
Oza, 2009 [180]	Single-arm trial	22 NAFLD patients (after attrition of 67%)	6-month, home-based lifestyle modification delivered in collaboration with physicians, hygienists, dietitians, nurses	NE	Reduced (CT)	Reduced	Reduced
St George, 2009 [181]	Randomised controlled trial	143 NAFLD patients with elevated liver and metabolic risk factors	3 months, moderate- (6 sessions/10 weeks) *vs.* low-intensity (3 sessions/4 weeks) lifestyle counselling *vs.* control group	NE	NE	Reduced in both moderate- and low-intensity arms	Reduced only in the moderate-intensity arm

(*continued on next page*)

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Table 2 (*continued*)

Author, Year	Study design	Patients	Intervention (duration, type)	Outcomes			
				Liver histology	Liver fat by imaging (modality)	Liver enzymes	Insulin resistance[†]
Kirk, 2009 [155]	Randomised controlled trial	22 obese subjects	About 11 weeks, high carbohydrate (>180 g/d) *vs.* low carbohydrate (<60 g/d) energy-deficit diet	NE	Liver fat decreased to the same extent in both diets (MRS)	No change in both diets	Improved in both arms, to a greater extent in the low-carbohydrate diet
Viljanen, 2009 [182]	Single-arm trial	33 obese	6 weeks, very low calorie diet (all daily meals replaced by dietary products)	NE	Reduced (MRS)	GGT reduced, other enzymes NE	Reduced
Vilar Gomez, 2009 [183]	Randomised controlled trial (diet *vs.* diet and nutritional supplement)	30 (in the diet only arm)	6 months, low fat hypocaloric diet plus aerobic exercise	Significant improvement in steatosis, necroinflammation and fibrosis	NE	Reduced	Reduced
Shah, 2009 [184]	Randomised controlled trial	18 obese older adults	6-month, diet (n = 9) or diet + exercise (n = 9)	NE	Decreased to the same extent in both arms (MRS)	Unchanged in both arms	Decreased to the same extent in both arms
Elias, 2010 [185]	Single-arm trial	31 NAFLD	6-month, low fat hypocaloric diet	NE	Reduced (only among 16 adherent patients; lost >5% of initial body weight) (CT)	Reduced (only among 17 adherent patients)	Reduced (only among 17 adherent patients)
Albu, 2010 [186]	Single-arm trial within the Look AHEAD study	58 obese with type 2 diabetes	1 year, diet and exercise	NE	Reduced (CT)	NE	Reduced
Lazo, 2010 [140]	Randomised controlled trial within the Look AHEAD study	96 type-2 diabetes patients	12 months, intensive lifestyle intervention *vs.* control group who received diabetes support and education	NE	Reduced (MRS)	No change	Not shown
Promrat, 2010 [148]	Randomised controlled trial	31 NASH	48 weeks intensive lifestyle intervention of diet, exercise, and behaviour modification *vs.* structured education	Reduced NAS and steatosis. No significant reduction in fibrosis	NE	Reduced	No significant reduction
Moscatiello, 2011 [187]	Controlled trial	68 NAFLD patients in the treatment protocol, and 82 who refused were the controls	3 months, CBT program and 2 years follow-up. CBT program based on 13 group sessions *vs.* a standard dietary prescription	NE	NE	Reduced	Reduced
Haufe, 2011 [156]	Randomised controlled trial	102 overweight and obese	6 months, reduced carbohydrate or reduced fat, energy restricted diet	NE	Reduced to a similar extent (MRS)	Reduced to a similar extent	Reduced to a similar extent

Study	Trial type	Population	Intervention	Histology	Steatosis (imaging)	Liver enzymes	Insulin resistance[†]
Browning, 2011 [154]	Controlled trial	18 NAFLD	2 weeks, carbohydrate-restricted (<20 g/d) vs. calorie-restricted (1,200–1,500 kcal/d) diet	NE	Reduced in both arms (MRS), to a greater extent in the low carbohydrate diet	Unchanged ALT, reduced AST in both arms, to a similar extent	NE
Sun, 2012 [188]	Randomised controlled trial	NAFLD with elevated liver enzymes; 674 in intervention group and 332 in control	12 months, lifestyle modification intervention including low fat diet and exercise vs. information on principles of healthy eating	NE	Unchanged (CT)	Reduced	Reduced
Bozzetto, 2012 [43]	Randomised controlled trial	45 Type 2 diabetes patients	8-week, isocaloric high-MUFA diet vs. high-carbohydrate/high-fiber/low-glycemic index diet, both arms with or without physical activity program	NE	Reduced more with the high-MUFA diet, regardless of physical activity (MRS)	Unchanged	Unchanged
Ryan, 2013 [44]	Randomised crossover trial	12 non-diabetic NAFLD	6-week, isocaloric Mediterranean diet vs. low fat-high carbohydrate diet, in random order with a 6-week wash-out period	NE	Reduced more with the Mediterranean diet	Unchanged	Reduced with the Mediterranean diet
Eckard, 2013 [143]	Randomised controlled trial	41 NAFLD (88% with NASH)	6 months, 4 lifestyle modification subgroups: standard care, low fat diet and moderate exercise, moderate-fat/low-processed-carbohydrate diet and moderate exercise, or moderate exercise only	Reduced NAS in pre- to post- comparison in the joint arms, with no significant difference between arms. No change in fibrosis	NE	Reduced in pre- to post- comparison in the joint arms, with no significant difference between arms	Unchanged
Scaglioni, 2013 [189]	Single-arm trial	12 NAFLD	3 months, diet, physical exercise and behaviour therapy	NE	Reduced (AUS)	Reduced	Unchanged
Wong, 2013 [190]	Randomised controlled trial	154 NAFLD	12 months, community-based dietitian-led lifestyle modification program at 2 community centres vs. usual care	NE	Reduced (MRS)	Reduced	NE
Yoshimura, 2014 [191]	Randomised controlled trial	33 adults with visceral adiposity	12 weeks, calorie restriction alone vs. calorie restriction plus aerobic exercise	NE	Reduced in both arms with no difference between arms (CT)	Unchanged	Reduced in both arms with no difference between arms
Trovato, 2015 [42]	Single-arm trial	90 non-diabetic, obese NAFLD	6 months, Mediterranean Diet and physical exercise	NE	Reduced (AUS)	Unchanged	Reduced
Vilar Gomez, 2015 [12]	Single-arm trial	293 NASH (261 with repeated biopsies)	52 weeks, low fat hypocaloric diet combined with exercise	Reduced steatosis, NASH and fibrosis	NE	Reduced	Reduced

NE, not evaluated; MRS, magnetic resonance spectroscopy; CT, computed tomography; AUS, abdominal ultrasound.
[†] Defined by improvement in serum insulin or Homeostasis Model Assessment for Insulin Resistance (HOMA-IR), or euglycemic-hyperinsulinenmic clamp.

Review

52 weeks of lifestyle intervention

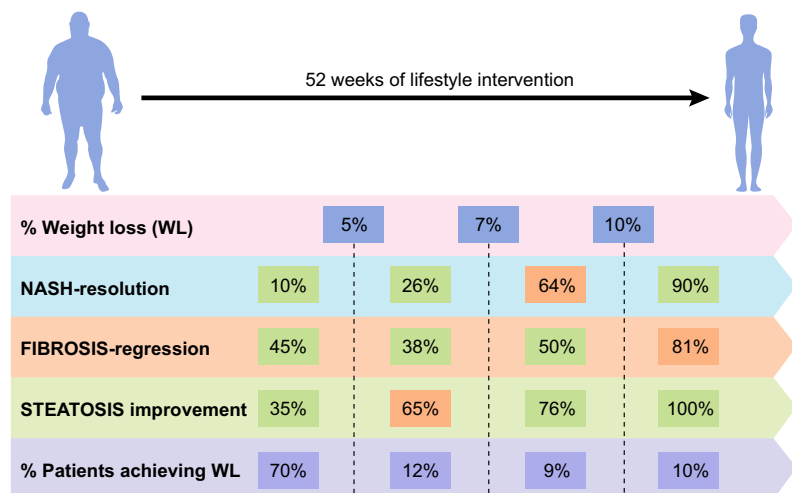|		5%	7%	10%
% Weight loss (WL)		5%	7%	10%
NASH-resolution	10%	26%	64%	90%
FIBROSIS-regression	45%	38%	50%	81%
STEATOSIS improvement	35%	65%	76%	100%
% Patients achieving WL	70%	12%	9%	10%

Fig. 3. Probability of reaching NASH resolution, fibrosis regression (at least one stage) and steatosis improvement in patients with NASH under lifestyle intervention according to percentage of weight loss (modified from Vilar-Gomez et al.[12]).

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haemoglobin A1c levels remained below pre-intervention levels, and the reduction remained clinically meaningful.[162] Nevertheless, in the study by Vilar-Gomez et al.[12] just 10% of patients (29/293) reached a 10% weight loss and more than 70% of the cohort (208/293) did not lose 5% of total body weight.

In patients with successful NASH resolution the key point is to prevent weight regain. In the Look AHEAD study, which included 5,145 overweight type 2 diabetes patients,[163] long-term lifestyle intervention produced ⩾5% weight loss at eight years in 50% of participants. The key factors influencing long-term weight loss were intensity of physical activity and percentage of weight loss during the first year. The 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults provides practical recommendations for weight reduction; high intensity (i.e., ⩾14 sessions in six months) comprehensive weight loss interventions, and for weight loss maintenance; a long-term (⩾1 year) comprehensive program that provides regular contact (monthly or more frequently).[137]

The role of the multidisciplinary approach and behavioural therapy in the lifestyle treatment of NASH

One approach to improve the self-management in NAFLD patients may be by implementing a "multi-disciplinary team approach" in which patients will be followed by physicians, dieticians, psychologists and physical activity supervisors.[164] Unfortunately, in many cases a full multidisciplinary team is not available for the patient due to limited resources. Either way, the active support of the physicians is much needed, since the physician's advice is a catalyst for lifestyle change,[165] and several studies indicate that physician's advice to lose weight has positive effects on the probability of keeping the

diet and exercise recommendations[166] and on the patients' motivation for weight loss.[167] Furthermore, general practitioners and hepatologists treating NAFLD patients should provide information and refer the patients to appropriate resources about NAFLD implications and treatment and have training in behavioural therapy. Similarly to the treatment approach in other chronic diseases, healthcare providers need to discuss with their patients the broader picture of NAFLD complications; liver cancer, increased risk of diabetes, cardiovascular disease, with the message that risk reduction is possible.[168] In a recent cross-sectional study among 146 patients with NAFLD, a better nutritional behaviour was associated with higher patient's perceptions of understanding what NAFLD is, believing in treatment effectiveness and a higher self-efficacy.[169] The 5 A's model (*ask, advise, assess, assist, and arrange*) may be useful as a tool to assist clinicians advising patients with NAFLD to modify their behaviour, assessing their interest in doing so, assisting in their efforts to change, and arranging appropriate follow-up meetings.[170]

A practical guide for behavioural therapy in the lifestyle treatment of NASH

NAFLD patients rarely receive support to encourage meaningful and sustainable changes to diet and physical activity behaviour. Given the strength of evidence demonstrating that lifestyle changes are effective, knowledge of the clinical care team will not be a limitation. The lack of effective use of lifestyle interventions is most likely due to the lack of training given to clinical care teams with the aim of delivering effective behaviour change interventions (i.e., use of behaviour change and brief motivational techniques). Behaviour change typically involves three stages, described in Fig. 4.

Summary & conclusions

Lifestyle change, including dietary habits and physical activity, are and should be the first line of treatment in NAFLD and NASH. Weight reduction is the most established treatment for both NAFLD and NASH, with a clear dose-response association. Generally, any form of healthy diet (low fat or low carbohydrates or Mediterranean diet), which will lead to caloric reduction and is acceptable by the patient, should be encouraged. For those who find caloric restriction difficult, changing dietary composition without necessarily reducing caloric intake may offer a more feasible alternative, although the benefit to liver health is not as marked as weight reduction. The importance of weight loss is highlighted in people with NASH, where weight loss >7% is associated with a clinically meaningful regression of disease status. Exercise produces significant but modest changes in liver fat (vs. weight loss). However, given the strong cardiovascular benefits of
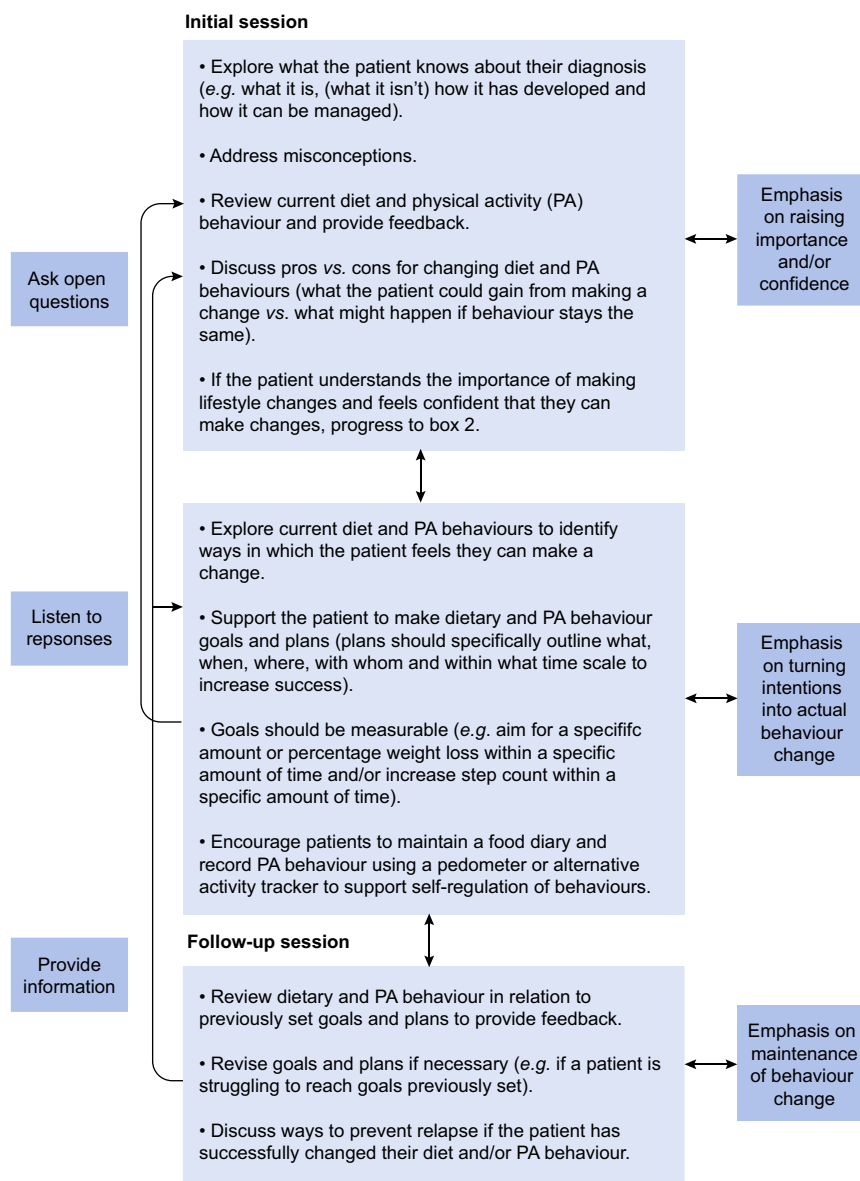
Initial session

Ask open questions

• Explore what the patient knows about their diagnosis (*e.g.* what it is, (what it isn't) how it has developed and how it can be managed).

• Address misconceptions.

• Review current diet and physical activity (PA) behaviour and provide feedback.

• Discuss pros *vs.* cons for changing diet and PA behaviours (what the patient could gain from making a change *vs.* what might happen if behaviour stays the same).

• If the patient understands the importance of making lifestyle changes and feels confident that they can make changes, progress to box 2.

Emphasis on raising importance and/or confidence

Listen to repsonses

• Explore current diet and PA behaviours to identify ways in which the patient feels they can make a change.

• Support the patient to make dietary and PA behaviour goals and plans (plans should specifically outline what, when, where, with whom and within what time scale to increase success).

• Goals should be measurable (*e.g.* aim for a specifc amount or percentage weight loss within a specific amount of time and/or increase step count within a specific amount of time).

• Encourage patients to maintain a food diary and record PA behaviour using a pedometer or alternative activity tracker to support self-regulation of behaviours.

Emphasis on turning intentions into actual behaviour change

Provide information

Follow-up session

• Review dietary and PA behaviour in relation to previously set goals and plans to provide feedback.

• Revise goals and plans if necessary (*e.g.* if a patient is struggling to reach goals previously set).

• Discuss ways to prevent relapse if the patient has successfully changed their diet and/or PA behaviour.

Emphasis on maintenance of behaviour change

Fig. 4. A practical guide for behavioural therapy in the lifestyle treatment of NASH.[171]

exercise, the optimal placement for exercise is likely as an adjunct to dietary manipulation, whether in NAFLD or NASH. Combined, this evidence strongly supports the role of lifestyle as a primary therapy for the management of NAFLD and NASH. The question is no longer whether lifestyle is an effective clinical therapy; the question is now how do we implement lifestyle as a therapy in everyday clinical care.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose

regarding funding or conflict of interest with respect to this manuscript.

Authors' contribution

All three authors contributed equally in the elaboration of the manuscript.

Review

Review

References

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

[2] Farrell GC, van Rooyen D, Gan L, Chitturi S. NASH is an inflammatory disorder: pathogenic, prognostic and therapeutic implications. Gut Liver 2012;6:149–171.

[3] 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;34:274–285.

[4] Charlton MR, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA. Frequency and outcomes of liver transplantation for nonalcoholic steato-hepatitis in the United States. Gastroenterology 2011;141:1249–1253.

[5] Shaker M, Tabbaa A, Albeldawi M, Alkhouri N. Liver transplantation for nonalcoholic fatty liver disease: new challenges and new opportunities. World J Gastroenterol 2014;20:5320–5330.

[6] Shen J, Wong GL, Chan HL, Chan HY, Yeung DK, Chan RS, et al. PNPLA3 gene polymorphism accounts for fatty liver in community subjects without metabolic syndrome. Aliment Pharmacol Ther 2014;39:532–539.

[7] Wang X, Liu Z, Wang K, Wang Z, Sun X, Zhong L, et al. Additive effects of the risk alleles of PNPLA3 and TM6SF2 on non-alcoholic fatty liver disease (NAFLD) in a Chinese population. Front Genet 2016;7:140.

[8] Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73–84.

[9] Zelber-Sagi S, Lotan R, Shlomai A, Webb M, Harrari G, Buch A, et al. Predictors for incidence and remission of NAFLD in the general population during a seven-year prospective follow-up. J Hepatol 2012;56:1145–1151.

[10] Koopman KE, Caan MW, Nederveen AJ, Pels A, Ackermans MT, Fliers E, et al. Hypercaloric diets with increased meal frequency, but not meal size, increase intrahepatic triglycerides: a randomized controlled trial. Hepatology 2014;60:545–553.

[11] Diabetes Obesity. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64:1388–1402.

[12] Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight loss through lifestyle modifica-tion significantly reduces features of nonalcoholic steatohepatitis. Gastroen-terology 2015;149:367–378, [Quiz e314–e365].

[13] Storlien LH, Kraegen EW, Chisholm DJ, Ford GL, Bruce DG, Pascoe WS. Fish oil prevents insulin resistance induced by high-fat feeding in rats. Science 1987;237:885–888.

[14] Sekiya M, Yahagi N, Matsuzaka T, Najima Y, Nakakuki M, Nagai R, et al. Polyunsaturated fatty acids ameliorate hepatic steatosis in obese mice by SREBP-1 suppression. Hepatology 2003;38:1529–1539.

[15] Levy JR, Clore JN, Stevens W. Dietary n-3 polyunsaturated fatty acids decrease hepatic triglycerides in Fischer 344 rats. Hepatology 2004;39:608–616.

[16] Musso G, Gambino R, De Michieli F, Cassader M, Rizzetto M, Durazzo M, et al. Dietary habits and their relations to insulin resistance and postprandial lipemia in nonalcoholic steatohepatitis. Hepatology 2003;37:909–916.

[17] Toshimitsu K, Matsuura B, Ohkubo I, Niiya T, Furukawa S, Hiasa Y, et al. Dietary habits and nutrient intake in non-alcoholic steatohepatitis. Nutrition 2007;23:46–52.

[18] Cortez-Pinto H, Jesus L, Barros H, Lopes C, Moura MC, Camilo ME. How different is the dietary pattern in non-alcoholic steatohepatitis patients? Clin Nutr 2006;25:816–823.

[19] Zelber-Sagi S, Nitzan-Kaluski D, Goldsmith R, Webb M, Blendis L, Halpern Z, et al. Long term nutritional intake and the risk for non-alcoholic fatty liver disease (NAFLD): a population based study. J Hepatol 2007;47:711–717.

[20] Rosqvist F, Iggman D, Kullberg J, Cedernaes J, Johansson HE, Larsson A, et al. Overfeeding polyunsaturated and saturated fat causes distinct effects on liver and visceral fat accumulation in humans. Diabetes 2014;63:2356–2368.

[21] Bjermo H, Iggman D, Kullberg J, Dahlman I, Johansson L, Persson L, et al. Effects of n-6 PUFAs compared with SFAs on liver fat, lipoproteins, and inflammation in abdominal obesity: a randomized controlled trial. Am J Clin Nutr 2012;95:1003–1012.

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

[23] Lu W, Li S, Li J, Wang J, Zhang R, Zhou Y, et al. Effects of omega-3 fatty acid in nonalcoholic fatty liver disease: a meta-analysis. Gastroenterol Res Pract 2016;2016:1459790.

[24] 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(4):1211–1221.

[25] Sanyal AJ, Abdelmalek MF, Suzuki A, Cummings OW, Chojkier MEPE-A Study Group. No significant effects of ethyl-eicosapentanoic acid on histologic features of nonalcoholic steatohepatitis in a phase 2 trial. Gastroenterology 2014;147:377–384, e371.

[26] Argo CK, Patrie JT, Lackner C, Henry TD, de Lange EE, Weltman AL, et al. Effects of n-3 fish oil on metabolic and histological parameters in NASH: a double-blind, randomized, placebo-controlled trial. J Hepatol 2015;62:190–197.

[27] Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. Am J Clin Nutr 2003;77:1146–1155.

[28] Garg A. High-monounsaturated-fat diets for patients with diabetes mellitus: a meta-analysis. Am J Clin Nutr 1998;67:577S–582S.

[29] Grosso G, Mistretta A, Frigiola A, Gruttadauria S, Biondi A, Basile F, et al. Mediterranean diet and cardiovascular risk factors: a systematic review. Crit Rev Food Sci Nutr 2014;54:593–610.

[30] Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013;368:1279–1290.

[31] Salas-Salvado J, Bullo M, Estruch R, Ros E, Covas MI, Ibarrola-Jurado N, et al. Prevention of diabetes with Mediterranean diets: a subgroup analysis of a randomized trial. Ann Intern Med 2014;160:1–10.

[32] Uribarri J, Del Castillo MD, de la Maza MP, Filip R, Gugliucci A, Luevano-Contreras C, et al. Dietary advanced glycation end products and their role in health and disease. Advances in nutrition 2015;6:461–473.

[33] Kellow NJ, Savige GS. Dietary advanced glycation end-product restriction for the attenuation of insulin resistance, oxidative stress and endothelial dysfunction: a systematic review. Eur J Clin Nutr 2013;67:239–248.

[34] Singh R, Barden A, Mori T, Beilin L. Advanced glycation end-products: a review. Diabetologia 2001;44:129–146.

[35] Koschinsky T, He CJ, Mitsuhashi T, Bucala R, Liu C, Buenting C, et al. Orally absorbed reactive glycation products (glycotoxins): an environmental risk factor in diabetic nephropathy. Proc Natl Acad Sci USA 1997;94:6474–6479.

[36] Ramasamy R, Yan SF, Schmidt AM. Advanced glycation endproducts: from precursors to RAGE: round and round we go. Amino Acids 2012;42:1151–1161.

[37] Goldberg T, Cai W, Peppa M, Dardaine V, Baliga BS, Uribarri J, et al. Advanced glycoxidation end products in commonly consumed foods. J Am Diet Assoc 2004;104:1287–1291.

[38] Uribarri J, Woodruff S, Goodman S, Cai W, Chen X, Pyzik R, et al. Advanced glycation end products in foods and a practical guide to their reduction in the diet. J Am Diet Assoc 2010;110:911–916, e912.

[39] Hyogo H, Yamagishi S, Iwamoto K, Arihiro K, Takeuchi M, Sato T, et al. Elevated levels of serum advanced glycation end products in patients with non-alcoholic steatohepatitis. J Gastroenterol Hepatol 2007;22:1112–1119.

[40] Schmidt AM. Soluble RAGEs – Prospects for treating & tracking metabolic and inflammatory disease. Vascul Pharmacol 2015;72:1–8.

[41] Zelber-Sagi S, Salomone F, Kolodkin-Gal I, Erez N, Buch A, Yeshua H, et al. Protective role of soluble receptor for advanced glycation end-products in patients with non-alcoholic fatty liver disease. Dig Liver Dis 2017;49:523–529.

[42] Trovato FM, Catalano D, Martines GF, Pace P, Trovato GM. Mediterranean diet and non-alcoholic fatty liver disease: the need of extended and comprehen-sive interventions. Clin Nutr 2015;34:86–88.

[43] Bozzetto L, Prinster A, Annuzzi G, Costagliola L, Mangione A, Vitelli A, et al. Liver fat is reduced by an isoenergetic MUFA diet in a controlled randomized study in type 2 diabetic patients. Diabetes Care 2012;35:1429–1435.

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

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

[46] Moriya A, Iwasaki Y, Ohguchi S, Kayashima E, Mitsumune T, Taniguchi H, et al. Roles of alcohol consumption in fatty liver: a longitudinal study. J Hepatol 2015;62:921–927.

[47] Dunn W, Xu R, Schwimmer JB. Modest wine drinking and decreased prevalence of suspected nonalcoholic fatty liver disease. Hepatology 2008;47:1947–1954.

[48] Dixon JB, Bhathal PS, O'Brien PE. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. Gastroenterology 2001;121:91–100.

[49] Kwon HK, Greenson JK, Conjeevaram HS. Effect of lifetime alcohol consumption on the histological severity of non-alcoholic fatty liver disease. Liver Int 2014;34:129–135.

[50] 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;30:546–552.

[51] Dunn W, Sanyal AJ, Brunt EM, Unalp-Arida A, Donohue M, McCullough AJ, et al. Modest alcohol consumption is associated with decreased prevalence of steatohepatitis in patients with non-alcoholic fatty liver disease (NAFLD). J Hepatol 2012;57:384–391.

[52] Howard BV, Wylie-Rosett J. Sugar and cardiovascular disease: A statement for healthcare professionals from the Committee on Nutrition of the Council on Nutrition, Physical Activity, and Metabolism of the American Heart Association. Circulation 2002;106:523–527.

[53] Ouyang X, Cirillo P, Sautin Y, McCall S, Bruchette JL, Diehl AM, et al. Fructose consumption as a risk factor for non-alcoholic fatty liver disease. J Hepatol 2008;48:993–999.

[54] Assy N, Nasser G, Kamayse I, Nseir W, Beniashvili Z, Djibre A, et al. Soft drink consumption linked with fatty liver in the absence of traditional risk factors. Can J Gastroenterol 2008;22:811–816.

[55] Abid A, Taha O, Nseir W, Farah R, Grosovski M, Assy N. Soft drink consumption is associated with fatty liver disease independent of metabolic syndrome. J Hepatol 2009;51:918–924.

[56] Poulsom R. Morphological changes of organs after sucrose or fructose feeding. Prog Biochem Pharmacol 1986;21:104–134.

[57] Herman RH, Zakim D, Stifel FB. Effect of diet on lipid metabolism in experimental animals and man. Fed Proc 1970;29:1302–1307.

[58] Vos MB, McClain CJ. Fructose takes a toll. Hepatology 2009;50:1004–1006.

[59] Bergheim I, Weber S, Vos M, Kramer S, Volynets V, Kaserouni S, et al. Antibiotics protect against fructose-induced hepatic lipid accumulation in mice: role of endotoxin. J Hepatol 2008;48:983–992.

[60] Vos MB, Lavine JE. Dietary fructose in nonalcoholic fatty liver disease. Hepatology 2013;57:2525–2531.

[61] Choi JW, Ford ES, Gao X, Choi HK. Sugar-sweetened soft drinks, diet soft drinks, and serum uric acid level: the Third National Health and Nutrition Examination Survey. Arthritis Rheum 2008;59:109–116.

[62] Afzali A, Weiss NS, Boyko EJ, Ioannou GN. Association between serum uric acid level and chronic liver disease in the United States. Hepatology 2010;52:578–589.

[63] Xu C, Yu C, Xu L, Miao M, Li Y. High serum uric acid increases the risk for nonalcoholic Fatty liver disease: a prospective observational study. PLoS One 2010;5:e11578.

[64] Zelber-Sagi S, Ben-Assuli O, Rabinowich L, Goldstein A, Magid A, Shalev V, et al. The association between the serum levels of uric acid and alanine aminotransferase in a population-based cohort. Liver Int 2015;59:109–116.

[65] Leung C, Herath CB, Jia Z, Goodwin M, Mak KY, Watt MJ, et al. Dietary glycotoxins exacerbate progression of experimental fatty liver disease. J Hepatol 2014;60:832–838.

[66] Ma J, Fox CS, Jacques PF, Speliotes EK, Hoffmann U, Smith CE, et al. Sugar-sweetened beverage, diet soda, and fatty liver disease in the Framingham Heart Study cohorts. J Hepatol 2015;63:462–469.

[67] Maersk M, Belza A, Stodkilde-Jorgensen H, Ringgaard S, Chabanova E, Thomsen H, et al. Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat depot: a 6-mo randomized intervention study. Am J Clin Nutr 2012;95:283–289.

[68] Abdelmalek MF, Suzuki A, Guy C, Unalp-Arida A, Colvin R, Johnson RJ, et al. Increased fructose consumption is associated with fibrosis severity in patients with nonalcoholic fatty liver disease. Hepatology 2010;51:1961–1971.

[69] Sawada N, Inoue M, Iwasaki M, Sasazuki S, Shimazu T, Yamaji T, et al. Consumption of n-3 fatty acids and fish reduces risk of hepatocellular carcinoma. Gastroenterology 2012;142:1468–1475.

[70] Ioannou GN, Morrow OB, Connole ML, Lee SP. Association between dietary nutrient composition and the incidence of cirrhosis or liver cancer in the United States population. Hepatology 2009;50:175–184.

[71] Fedirko V, Lukanova A, Bamia C, Trichopolou A, Trepo E, Nothlings U, et al. Glycemic index, glycemic load, dietary carbohydrate, and dietary fiber intake and risk of liver and biliary tract cancers in Western Europeans. Ann Oncol 2013;24:543–553.

[72] Yang Y, Zhang D, Feng N, Chen G, Liu J, Chen G, et al. Increased intake of vegetables, but not fruit, reduces risk for hepatocellular carcinoma: a meta-analysis. Gastroenterology 2014;147:1031–1042.

[73] Turati F, Trichopoulos D, Polesel J, Bravi F, Rossi M, Talamini R, et al. Mediterranean diet and hepatocellular carcinoma. J Hepatol 2014;60:606–611.

[74] Vitaglione P, Morisco F, Mazzone G, Amoruso DC, Ribecco MT, Romano A, et al. Coffee reduces liver damage in a rat model of steatohepatitis: the underlying mechanisms and the role of polyphenols and melanoidins. Hepatology 2010;52:1652–1661.

[75] Salomone F, Li Volti G, Vitaglione P, Morisco F, Fogliano V, Zappala A, et al. Coffee enhances the expression of chaperones and antioxidant proteins in rats with nonalcoholic fatty liver disease. Transl Res 2013;163:593–602.

[76] Shi H, Dong L, Dang X, Liu Y, Jiang J, Wang Y, et al. Effect of chlorogenic acid on LPS-induced proinflammatory signaling in hepatic stellate cells. Inflamm Res 2013;62:581–587.

[77] Shang F, Li X, Jiang X. Coffee consumption and risk of the metabolic syndrome: A meta-analysis. Diabetes Metab 2016;42:80–87.

[78] Ding M, Bhupathiraju SN, Chen M, van Dam RM, Hu FB. Caffeinated and decaffeinated coffee consumption and risk of type 2 diabetes: a systematic review and a dose-response meta-analysis. Diabetes Care 2014;37:569–586.

[79] Molloy JW, Calcagno CJ, Williams CD, Jones FJ, Torres DM, Harrison SA. Association of coffee and caffeine consumption with fatty liver disease, nonalcoholic steatohepatitis, and degree of hepatic fibrosis. Hepatology 2012;55:429–436.

[80] Zelber-Sagi S, Salomone F, Webb M, Lotan R, Yeshua H, Halpern Z, et al. Coffee consumption and nonalcoholic fatty liver onset: a prospective study in the general population. Transl Res 2015;165:428–436.

[81] Anty R, Marjoux S, Iannelli A, Patouraux S, Schneck AS, Bonnafous S, et al. Regular coffee but not espresso drinking is protective against fibrosis in a cohort mainly composed of morbidly obese European women with NAFLD undergoing bariatric surgery. J Hepatol 2012;57:1090–1096.

[82] Bambha K, Wilson LA, Unalp A, Loomba R, Neuschwander-Tetri BA, Brunt EM, et al. Coffee consumption in NAFLD patients with lower insulin resistance is associated with lower risk of severe fibrosis. Liver Int 2014;34:1250–1258.

[83] Catalano D, Martines GF, Tonzuso A, Pirri C, Trovato FM, Trovato GM. Protective role of coffee in non-alcoholic fatty liver disease (NAFLD). Dig Dis Sci 2010;55:3200–3206.

[84] Birerdinc A, Stepanova M, Pawloski L, Younossi ZM. Caffeine is protective in patients with non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2012;35:76–82.

[85] Setiawan VW, Wilkens LR, Lu SC, Hernandez BY, Le Marchand L, Henderson BE. Association of coffee intake with reduced incidence of liver cancer and death from chronic liver disease in the US multiethnic cohort. Gastroenterology 2015;148:118–125, [Quiz e115].

[86] Bravi F, Bosetti C, Tavani A, Gallus S, La Vecchia C. Coffee reduces risk for hepatocellular carcinoma: an updated meta-analysis. Clin Gastroenterol Hepatol 2013;11:1413–1421, e141.

[87] Lirussi F, Azzalini L, Orando S, Orlando R, Angelico F. Antioxidant supplements for non-alcoholic fatty liver disease and/or steatohepatitis. Cochrane Database Syst Rev 2007:CD004996.

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

[89] Wei J, Lei GH, Fu L, Zeng C, Yang T, Peng SF. Association between dietary vitamin C intake and non-alcoholic fatty liver disease: a cross-sectional study among middle-aged and older adults. PLoS One 2016;11:e0147985.

[90] Han JM, Jo AN, Lee SM, Bae HS, Jun DW, Cho YK, et al. Associations between intakes of individual nutrients or whole food groups and non-alcoholic fatty liver disease among Korean adults. J Gastroenterol Hepatol 2014;29:1265–1272.

[91] Da Silva HE, Arendt BM, Noureldin SA, Therapondos G, Guindi M, Allard JP. A cross-sectional study assessing dietary intake and physical activity in Canadian patients with nonalcoholic fatty liver disease vs healthy controls. J Acad Nutr Diet 2014;114:1181–1194.

[92] Madan K, Bhardwaj P, Thareja S, Gupta SD, Saraya A. Oxidant stress and antioxidant status among patients with nonalcoholic fatty liver disease (NAFLD). J Clin Gastroenterol 2006;40:930–935.

[93] Chan R, Wong VW, Chu WC, Wong GL, Li LS, Leung J, et al. Diet-quality scores and prevalence of nonalcoholic fatty liver disease: a population study using proton-magnetic resonance spectroscopy. PLoS One 2015;10:e0139310.

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[94] Guerrerio AL, Colvin RM, Schwartz AK, Molleston JP, Murray KF, Diehl A, et al. Choline intake in a large cohort of patients with nonalcoholic fatty liver disease. Am J Clin Nutr 2012;95:892–900.

[95] Kitson MT, Roberts SK. D-livering the message: the importance of vitamin D status in chronic liver disease. J Hepatol 2012;57:897–909.

[96] Abramovitch S, Dahan-Bachar L, Sharvit E, Weisman Y, Ben Tov A, Brazowski E, et al. Vitamin D inhibits proliferation and profibrotic marker expression in hepatic stellate cells and decreases thioacetamide-induced liver fibrosis in rats. Gut 2011;60:1728–1737.

[97] Eliades M, Spyrou E, Agrawal N, Lazo M, Brancati FL, Potter JJ, et al. Meta-analysis: vitamin D and non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2013;38:246–254.

[98] Bril F, Maximos M, Portillo-Sanchez P, Biernacki D, Lomonaco R, Subbarayan S, et al. Relationship of vitamin D with insulin resistance and disease severity in non-alcoholic steatohepatitis. J Hepatol 2015;62:405–411.

[99] Nelson JE, Roth CL, Wilson LA, Yates KP, Aouizerat B, Morgan-Stevenson V, et al. Vitamin D deficiency is associated with increased risk of non-alcoholic steatohepatitis in adults with non-alcoholic fatty liver disease: possible role for MAPK and NF-kappaB? Am J Gastroenterol 2016;111:852–863.

[100] Spiro A, Buttriss JL. Vitamin D: An overview of vitamin D status and intake in Europe. Nutr Bull 2014;39:322–350.

[101] Barchetta I, Del Ben M, Angelico F, Di Martino M, Fraioli A, La Torre G, et al. No effects of oral vitamin D supplementation on non-alcoholic fatty liver disease in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. BMC Med 2016;14:92.

[102] Kitson MT, Pham A, Gordon A, Kemp W, Roberts SK. High-dose vitamin D supplementation and liver histology in NASH. Gut 2016;65:717–718.

[103] Levine JA. Sick of sitting. Diabetologia 2015;58:1751–1758.

[104] Grontved A, Hu FB. Television viewing and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: a meta-analysis. JAMA 2011;305:2448–2455.

[105] Laaksonen DE, Lakka HM, Salonen JT, Niskanen LK, Rauramaa R, Lakka TA. Low levels of leisure-time physical activity and cardiorespiratory fitness predict development of the metabolic syndrome. Diabetes Care 2002;25:1612–1618.

[106] Chu AH, Moy FM. Joint association of sitting time and physical activity with metabolic risk factors among middle-aged Malays in a developing country: a cross-sectional study. PLoS One 2013;8:e61723.

[107] Dunstan DW, Salmon J, Healy GN, Shaw JE, Jolley D, Zimmet PZ, et al. Association of television viewing with fasting and 2-h postchallenge plasma glucose levels in adults without diagnosed diabetes. Diabetes Care 2007;30:516–522.

[108] Wijndaele K, Healy GN, Dunstan DW, Barnett AG, Salmon J, Shaw JE, et al. Increased cardiometabolic risk is associated with increased TV viewing time. Med Sci Sports Exerc 2010;42:1511–1518.

[109] Healy GN, Dunstan DW, Salmon J, Cerin E, Shaw JE, Zimmet PZ, et al. Breaks in sedentary time: beneficial associations with metabolic risk. Diabetes Care 2008;31:661–666.

[110] Ryu S, Chang Y, Jung HS, Yun KE, Kwon MJ, Choi Y, et al. Relationship of sitting time and physical activity with non-alcoholic fatty liver disease. J Hepatol 2015;63:1229–1237.

[111] Abadi A, Glover EI, Isfort RJ, Raha S, Safdar A, Yasuda N, et al. Limb immobilization induces a coordinate down-regulation of mitochondrial and other metabolic pathways in men and women. PLoS One 2009;4:e6518.

[112] Santaliestra-Pasias AM, Mouratidou T, Huybrechts I, Beghin L, Cuenca-Garcia M, Castillo MJ, et al. Increased sedentary behaviour is associated with unhealthy dietary patterns in European adolescents participating in the HELENA study. Eur J Clin Nutr 2014;68:300–308.

[113] Morris JN, Heady JA, Raffle PA, Roberts CG, Parks JW. Coronary heart-disease and physical activity of work. Lancet 1953;265:1053–1057.

[114] Perseghin G, Lattuada G, De Cobelli F, Ragogna F, Ntali G, Esposito A, et al. Habitual physical activity is associated with intrahepatic fat content in humans. Diabetes Care 2007;30:683–688.

[115] 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.

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

[117] Newton JL, Jones DE, Henderson E, Kane L, Wilton K, Burt AD, et al. Fatigue in non-alcoholic fatty liver disease (NAFLD) is significant and associates with inactivity and excessive daytime sleepiness but not with liver disease severity or insulin resistance. Gut 2008;57:807–813.

[118] Snowling NJ, Hopkins WG. Effects of different modes of exercise training on glucose control and risk factors for complications in type 2 diabetic patients: a meta-analysis. Diabetes Care 2006;29:2518–2527.

[119] Thomas DE, Elliott EJ, Naughton GA. Exercise for type 2 diabetes mellitus. Cochrane Database Syst Rev 2006:CD002968.

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

[121] Keating SE, Hackett DA, George J, Johnson NA. Exercise and non-alcoholic fatty liver disease: a systematic review and meta-analysis. J Hepatol 2012;57:157–166.

[122] Hashida R, Kawaguchi T, Bekki M, Omoto M, Matsuse H, Nago T, et al. Aerobic vs. resistance exercise in non-alcoholic fatty liver disease: A systematic review. J Hepatol 2017;66:142–152.

[123] 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;63:174–182.

[124] Zhang HJ, He J, Pan LL, Ma ZM, Han CK, Chen CS, et al. Effects of moderate and vigorous exercise on nonalcoholic fatty liver disease: a randomized clinical trial. JAMA Intern Med 2016;176:1074–1082.

[125] Zhang HJ, Pan LL, Ma ZM, Chen Z, Huang ZF, Sun Q, et al. Long-term effect of exercise on improving fatty liver and cardiovascular risk factors in obese adults: A 1-year follow-up study. Diabetes Obes Metab 2017;19:284–289.

[126] Pugh CJ, Sprung VS, Jones H, Richardson P, Shojaee-Moradie F, Umpleby AM, et al. Exercise-induced improvements in liver fat and endothelial function are not sustained 12 months following cessation of exercise supervision in nonalcoholic fatty liver disease. Int J Obes (Lond) 2016;40:1927–1930.

[127] 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;30:139–146.

[128] Cuthbertson DJ, Shojaee-Moradie F, Sprung VS, Jones H, Pugh CJ, Richardson P, et al. Dissociation between exercise-induced reduction in liver fat and changes in hepatic and peripheral glucose homoeostasis in obese patients with non-alcoholic fatty liver disease. Clin Sci (Lond) 2016;130:93–104.

[129] Shojaee-Moradie F, Cuthbertson DJ, Barrett M, Jackson NC, Herring R, Thomas EL, et al. Exercise training reduces liver fat and increases rates of VLDL clearance but not VLDL production in NAFLD. J Clin Endocrinol Metab 2016;101:4219–4228.

[130] van der Poorten D, Milner KL, Hui J, Hodge A, Trenell MI, Kench JG, et al. Visceral fat: a key mediator of steatohepatitis in metabolic liver disease. Hepatology 2008;48:449–457.

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

[132] Hallsworth K, Thoma C, Hollingsworth KG, Cassidy S, Anstee QM, Day CP, et al. Modified high-intensity interval training reduces liver fat and improves cardiac function in non-alcoholic fatty liver disease: a randomized controlled trial. Clin Sci (Lond) 2015;129:1097–1105.

[133] Houghton D, Thoma C, Hallsworth K, Cassidy S, Hardy T, Burt AD, et al. Exercise reduces liver lipids and visceral adiposity in patients with nonal-coholic steatohepatitis in a randomized controlled trial. Clin Gastroenterol Hepatol 2017;15:96–102, e3.

[134] Fealy CE, Haus JM, Solomon TP, Pagadala M, Flask CA, McCullough AJ, et al. Short-term exercise reduces markers of hepatocyte apoptosis in nonalco-holic fatty liver disease. J Appl Physiol 1985;2012:1–6.

[135] 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;27:103–107.

[136] Kantartzis K, Thamer C, Peter A, Machann J, Schick F, Schraml C, et al. High cardiorespiratory fitness is an independent predictor of the reduction in liver fat during a lifestyle intervention in non-alcoholic fatty liver disease. Gut 2009;58:1281–1288.

[137] Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. J Am Coll Cardiol 2014;63:2985–3023.

[138] Peng L, Wang J, Li F. Weight reduction for non-alcoholic fatty liver disease. Cochrane Database Syst Rev 2011:CD003619.

[139] Uusitupa M. Lifestyle changes and cardiovascular risk reduction in diabetes. Lancet Diabetes Endocrinol 2016;4:877–878.

[140] Lazo M, Solga SF, Horska A, Bonekamp S, Diehl AM, Brancati FL, et al. Effect of a 12-month intensive lifestyle intervention on hepatic steatosis in adults with type 2 diabetes. Diabetes Care 2010;33:2156–2163.

[141] Patel NS, Doycheva I, Peterson MR, Hooker J, Kisselva T, Schnabl B, et al. Effect of weight loss on magnetic resonance imaging estimation of liver fat and volume in patients with nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol 2015;13:561–568, e561.

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

[143] Eckard C, Cole R, Lockwood J, Torres DM, Williams CD, Shaw JC, et al. Prospective histopathologic evaluation of lifestyle modification in nonalcoholic fatty liver disease: a randomized trial. Therap Adv Gastroenterol 2013;6:249–259.

[144] Ross R, Hudson R, Stotz PJ, Lam M. Effects of exercise amount and intensity on abdominal obesity and glucose tolerance in obese adults: a randomized trial. Ann Intern Med 2015;162:325–334.

[145] Vissers D, Hens W, Taeymans J, Baeyens JP, Poortmans J, Van Gaal L. The effect of exercise on visceral adipose tissue in overweight adults: a systematic review and meta-analysis. PLoS One 2013;8:e56415.

[146] Look ARG, Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013;369:145–154.

[147] Byers T, Sedjo RL. Body fatness as a cause of cancer: epidemiologic clues to biologic mechanisms. Endocr Relat Cancer 2015;22:R125–R134.

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

[149] 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.

[150] 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;43:1060–1066.

[151] Glass LM, Dickson RC, Anderson JC, Suriawinata AA, Putra J, Berk BS, et al. Total body weight loss of >/= 10 % is associated with improved hepatic fibrosis in patients with nonalcoholic steatohepatitis. Dig Dis Sci 2015;60:1024–1030.

[152] Vilar-Gomez E, Yasells-Garcia A, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, et al. Development and validation of a noninvasive prediction model for nonalcoholic steatohepatitis resolution after lifestyle intervention. Hepatology 2016;63:1875–1887.

[153] Ryan MC, Abbasi F, Lamendola C, Carter S, McLaughlin TL. Serum alanine aminotransferase levels decrease further with carbohydrate than fat restriction in insulin-resistant adults. Diabetes Care 2007;30:1075–1080.

[154] Browning JD, Baker JA, Rogers T, Davis J, Satapati S, Burgess SC. Short-term weight loss and hepatic triglyceride reduction: evidence of a metabolic advantage with dietary carbohydrate restriction. Am J Clin Nutr 2011;93:1048–1052.

[155] Kirk E, Reeds DN, Finck BN, Mayurranjan SM, Patterson BW, Klein S. Dietary fat and carbohydrates differentially alter insulin sensitivity during caloric restriction. Gastroenterology 2009;136:1552–1560.

[156] Haufe S, Engeli S, Kast P, Bohnke J, Utz W, Haas V, et al. Randomized comparison of reduced fat and reduced carbohydrate hypocaloric diets on intrahepatic fat in overweight and obese human subjects. Hepatology 2011;53:1504–1514.

[157] 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;387:679–690.

[158] Armstrong MJ, Gaunt P, Newsome PN. Identifying patients with nonalcoholic steatohepatitis that are nonresponders to therapy. Hepatology 2016;64:2265–2266.

[159] Centis E, Moscatiello S, Bugianesi E, Bellentani S, Fracanzani AL, Calugi S, et al. Stage of change and motivation to healthier lifestyle in non-alcoholic fatty liver disease. J Hepatol 2013;58:771–777.

[160] Mlynarsky L, Schlesinger D, Lotan R, Webb M, Halpern Z, Santo E, et al. Non-alcoholic fatty liver disease is not associated with a lower health perception. World J Gastroenterol 2016;22:4362–4372.

[161] Haufe S, Haas V, Utz W, Birkenfeld AL, Jeran S, Bohnke J, et al. Long-lasting improvements in liver fat and metabolism despite body weight regain after dietary weight loss. Diabetes Care 2013;36:3786–3792.

[162] Look AHEAD Research Group, Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. Arch Intern Med 2010;170:1566–1575.

[163] Look AHEAD Research Group. Eight years weight losses with an intensive lifestyle intervention: the look AHEAD study. Obesity 2014;22:5–13.

[164] Bellentani S, Dalle Grave R, Suppini A, Marchesini GFatty Liver Italian Network. Behavior therapy for nonalcoholic fatty liver disease: The need for a multidisciplinary approach. Hepatology 2008;47:746–754.

[165] Kreuter MW, Chheda SG, Bull FC. How does physician advice influence patient behavior? Evidence for a priming effect. Arch Fam Med 2000;9:426–433.

[166] Loureiro ML, Nayga Jr RM. Obesity, weight loss, and physician's advice. Soc Sci Med 2006;62:2458–2468.

[167] Huang J, Yu H, Marin E, Brock S, Carden D, Davis T. Physicians' weight loss counseling in two public hospital primary care clinics. Acad Med 2004;79:156–161.

[168] Merz CN, Buse JB, Tuncer D, Twillman GB. Physician attitudes and practices and patient awareness of the cardiovascular complications of diabetes. J Am Coll Cardiol 2002;40:1877–1881.

[169] Zelber-Sagi S, Bord S, Dror-Lavi G, Smith ML, Towne Jr SD, Buch A, et al. Role of illness perception and self-efficacy in lifestyle modification among non-alcoholic fatty liver disease patients. World J Gastroenterol 2017;23:1881–1890.

[170] Whitlock EP, Orleans CT, Pender N, Allan J. Evaluating primary care behavioral counseling interventions: an evidence-based approach. Am J Prev Med 2002;22:267–284.

[171] Hallsworth K, Avery L, Trenell MI. Targeting lifestyle behavior change in adults with NAFLD during a 20-min consultation: summary of the dietary and exercise literature. Curr Gastroenterol Rep 2016;18:11.

[172] 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;53:413–419.

[173] Petersen KF, Dufour S, Befroy D, Lehrke M, Hendler RE, Shulman GI. Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. Diabetes 2005;54:603–608.

[174] Huang MA, Greenson 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;100:1072–1081.

[175] Zelber-Sagi S, Kessler A, Brazowsky E, Webb M, Lurie Y, Santo M, et al. A double-blind randomized placebo-controlled trial of orlistat for the treatment of nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2006;4:639–644.

[176] Benjaminov O, Beglaibter N, Gindy L, Spivak H, Singer P, Wienberg M, et al. The effect of a low-carbohydrate diet on the nonalcoholic fatty liver in morbidly obese patients before bariatric surgery. Surg Endosc 2007;21:1423–1427.

[177] Tendler D, Lin S, Yancy Jr 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;52:589–593.

[178] Yamamoto M, Iwasa M, Iwata K, Kaito M, Sugimoto R, Urawa N, et al. Restriction of dietary calories, fat and iron improves non-alcoholic fatty liver disease. J Gastroenterol Hepatol 2007;22:498–503.

[179] de Luis DA, Aller R, Izaola O, Sagrado MG, Conde R, Gonzalez JM. Effect of a hypocaloric diet in transaminases in nonalcoholic fatty liver disease and obese patients, relation with insulin resistance. Diabetes Res Clin Pract 2008;79:74–78.

[180] Oza N, Eguchi Y, Mizuta T, Ishibashi E, Kitajima Y, Horie H, et al. A pilot trial of body weight reduction for nonalcoholic fatty liver disease with a home-based lifestyle modification intervention delivered in collaboration with interdisciplinary medical staff. J Gastroenterol 2009;44:1203–1208.

[181] St George A, Bauman A, Johnston A, Farrell G, Chey T, George J. Effect of a lifestyle intervention in patients with abnormal liver enzymes and metabolic risk factors. J Gastroenterol Hepatol 2009;24:399–407.

[182] Viljanen AP, Iozzo P, Borra R, Kankaanpaa M, Karmi A, Lautamaki R, et al. Effect of weight loss on liver free fatty acid uptake and hepatic insulin resistance. J Clin Endocrinol Metab 2009;94:50–55.

[183] Vilar Gomez E, Rodriguez De Miranda A, Gra Oramas B, Arus Soler E, Llanio Navarro R, Calzadilla Bertot L, et al. Clinical trial: a nutritional supplement Viusid, in combination with diet and exercise, in patients with nonalcoholic fatty liver disease. Aliment Pharmacol Ther 2009;30:999–1009.

[184] 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 2009;17:2162–2168.

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[185] Elias MC, Parise ER, de Carvalho L, Szejnfeld D, Netto JP. Effect of 6-month nutritional intervention on non-alcoholic fatty liver disease. Nutrition 2010;26:1094–1099.

[186] Albu JB, Heilbronn LK, Kelley DE, Smith SR, Azuma K, Berk ES, et al. Metabolic changes following a 1-year diet and exercise intervention in patients with type 2 diabetes. Diabetes 2010;59:627–633.

[187] Moscatiello S, Di Luzio R, Bugianesi E, Suppini A, Hickman IJ, Di Domizio S, et al. Cognitive-behavioral treatment of nonalcoholic Fatty liver disease: a propensity score-adjusted observational study. Obesity 2011;19:763–770.

[188] Sun WH, Song MQ, Jiang CQ, Xin YN, Ma JL, Liu YX, et al. Lifestyle intervention in non-alcoholic fatty liver disease in Chengyang District, Qingdao, China. World J Hepatol 2012;4:224–230.

[189] Scaglioni F, Marino M, Ciccia S, Procaccini A, Busacchi M, Loria P, et al. Short-term multidisciplinary non-pharmacological intervention is effective in reducing liver fat content assessed non-invasively in patients with nonalcoholic fatty liver disease (NAFLD). Clin Res Hepatol Gastroenterol 2013;37:353–358.

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

[191] Yoshimura E, Kumahara H, Tobina T, Matsuda T, Ayabe M, Kiyonaga A, et al. Lifestyle intervention involving calorie restriction with or without aerobic exercise training improves liver fat in adults with visceral adiposity. J Obes 2014;2014:197216.

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