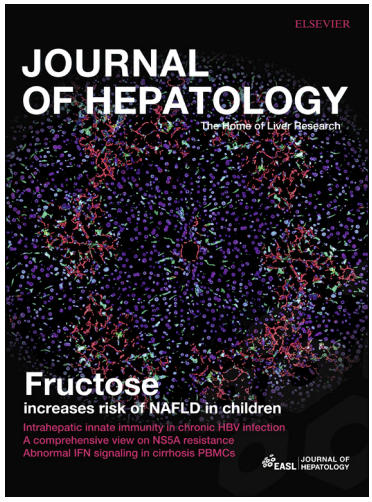

Review

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Invited Review

Treatment of NAFLD with diet, physical activity and exercise

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Key points

1. The Mediterranean diet can reduce liver fat even without weight loss and is the most recommended dietary pattern in NAFLD.
2. Fructose consumption is associated with alteration in gut microbiota, increased intestinal permeability, endotoxemia, increased hepatic TNF production and lipid peroxidation promoting hepatic steatosis and NAFLD.
3. Drinking coffee reduces HCC risk. The hepatoprotective effects of coffee may be linked not only to caffeine but also to its polyphenolic fraction
4. Sedentary behaviour and physical activity they 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.
5. A '*triple hit behavioural phenotype*' of 1) sedentary behaviour, 2) low physical activity, and 3) poor diet have been defined.
6. Losing weight decreases cardiovascular and diabetes risk and also regresses liver disease.
7. Weight reductions of ≥ 10% are required for inducing near universal NASH resolution or fibrosis improvement by at least one stage.
8. 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 normalization of ALT (≤19 in females or ≤30 in males) and weight loss percentage ≥ 10%.
9. The 5 *A*'s model (***ask, advise, assess, assist, and arrange***) may be useful as a tool to assist clinicians advising NAFLD patients to modify their behaviour,

assessing their interest in doing so, assisting in their efforts to change, and arranging appropriate follow-up.

Summary

Lifestyle intervention can be useful across all the spectrum of NAFLD patients. Losing weight decreases cardiovascular / diabetes risk and also regresses liver disease. Weight reductions of ≥ 10% are required for inducing near universal NASH resolution or fibrosis improvement by at least one stage. However, modest weight losses (>5%) also produce important benefits on NAS and its components. In addition, to improve the success of this intervention we need to explore, beyond total calories and type of weight loss diet, the role of micro and macronutrients, evidence-based benefits of physical activity and exercise and finally supporting these modifications through established behaviour change models and techniques.

The Mediterranean diet can reduce liver fat even without weight loss and is the most recommended dietary pattern in NAFLD. The Mediterranean diet is characterized by reduced carbohydrates 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 acids 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 1) sedentary behaviour, 2) low physical activity, and 3) 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, and 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 due to 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]. Risk of detrimental outcomes is increased in patients with significant fibrosis, or steatohepatitis being 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 around 2 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 NAFLD patients at risk of progression in order to implement therapeutic interventions leading to prevent/reverse the deleterious consequences of advanced NASH.

Patients with NAFLD are frequently obese and diabetics, and insulin resistance is a key pathogenic trigger. Four phenotypes of patients with NAFLD have been defined: obese, type 2 diabetes, metabolic syndrome and lean patients. PNPLA3 is the genetic hallmark of NAFLD. Patients bearing genotype GG show 3 times increased risk for NAFLD. This raised risk is more evident in patients without metabolic syndrome [6]. Indeed, TM6SF2 mutation has additive effect on NAFLD risk [7].

Lifestyle intervention can be useful across the spectrum of NAFLD patients. In simple steatosis, losing weight can decrease cardiovascular / diabetes risk and in patients with steatohepatitis / fibrosis this intervention can also lead to regression of liver disease. However, to improve the success of this intervention we need to explore the role of nutrition (micro and macronutrients together with type of diet and calories), the clinical benefits of increasing physical activity and exercise and finally the evidenced-based behaviour change models and techniques for the long-term maintenance of lifestyle modifications.

Role of macro and micronutrients in NAFLD

Role of energy restriction

Over-caloric consumption leading to obesity and related comorbidities is a leading risk factor for NAFLD [8]. Furthermore, weight gain by itself, even if as modest as 3-5 Kg predicts the development of NAFLD, regardless of baseline BMI [9]. Interestingly, not only over caloric consumption but also the way it is distributed throughout the day affects liver fat accumulation. In 6 weeks RCT**,** high-fat-high-sugar or high-sugar hyper-caloric diets were consumed either together with main meals or between them as snaking. Only the latter increased liver fat (by MRS) and abdominal fat (by 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 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 as compared to age, gender and BMI matched controls, is richer in saturated fat and cholesterol and poorer in polyunsaturated fatty acids (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 polyunsaturated (PUFA) and saturated fat (SFA) has distinct effects on liver and visceral fat accumulation in humans; 7 weeks RCT of overeating SFAs or omega 6-PUFAs led to similar weight gain, but the SFAs, markedly increased liver fat compared with PUFAs and caused a twofold larger increase in visceral fat than PUFAs [20]. Similarly, a 10 weeks RCT of isocaloric diets demonstrated that omega 6-PUFAs intake reduce 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 potential beneficial effect on liver fat reduction [22]. In a later meta-analysis of 10 RCTs, omega-3 treatment was beneficial in terms of decreased amount of liver fat and improved gamma-glutamyl transferase (GGT), but it was not significantly efficient in reduction of ALT and aspartate aminotransferase (AST)[23]. Recent RCTs, which included liver histology, enabled to learn on its effect on NASH and fibrosis, but

results are conflicting, mostly indicating a beneficial effect for liver fat reduction (for DHA containing supplements, not for EPA alone) but not NASH or fibrosis [24-26]. Furthermore, in contrast to experimental findings, there was no consistent significant effect on insulin resistance [25, 26]. In summary, different types of fat have different effects in NAFLD and NASH. Therefore, a simple reduction on total fat intake is *in*appropriate.

The traditional Mediterranean diet (MD) is characterized by a high intake of olive oil (which is rich in monounsaturated-fat-MUFA), nuts, fruits & vegetables, legumes and fish and a low intake of red meat, processed meats, and sweets (wine in moderation), and in contrast to the low fat diet which contains up-to 30% fat, the Mediterranean diet contains 40% of the calories as fat, mostly MUFA and omega-3 PUFA. MUFA has a favourable effect on lipid profile [27, 28]. Moreover, Mediterranean diet plays an important beneficial role in metabolic profile of humans [29] and has been demonstrated to reduce the risk for cardiovascular disease [30] and diabetes [31], two endpoints which are highly relevant to NAFLD patients. Interestingly, one of the principles of the Mediterranean diet is to minimize 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 in the diet. AGEs are related with the aetiology of diabetes and other metabolic alterations [34, 37, 38], and have been demonstrated 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 demonstrated 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 diet pattern leads to a significant decrease in liver fat among overweight patients with NAFLD [42]. This was supported by two short-term randomized trials in NAFLD patients with or without type-2 diabetes. In both studies, patients were assigned to two isocaloric diets: either low fat high-carbohydrate diet or 8-weeks high-MUFA diet in one study and 6-weeks Mediterranean diet in the other study. 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 stable weight in both groups [43, 44]. However, longer-term trials testing the Mediterranean diet are needed. Importantly, the Mediterranean diet is also characterized by reduced carbohydrates 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.

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-cirrhotic patients should avoid alcohol since any regular alcohol consumption puts then at a greater risk for HCC [45]. However, uncertainty remains regarding moderate alcohol consumption (up-to 2 drinks per day), among non-cirrhotic patients, since several studies have shown a protective association of moderate alcohol consumption with NAFLD [46-50] and NASH [51]. The protective effect may be specific for wine, since modest drinkers of up to 10g of alcohol a day from wine, but not from other types of alcoholic beverages, had a lower prevalence of

unexplained elevated ALT compared to non-drinkers in a national cross-sectional survey [47].

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

Added sugars

Added sugar refers to refined sugars (sucrose, fructose and high fructose corn syrup - HFCS) added to sugared sweetened beverages (SSB) and incorporated into food, fruit drinks, and other beverages [52]. There is convincing evidence from epidemiological studies for the 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, fructose is associated in animal studies with alteration in intestinal micro flora, increased gut permeability, endotoxemia, increased hepatic TNF production, lipid peroxidation and hepatic steatosis [58, 59], and a growing body of evidence supports its role 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 demonstrated to be associated with the development of cirrhosis [62], NAFLD [63] and had a positive dose-response association with elevated serum ALT regardless of BMI [64]. In addition, cola soft drinks contain caramel colouring, which is rich in AGEs that may increase insulin resistance, inflammation and exacerbates liver injury, steatohepatitis, and liver fibrosis[39, 65].

Indeed, in the Framingham Heart Study cohort, that included cross-sectional analysis of fat infiltration in the liver by computed tomography in 2634 people and ALT measurement in 5908 participants, a dose-response association was observed 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, 1 liter/day of regular cola but not isocaloric semi skim milk or aspartame-sweetened diet cola led to increased liver fat [67]. Fructose-containing soft drinks were also demonstrated in an observational study to be associated with a 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.

Role of dietary composition in the risk for transition from NASH to HCC

Little is known about the association between dietary composition and hepatocellular carcinoma (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, consumption of 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 higher risk of cirrhosis or liver cancer [70]. Among 477,206 participants of the European Prospective Investigation into Cancer and Nutrition cohort, the risk for 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 fiber [71]. Accordingly, in a meta-analysis of observational studies the intake of vegetables, but not fruit, was associated with lower risk for hepatocellular carcinoma, which decreased by 8% for every 100g/d increase in vegetable intake [72]. Interestingly, the Mediterranean diet pattern, which is based on high consumption of fish, vegetables and fiber with low consumption of sugar, has been demonstrated to be associated with lower odds for liver cancer, although in a case-control study [73].

Additional way to reduce HCC risk is by drinking coffee. 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 reduction in: hepatic fat accumulation, systemic 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 for the 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 from HCC [85, 86]. In a US Multi-ethnic prospective cohort, which included 162,022 participants, compared with non-coffee drinkers, those who drank 2-3 cups per day had a 38% reduction in risk for HCC and 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 coffee per day had a 46% reduction in risk 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, body mass index, 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 efficacy of antioxidants in animal models, the efficacy of antioxidant therapy in humans has not been demonstrated or properly tested [87], with the exception of vitamin E in the form of high dose supplement [88]. A recent study tested the cross-sectional association between ultrasound diagnosed NAFLD and dietary vitamin C intake among 3471 subjects, demonstrating a significant inverse, energy-adjusted, association among men or normal weight subgroups [89]. In another cross-sectional study a significant positive association between low vitamin C intake and NAFLD was also demonstrated in the male population [90]. In contrast, other smaller studies did not find such association [91, 92]. In a large cross-sectional population-based study in Hong Kong an inverse association with MRS diagnosed NAFLD was demonstrated with intake of vitamin C as well as vegetables, legumes and fruits, and the joint consumption of these foods, creating a Dietary Quality Index, was negatively associated with 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 and a similar trend was noted in both premenopausal women and men [94]. Choline is particularly abundant in egg yolks and animal sources of protein.

Vitamin D has several favorable metabolic effects and according to experimental data it is acting 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 another large study of 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 for women, the lowest in Spain (44, in women) and the highest Finland (330, in men)[100], whereas the Dietary Reference Intakes (DRI) 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 *in*activity, 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 together [106]. Beyond cardio-metabolic health, 3+hrs 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, including activities such as sitting, is reported to be higher in people predisposed to the metabolic syndrome, excessive adiposity and T2DM [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 triglycerides 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 needs 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 that identify 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 down- and up-regulate 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 1) sedentary behaviour, 2) low physical activity, and 3) 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 Prof 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 deckers" bus. Cross-sectional studies suggest that people with NAFLD have lower levels of physical 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 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 IR, impaired glucose tolerance, or T2DM [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 randomised control trials 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 twenty four 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, lashing in the main 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 in 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. More recent, 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 as a consequence, 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 VLDL 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 linked 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 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 mediators of response to exercise in NAFLD can be seen in **Figure 2**.

Data reporting the effects of exercise in people with NASH are limited. To date, only 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 will 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/wk) 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 first end-point 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 (summarized in **Table 2**). Marked differences in the study design including various forms of lifestyle intervention with different diets and physical activity regimens, absence of standardized 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 WL is required to induce 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-randomized 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 of the effect of lifestyle

changes in patients with NASH, those who lost 10% or more 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 of a program of lifestyle changes through a hypocaloric diet combined with exercise on histological features of NASH in a large cohort of patients followed in the routine clinical practice during 12 months, and examined the relationship between the degree of weight reduction and the improvements in overall histological parameters. This study 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) (**Figure 3**). In a post-hoc analysis of this study, patients with weight loss between 7 and 10% and "unfavourable" risk factors such as female sex, presence of diabetes, a BMI >35 or many ballooned cells at baseline had lower rates of NASH resolution. On the other hand, 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 recommends that in overweight/obese NAFLD, a 7–10% weight loss is the target of most lifestyle interventions, and results in improvement of liver enzymes and histology (B1) [11].

The impact of weight loss on histological improvement depends on the degree of weight reduction independently 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 carbohydrates diet may seem more effective in reducing liver fat, but only on 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 months 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 significant similar 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 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 normalization of ALT (≤19 in females or ≤30 in males) and weight loss percentage [152]. Taking into account all these 5 variables a NASH resolution calculator (available at http://www.aeeh.es/calculadora-nashres/) has been developed and could be useful in the management of patients undergoing intervention focused on weight loss. In the cohort of 261 patients treated with lifestyle intervention during 52 weeks (140 in derivation set / 121 in temporary validation set) NASHRES calculator demonstrate 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, versus placebo[157]. NASHRES calculator allowed to correctly classifying 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 life-style modification

There is no doubt that lifestyle modification and weight loss pose a great challenge on both the patients and caregivers. NAFLD patients may have 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 utilization [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 reaching to only 3 to 4 kg weight reduction at 2 years follow-up[137]. Interestingly, even if there is weight regain after diet, there seems to be long lasting beneficial effect on liver fat and insulin resistance. In a study with 2 years follow-up after 6 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 4 years, despite partial weight regain 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 keep the patient without weight regain. In the Look AHEAD study, which included 5145 overweight type 2 diabetes patients, [163] long-term lifestyle intervention produced ≥5% weight loss at 8 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; a high-intensity (i.e., ≥14 sessions in 6m) 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 NAFLD patient's self-management may be an implementation of a "multidisciplinary 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 indicated 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 NAFLD patients the broader picture of 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 NAFLD patients, 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 NAFLD patients to modify their behaviour, assessing their interest in doing so, assisting in their efforts to change, and arranging appropriate follow-up [170].

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

NAFLD patients rarely receive support to make 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 of the clinical care teams in the delivery of effective behaviour change interventions (i.e., use of behaviour change and brief motivational techniques). Behaviour change typically involves three stages (see **Figure 4**).

Summary & conclusions

Lifestyle change, including dietary habits and physical activity, are and should be the first line treatment in NAFLD and NASH. Weight reduction is the most established treatment for both NAFLD and NASH, with a clear dose-response association. Any generally 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 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 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.

Figure legends

Figure 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 diets 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.

Figure 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.

Figure 3. Probability of reaching NASH-resolution, fibrosis regression and steatosis improvement in patients with NASH under lifestyle intervention according to percentage of weight loss (modified from Vilar-Gomez et al Ref#12)

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

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 S. 2015	All caffeinated coffee types	347	No	Yes (Fibrotest)
Bambha K. 2013	Caffeinated and decaffeinated	782	No	Yes
Anty R. 2012	Regular coffee, not espresso	195	NE	Yes
Birerdinc A. 2012	Caffeine intake	41,658	Yes	NE
Molloy JW. 2012	Regular coffee	306	No	Yes
Catalano D. 2010	Only espresso coffee	245	Yes	NE

Not evaluated :NE

2Table . 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]	Randomized 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 nondiabetic (with and without elevated ALT)	3months, hypocaloric low fat diet	NE	NE	Reduced	Reduced
Kantartzis, 2009 [136]	Single-arm trial	50 NAFLD	9 months, dietary counselling with up	NE	Reduced (MRS)	Reduced	Reduced

Author, Year	Study design	Patients	Intervention (duration, type)	Outcomes			
				Liver histology	Liver fat by imaging (modality)	Liver enzymes	Insulin resistance†
			to 10 sessions with a dietician				
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]	Randomized 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
Kirk, 2009 [155]	Randomized controlled trial	22 obese subjects	About 11 weeks, high-carbohydrate (>180g/d) vs. low-carbohydrate (<60g/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]	Randomized 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]	Randomized 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	Randomized	96 type-2	12 months,	NE	Reduced	No change	Not shown

Author, Year	Study design	Patients	Intervention (duration, type)	Outcomes			
				Liver histology	Liver fat by imaging (modality)	Liver enzymes	Insulin resistance†
[140]	controlled trial within the Look AHEAD study	diabetes patients	intensive lifestyle intervention vs. control group who received diabetes support and education		(MRS)		
Promrat, 2010 [148]	Randomized controlled trial	31 NASH	48 weeks intensive lifestyle intervention of diet, exercise, and behavior 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]	Randomized 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
Browning, 2011 [154]	Controlled trial	18 NAFLD	2 weeks, carbohydrate-restricted (<20 g/d) vs. calorie restricted (1200–1500 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]	Randomized 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]	Randomized controlled trial	Type-2 diabetes patients	8-week, isocaloric high-MUFA diet vs. high-carbohydrate/high-fiber/low-glycemic index diet, both arms with or	NE	Reduced more with the high-MUFA diet, regardless of physical activity (MRS)	Unchanged	Unchanged

Author, Year	Study design	Patients	Intervention (duration, type)	Outcomes			
				Liver histology	Liver fat by imaging (modality)	Liver enzymes	Insulin resistance†
			without physical activity program				
Ryan, 2013[44]	Randomized 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]	Randomized 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 behavior therapy	NE	Reduced (AUS)	Reduced	Unchanged
Wong, 2013 [190]	Randomized controlled trial	154 NAFLD	12 months, community-based dietitian-led lifestyle modification program at 2 community centers vs. usual care	NE	Reduced (MRS)	Reduced	NE
Yoshimura, 2014 [191]	Randomized, 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

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

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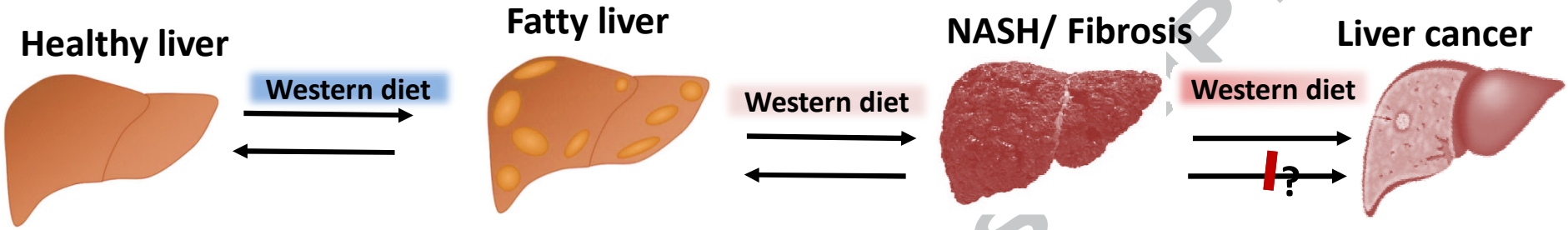
Figure 1. A summary of the nutritional treatment options (based on clinical trials or observational studies) through the course of NAFLD. Remission of steatosis can occur with weight reduction achieved by several types of diets or with isocaloric Mediterranean diet (which induces metabolic and anti-inflammatory 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.



Hypocaloric or Isocaloric - Mediterranean diet

Aerobic or resistance excercise

(Clinical trials)

≥7-10% Weight reduction
(Clinical trials)
by energy deficit of 500 - 750 kcal/day through either diet:
- **low fat**
- **low carb**
- **Mediterranean**

(Clinical trials)

Reduced fructose Mediterranean diet
(Observational studies)

Mediterranean diet
- **High fibers**
- **High fish**
- **High vegatables**
- **Low cholesterol**
- **Low sugar**

Drinks
- **Coffee ≥ 2-3 cups/day**
- **No alcohol in cirrhotics**

(Observational studies)

Figure 2. Benefits of exercise and physical activity in NAFLD: changes in the liver and changes to cardiovascular system

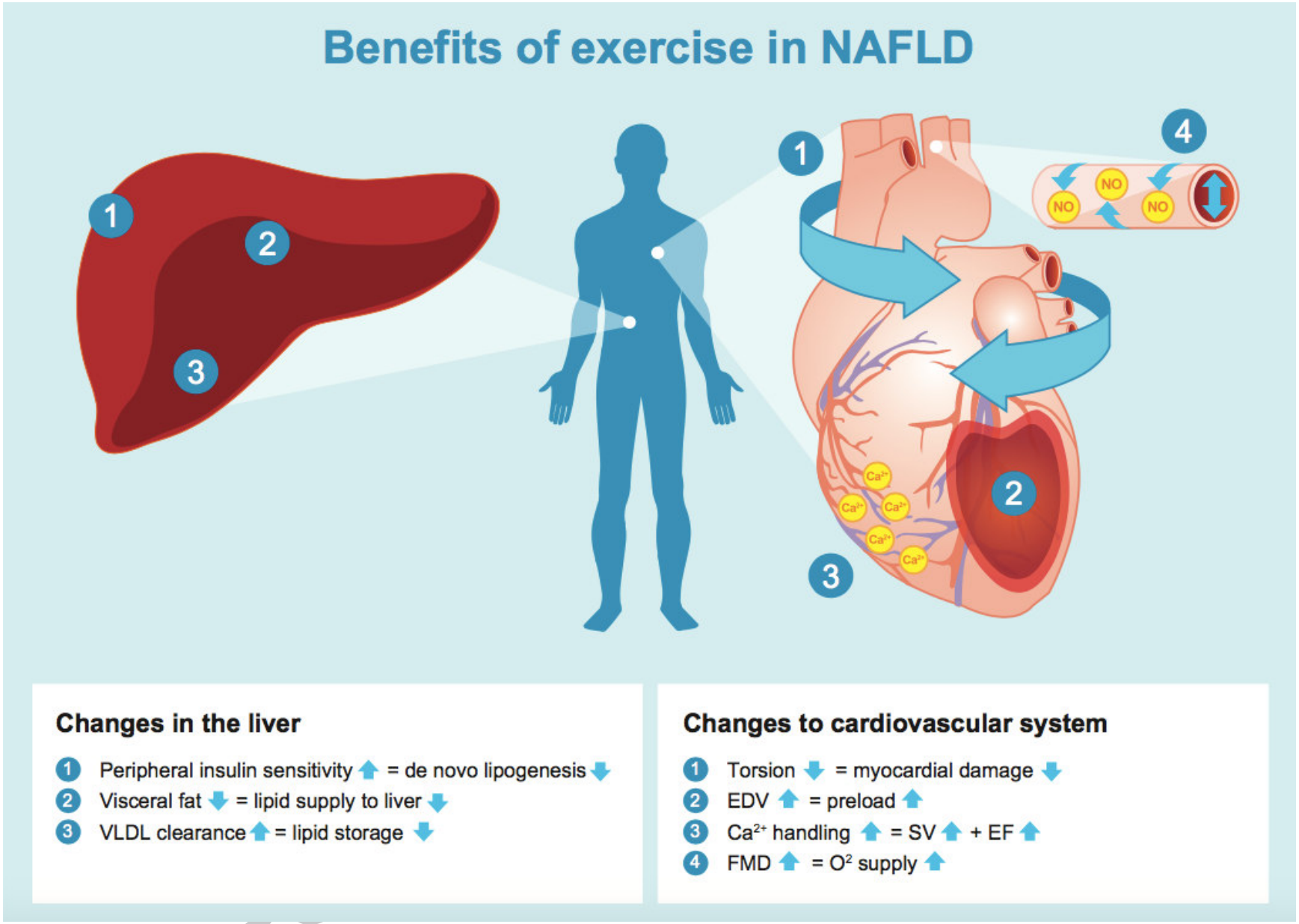


Figure 3. Probability of reaching NASH-resolution , fibrosis regression and steatosis improvement in patients with NASH under lifestyle intervention according to percentage of weight loss (modified from Vilar-Gomez et al Ref#12)

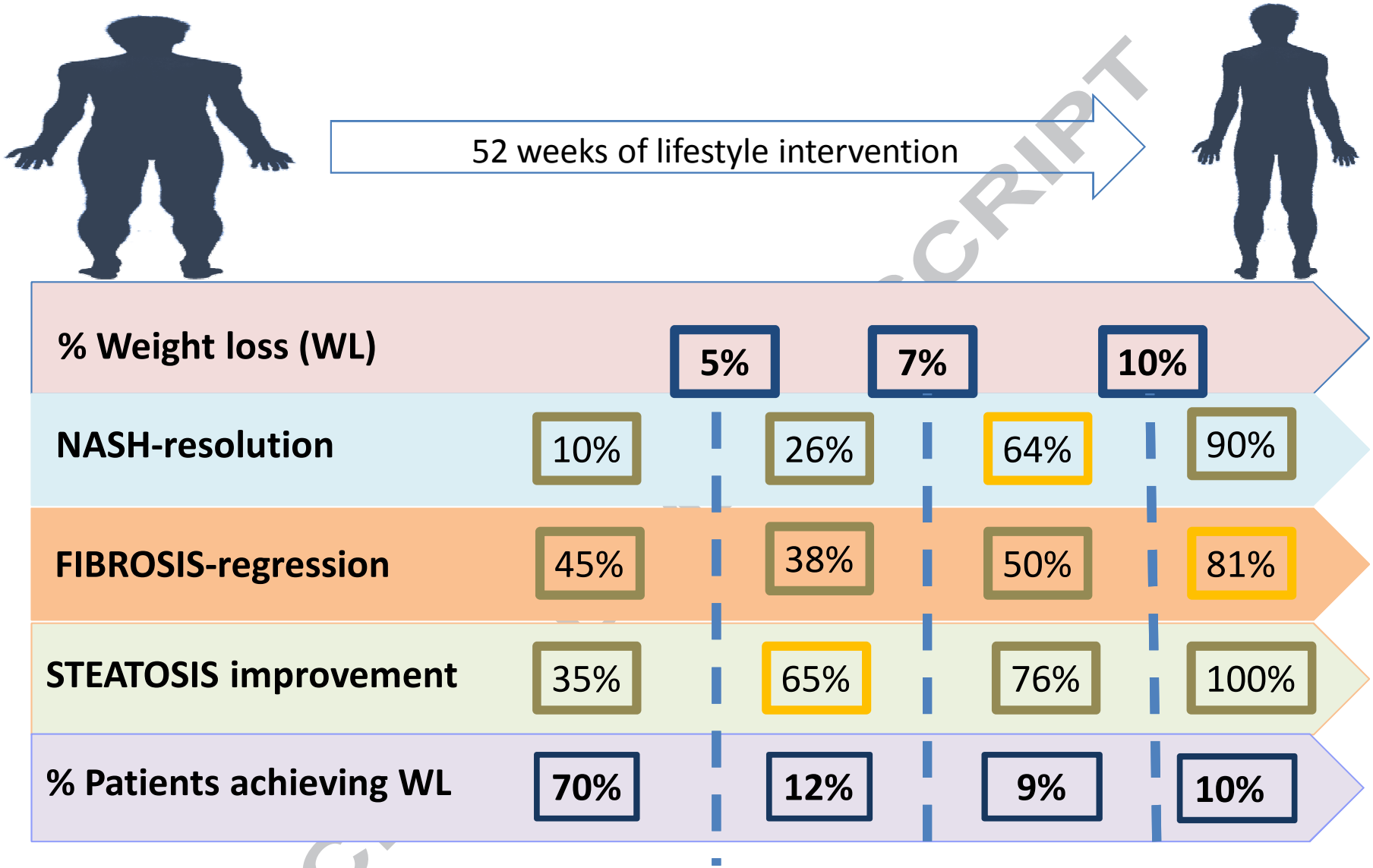


Figure 4. A practical guide for behavioural therapy in the lifestyle treatment of NASH

Stage 1: Determine whether the patient regards changing their diet and/or physical activity behaviour as important (i.e., whether they believe changing behaviour will make a difference) and whether they feel confident that they can make changes that will make a difference (i.e., whether they feel practically equipped to make changes and whether self-efficacy is high). If importance and confidence levels are high, then the patient is likely to feel motivated to move forward and make goals and plans. If not, the clinician should work with the patient to explore attitudes, beliefs, and self-efficacy first to increase the importance of making lifestyle behavior changes and to enhance self-efficacy.

Stage 2: Work with patients to make realistic goals and detailed plans that they feel are sustainable and sensitive to their everyday lives. These goals and plans should be capable of initiating a change in the target behaviour(s) if they have been developed in collaboration with the patient. Self-monitoring at this stage can help to self-regulate lifestyle behaviours and increases self-efficacy when the patient starts to attain their goals.

Stage 3: Equip patients with practical strategies such as methods to pre-plan ways to overcome barriers to prevent relapse and self-monitoring behaviour to positively reinforce any changes made (i.e., increase self-efficacy).