Lifestyle changes for the treatment of nonalcoholic fatty liver disease: a review of observational studies and intervention trials

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***Abstract*:** Nonalcoholic fatty liver disease (NAFLD) is emerging as a major public health problem because of its association with increased cardiovascular and liver-related morbidity and mortality. Both genetic factors and lifestyle contribute to the pathogenesis of NAFLD. Lifestyle, including dietary habits and physical activity, is a modifiable risk factor and thus represents the main target for the prevention and treatment of NAFLD. In this review, we summarize the evidence regarding nutritional aspects (i.e. total energy intake, saturated fat and carbohydrates intake, certain foods or drinks and dietary patterns as a whole) in the treatment of NAFLD. In addition, we analyze the evidence concerning the independent effect of physical activity, including aerobic and resistance training, in the treatment of NAFLD. A therapeutic algorithm according to results from intervention trials is also provided for clinicians and other healthcare professionals involved in the management of NAFLD.

Keywords: nonalcoholic fatty liver disease, diet, lifestyle, physical activity, coffee

Introduction

Nonalcoholic fatty liver disease (NAFLD) has been recognized as a major health burden. Estimates suggest that about 20–30% of adults in developed countries have excess fat accumulation in the liver [Propst *et al.* 1995; Bellentani *et al.* 2000; Falck-Ytter *et al.* 2001; Bedogni and Bellentani, 2004; Zelber-Sagi *et al.* 2006], 50% among people with diabetes and about 80% in obese and morbidly obese people [Bellentani *et al.* 2000; Del Gaudio *et al.* 2002; Gupte *et al.* 2004]. Data from the United States National Health and Nutrition Examination Surveys, collected between 1988 and 2008, show a twofold increased prevalence of NAFLD during this period, along with the increasing prevalence of metabolic alterations such as obesity and insulin resistance [Younossi *et al.* 2011]. Not only obesity but also weight gain is an important determinant in NAFLD incidence. A prospective study with 7 years of follow up emphasized that even a modest weight change of 3–5 kg is an independent predictor for the development and remission of NAFLD, regardless of baseline body mass index (BMI) [Zelber-Sagi *et al.* 2012]. The importance of modest weight gain, as low as 2 kg, in the development of NAFLD was also reported in two large Korean cohorts [Chang *et al.* 2009; Kim *et al.* 2009]. Indeed, it has been demonstrated that insulin resistance already develops during weight gain within the normal range of body weight [Erdmann *et al.* 2008] and that even modest weight gain results in increases in abdominal fat [Orr *et al.* 2008], which in turn cause free fatty acid (FFA) levels to increase in the portal and peripheral circulations [Ruderman *et al.* 1998]. In agreement with that, in a recent prospective cohort study, 13.5% of Hong Kong Chinese adults developed NAFLD within 3–5 years; this was associated with incident central obesity that developed in 31% of subjects with incident fatty liver and 6% of those without ($p < 0.001$) [Wong *et al.* 2015].

The major treatment offered for NAFLD remains lifestyle changes including weight reduction and prevention of weight gain, eating a healthy diet and performing regular physical activity. The literature testing these lifestyle components in animal studies, observational studies and clinical trials among NAFLD patients is reviewed here to provide a practical tool for clinicians treating NAFLD.

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Role of energy restriction

Current management of NAFLD includes gradual weight reduction achieved by diet with or without increased physical activity, which leads to an improvement in serum liver enzymes, reduced hepatic fatty infiltration, reduced degree of hepatic inflammation and less consistently reduced fibrosis [Eriksson *et al.* 1986; Palmer and Schaffner, 1990; Andersen *et al.* 1991; Ueno *et al.* 1997; Luyckx *et al.* 1998; Dixon *et al.* 2004; Shah *et al.* 2009]. Uncontrolled or nonrandomized studies, which evaluated histological outcome, demonstrated a beneficial effect of a balanced diet with a gradual weight reduction that resulted in reduced hepatic steatosis, inflammation and nonalcoholic steatohepatitis (NASH) score [Ueno *et al.* 1997; Huang *et al.* 2005]. In a randomized controlled trial (RCT), 32 NASH patients were randomized to receive intensive 48-week lifestyle intervention or basic education about healthy lifestyle. The NAFLD activity score (NAS) improved significantly in the treatment arm. Participants who reduced weight by $\geqslant$7% had significant improvements in steatosis, lobular inflammation, ballooning injury and NAS compared with those who reduced weight by $<$7% [Promrat *et al.* 2010]. In the Orlistat trial, a weight reduction of at least 9% was necessary to significantly improve NAS, although a 5% reduction was sufficient for improving steatosis [Harrison *et al.* 2009].

Another RCT tested the effect of a 12-month intensive lifestyle intervention on hepatic steatosis in patients with type 2 diabetes. The intervention included a moderate caloric restriction, increased physical activity and weekly meetings, whereas the control group received only general information on nutrition and physical activity. After 12 months, participants assigned to the intensive intervention lost more weight compared with the controls (–8.5% *versus* –0.05%; $p < 0.01$) and had a greater decline in steatosis (–50.8% *versus* –22.8%; $p = 0.04$), with a clear dose–response relationship between the level of weight loss and reduction of steatosis [Lazo *et al.* 2010].

A recent large RCT among 154 adults with NAFLD demonstrated that a 12-month lifestyle modification program (provided by a dietitian) led to 64% NAFLD remission rate in the intervention group *versus* 20% in the control group ($p < 0.001$) and a reduction in liver stiffness only in the intervention group [Wong *et al.* 2013]. Encouraging data on fibrosis regression following diet-induced weight reduction were recently published in a study from Cuba that included 261 NASH patients undergoing paired liver biopsies within 52 weeks. All patients who lost $\geqslant$10% of their weight had reductions in NAS, 90% had resolution of NASH, and 45% had regression of fibrosis [Vilar-Gomez *et al.* 2015].

Three relatively large sample size studies that addressed the effect of diet on alanine aminotransferase (ALT) levels demonstrated improvement or normalization with weight loss as low as 5% from initial body weight [Suzuki *et al.* 2005; Oza *et al.* 2009; St George *et al.* 2009]. Importantly, a meta-analysis of 23 trials (6 randomized, 5 with repeated liver biopsy) concluded that lifestyle modifications including weight reduction and/or increased physical activity consistently reduced liver fat and improved liver histopathology [Thoma *et al.* 2012].

A low carbohydrate diet may seem more effective in reducing liver fat, but this is only in the short term. Obese insulin-resistant individuals randomized to 16-week hypocaloric diets containing either 60% carbohydrate/25% fat or 40% carbohydrate/45% fat had a greater decrease in ALT levels with the latter diet, despite equal weight loss [Ryan *et al.* 2007]. In a shorter term study, liver triglycerides decreased significantly more during 2 weeks of diet in those on a carbohydrate-restricted diet than in those on a calorie-restricted diet [Browning *et al.* 2011]. Moreover, at 48 hours, intrahepatic lipid content was shown to decrease more with a low carbohydrate diet *versus* a low fat diet, but reduction was similar in both diets after 7% weight loss [Kirk *et al.* 2009].

In a large long-term RCT, a total of 102 overweight and obese subjects were randomized to 6-month reduced carbohydrate ($<$90 g carbohydrates and a minimum of 30% fat of total energy intake) or reduced fat ($<$20% fat of total energy intake) – both energy restricted diets (70% of regular energy intake). Significant reductions were observed in both diets in intrahepatic lipid content and ALT without any difference between the two diet regimens [Haufe *et al.* 2011]. It should be mentioned that both diets were designed to be healthy, including reduced saturated fat intake. A meta-analysis summarizing the results of RCTs that compared the effect of low carbohydrate *versus* low fat caloric restriction demonstrated that the two regimens yield similar liver fat and ALT reduction [Musso *et al.* 2012].

In recent years, the rs738409 G allele in the patatin-like phospholipase domain-containing 3 (PNPLA3) gene was demonstrated to be associated with NAFLD [Romeo *et al.* 2008]. PNPLA3 gene variants may also influence the decrease of liver fat induced by lifestyle changes. Following a hypocaloric low carbohydrate diet for 6 days, 8 subjects homozygous for the rs738409 G allele (148MM) had a 2.5-fold greater liver fat reduction compared with 10 subjects who were homozygous for the rs738409 C allele (148II) despite similar weight reduction [Sevastianova *et al.* 2011].

Role of nutritional composition: fats, carbohydrates and other nutrients

In light of the difficulty in reducing weight and maintaining the weight reduction in the long term [Katan, 2009], changing dietary composition without necessarily reducing caloric intake may offer a more realistic and feasible alternative for the treatment of NAFLD patients. Interestingly, an increasing number of patients have been described with normal BMI [Lee *et al.* 1998; Banerji *et al.* 1999; Chitturi *et al.* 2002; Pagano *et al.* 2002]; this is called 'lean NAFLD' [Younossi *et al.* 2012]. Epidemiological studies [Musso *et al.* 2003; Assy *et al.* 2008; Yasutake *et al.* 2009] indicate that normal weight NAFLD patients may consume unhealthy dietary composition compared with controls, therefore emphasizing the importance of dietary composition.

Types of dietary fats

The diet of normal weight NASH patients compared with age, gender and BMI matched controls seems to be richer in saturated fat and cholesterol and poorer in polyunsaturated fatty acids (PUFA) [Musso *et al.* 2003]. These results are supported by a study in which the ratio of polyunsaturated to saturated fatty acid intake in both NASH and fatty liver patients was lower than the ratio in randomly selected controls [Toshimitsu *et al.* 2007]. Furthermore, epidemiological observational studies implicated a lower consumption of omega-3 PUFA and a higher n-6/n-3 ratio among NAFLD and NASH patients compared with controls [Cortez-Pinto *et al.* 2006; Zelber-Sagi *et al.* 2007].

Experimental studies have shown that diets enriched with n-3 PUFA increase insulin sensitivity in rats [Storlien *et al.* 1987], reduce intrahepatic triglyceride content and ameliorate steatohepatitis [Sekiya *et al.* 2003; Levy *et al.* 2004].

A meta-analysis of clinical trials pertaining to the effect of n-3 PUFA supplementation on NAFLD in humans included 9 eligible trials that were heterogeneous in study design (uncontrolled and controlled), duration (2–12 months) and dose (0.83–3.7 g). The data show that, despite the significant heterogeneity, marine omega-3 fatty acid supplementation in humans is associated with a positive effect on liver fat and this effect was also observed when only RCTs were included in the analysis [Parker *et al.* 2012]. More recent RCTs included liver histology and enabled us to learn the effect on NASH and fibrosis. An RCT, which included 15–18 months of treatment with docosahexaenoic acid (DHA) plus eicosapentaenoic acid (EPA) 4 g/day indicated that erythrocyte DHA enrichment occurring with DHA plus EPA treatment was independently associated with a decrease in liver fat percentage, but no improvement in fibrosis scores occurred [Scorletti *et al.* 2014]. In contrast, in a phase IIb multicenter, double-blind RCT, an EPA supplement provided for 12 months at high (2700 mg/day) or low (1800 mg/day) dose to 243 NASH patients led to no significant reduction of steatosis, inflammation, ballooning or fibrosis scores. Furthermore, there were no significant effects on levels of liver enzymes, insulin resistance, adiponectin, keratin 18, high-sensitivity C-reactive protein or hyaluronic acid. The only positive findings were that the high dosage group reduced serum triglyceride levels and there were no treatment-related serious adverse events [Sanyal *et al.* 2014]. In agreement with these findings, a smaller 1-year RCT among 34 NASH patients demonstrated that n-3 PUFA at 3000 mg/day did not lead to significant changes in the overall histological activity, although n-3 therapy was associated with reduced liver fat on biopsy and MRI, independent of weight loss [Argo *et al.* 2015].

Interestingly, 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 hepatocellular carcinoma (HCC), irrespective of human hepatitis C virus (HCV) or hepatitis B virus (HBV) status [Sawada *et al.* 2012].

The conflicting results may stem in part from a different predisposing genotype that interacts with dietary intake of PUFA in determining liver

fat retention [Romeo *et al.* 2008]. In a clinical trial, treatment efficacy of DHA on liver steatosis was affected by the PNPLA3 genotype; the rs738409 G allele was associated with lower response and the rs738409 C allele with greater response to DHA supplementation in children with NAFLD [Nobili *et al.* 2013]. In another pediatric cohort, the omega-6/omega-3 fatty acid intake ratio was positively correlated with liver fat content and ALT levels only in individuals homozygous for the rs738409 G allele (148II) of PNPLA3 [Santoro *et al.* 2012].

The Practice Guideline of the American Association for the Study of Liver Diseases (AASLD) summarizes that it is premature to recommend omega-3 fatty acids for the specific treatment of NAFLD or NASH, but they may be considered as first-line agents to treat hypertriglyceridemia in patients with NAFLD [Chalasani *et al.* 2012]. A monounsaturated fatty acid (MUFA)/oleic acid and the Mediterranean diet (MD) seem to play an important role in the metabolic profile of humans [Grosso *et al.* 2014]; n-9 oleic acid is the most prevalent MUFA in the diet and olive oil is one of its major sources (other sources are, nuts and avocado). MUFA has been demonstrated to have a favorable effect on lipid profile [Mensink *et al.* 2003] by reducing plasma triacylglycerol and very low density lipoprotein (VLDL) cholesterol concentrations and modestly increasing high density lipoprotein (HDL) cholesterol without adversely affecting low density lipoprotein (LDL) cholesterol concentrations [Garg, 1998].

In rats, olive oil was demonstrated to decrease the accumulation of triglycerides in the liver by 30% [Hussein *et al.* 2007], contributed to the recovery of the liver from hepatic steatosis [Hernandez *et al.* 2005] and protected against the development of fibrosis [Szende *et al.* 1994]. It has been suggested that adherence to the MD pattern (quantified by score) leads to a significant decrease in liver fat after 6 months of intervention among overweight patients with NAFLD [Trovato *et al.* 2015]. In a randomized parallel group design trial, 37 men and 8 women with type 2 diabetes were assigned to 1 of 2 isocaloric diets: either a high carbohydrate/high fiber diet or a high MUFA diet for an 8-week period. Liver fat content decreased more in the MUFA group (-29%) than in the high carbohydrate/high fiber group (-4%), despite stable weight in both groups. The different dietary composition was carbohydrate 52% *versus* 40%, fat 30% *versus* 42%, and MUFA (mostly olive oil) 16% *versus* 28% for the high carbohydrate/high fiber diet and MUFA diet, respectively [Bozzetto *et al.* 2012]. These results are in agreement with the benefits of a MD diet that were demonstrated among 12 nondiabetic NAFLD patients in a randomized, crossover 6-week dietary intervention. All subjects were treated with both the MD and a control diet, a low fat, high carbohydrate diet (LF/HCD). There was a significant relative reduction in hepatic steatosis after the MD compared with the LF/HCD: 39% *versus* 7%, despite a very modest weight loss that was not different between the two diets. The MD diet was based on the traditional Cretan MD; olives, dried fruits, nuts, Greek yoghurt, fish and olive oil. The LF/HCD was low in saturated and unsaturated fat and higher in carbohydrate than the MD [Ryan *et al.* 2013]. Despite these promising results, longer-term trials testing the MD diet are needed.

Experimental studies have demonstrated that, in mice, excess cholesterol intake leads to the development of NAFLD even in the absence of obesity [Matsuzawa *et al.* 2007, Wouters *et al.* 2008] and a diet containing 1% cholesterol induces steatohepatitis more than a simple high fat diet [Savard *et al.* 2013]. However, results from observational studies have been conflicting. Some studies did not demonstrate different dietary intakes of cholesterol between NAFLD patients and controls [Cortez-Pinto *et al.* 2006; Zelber-Sagi *et al.* 2007], but Musso and colleagues demonstrated a higher cholesterol consumption among normal weight NASH patients *versus* BMI matched controls [Musso *et al.* 2003]. A study that supports the role of dietary cholesterol in NAFLD compared 12 normal weight NAFLD patients to 44 obese NAFLD patients, showing that dietary cholesterol intake was significantly higher, while the intake of PUFAs was significantly lower in the non obese group. Therefore, this altered cholesterol and PUFA intake may be associated with the development of NAFLD in non obese patients [Yasutake *et al.* 2009]. In a large, nationally representative epidemiological study, dietary cholesterol consumption was independently associated with the development of cirrhosis [Ioannou *et al.* 2009]. Consistently, serum non-HDL cholesterol is an independent predictor of NAFLD [Zelber-Sagi *et al.* 2014b].

These findings may indicate that impairment of cholesterol regulation may have a causal relationship with liver steatogenesis. Indeed, excess

intracellular cholesterol activates liver X receptors (LXRs) that regulate cholesterol homeostasis [Repa and Mangelsdorf, 2002], but induces hepatic steatosis [Fon Tacer and Rozman,. 2011] by activating sterol regulatory element-binding transcription factor 1c (SREBP-1c), a master transcriptional regulator of fatty acid synthesis in the liver [Schultz *et al.* 2000, Chen *et al.* 2004].

Types of dietary carbohydrates

'Naturally occurring sugar' refers to the sugar that is an integral constituent of whole fruit, vegetable and milk products, whereas 'added sugar' refers to sucrose or other refined sugars in soft drinks and incorporated into food, fruit drinks and other beverages [Howard and Wylie-Rosett, 2002]. Soft drinks are the leading source of added sugar in the world [Gaby, 2005]. Rats and humans that are fed either sucrose or fructose enriched diets develop fatty livers [Herman *et al.* 1970; Poulsom, 1986; Le *et al.* 2009; Sobrecases *et al.* 2010]. In addition, cola soft drinks contain caramel coloring, which is rich in advanced glycation end products (AGEs) that may increase insulin resistance and inflammation [Gaby, 2005]. Fructose also seems to be associated with alteration in intestinal microflora and a growing body of evidence supports a role for increased gut permeability and endotoxin in rodent and human NAFLD [Federico *et al.* 2016]. In animal studies, a high fructose diet induces changes similar to those seen in models of chronic alcohol intake and high fat diets, including increased gut permeability, endotoxemia, increased hepatic tumor necrosis factor alpha (TNF-α) production and hepatic steatosis [Federico *et al.* 2016]. Hepatic lipid accumulation, endotoxin levels in portal blood, lipid peroxidation and TNF-α expression were significantly higher in mice consuming fructose compared with glucose, sucrose or controls. Concomitant treatment of fructose fed mice with antibiotics markedly reduced hepatic lipid accumulation [Bergheim *et al.* 2008].

Several observational studies have been published on the association between soft drinks consumption and NAFLD, demonstrating a positive association [Zelber-Sagi *et al.* 2007; Assy *et al.* 2008; Ouyang *et al.* 2008; Abid *et al.* 2009]. Recently, the association between sugar-sweetened beverages (SSB), diet soda and fatty liver disease was tested in the Framingham Heart Study cohorts that included computed tomography (CT) in 2634 participants and ALT measurement in 5908 participants. A dose–response relationship was observed between SSB and fatty liver disease, with a 55% increased risk of fatty liver disease in daily consumers of SSB compared with non-SSB consumers. In addition, SSB 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 [Ma *et al.* 2015].

These findings are supported by an RCT in which overweight subjects (n = 47) were randomly assigned to 4 different test drinks (1 l/day for 6 months): regular cola, isocaloric semi-skimmed milk, aspartame-sweetened diet cola and water. The relative change in liver fat between baseline and the end of 6-month intervention was significantly higher in the regular cola group than in the 3 other groups [Maersk *et al.* 2012]. A large-scale study of 427 NAFLD patients expanded the understanding of the hepatic damage that may be related to overconsumption of fructose-containing beverages. After controlling for age, sex, BMI and total calorie intake, daily consumption of fructose-containing beverages was significantly associated with higher fibrosis stage [odds ratio (OR) = 3.2; 95% confidence interval (CI) 1.4–7.4 for $\geqslant$7 *versus* <7 servings per week) [Abdelmalek *et al.* 2010].

One of the pathways by which SSBs can lead to fibrosis is by increasing serum uric acid (UA) levels in a dose–response manner. This increase stems from the large amounts of fructose in SSBs, which is the only carbohydrate known to increase uric acid levels [Choi *et al.* 2008]. A prospective observational study showed that elevation of serum UA levels independently predicted an increased risk for incident NAFLD [Xu *et al.* 2010]. In a cross-sectional analysis of real-world data of 82,608 people, obtained from a large health maintenance organization, a significant positive dose–response association between serum UA levels and the rate of elevated serum ALT was demonstrated in both men and women, and regardless of BMI [Zelber-Sagi *et al.* 2015a]. Elevated serum UA levels reflect and may also cause oxidative stress, insulin resistance and metabolic syndrome and, indeed, serum UA levels were demonstrated to be associated with the development of cirrhosis and the presence of elevated serum liver enzymes after adjustment for causes and risk factors of chronic liver disease (CLD) [Afzali *et al.* 2010].

Gene–diet interactions that contribute to fat accumulation in the liver have been identified with regard to carbohydrate and sugar consumption [Goran *et al.* 2012]. In a study of 153 Hispanic children, a nutrigenetic analysis revealed liver fat to be directly correlated with carbohydrate ($r = 0.38$, $p = 0.02$) and total sugar ($r = 0.33$, $p = 0.04$) intakes only in children homozygous for the rs738409 G allele (148MM) but not in the CC and CG genotypes, indicating a genetically determined metabolic response to dietary carbohydrates [Davis *et al.* 2010]. Trials assessing specific dietary interventions, based on genetic background, should be performed.

Other nutrients

Observational studies have demonstrated a favourable impact of coffee intake on health and in particular a protective effect from the metabolic syndrome [Grosso *et al.* 2015]. Several epidemiological studies, including prospective cohorts, have also indicated an inverse association between coffee consumption and liver cirrhosis and cancer development independently of etiology [Saab *et al.* 2013]. In recent years, cross-sectional studies have suggested an inverse association of coffee consumption with liver fibrosis in patients with NAFLD [Anty *et al.* 2012; Molloy *et al.* 2012; Bambha *et al.* 2014]. In the only study conducted so far, including both a prospective and cross-sectional cohorts from the Israeli general population, incident fatty liver diagnosed by abdominal ultrasound and quantified noninvasively by hepatorenal-ultrasound index and SteatoTest was not associated with baseline coffee consumption. However, in the cross- sectional cohort, high coffee consumption (⩾3 cups per day) was associated with lower odds for presumed clinically significant fibrosis measured by the FibroTest, also with adjustment for potential confounders [Zelber-Sagi *et al.* 2015b].

The specific components of coffee exerting beneficial effects have been partially elucidated [Godos *et al.* 2014]. Coffee contains hundreds of chemical ingredients including polyphenols, melanoidins and caffeine. Recently, caffeine was shown to inhibit hepatic stellate cell proliferation *in vitro* [Shim *et al.* 2013]. However, the hepatoprotective effects of coffee may be linked not only to caffeine but also to its polyphenolic fraction. In fact, in rats fed a high fat diet, consumption of decaffeinated coffee was demonstrated to be effective in preventing liver damage by inducing the expression of endogenous chaperones and antioxidant proteins [Vitaglione *et al.* 2010; Salomone *et al.* 2014]. The antioxidant activity of coffee appears relevant because progression of fibrosis in patients with NASH is associated with a lack of endogenous antioxidant defense [Salomone *et al.* 2013]. Other dietary polyphenols such as anthocyanins are promising candidates in the treatment of NAFLD and components of metabolic syndrome [Salamone *et al.* 2012a, 2012b], although RCTs are needed to establish their effects in patients.

A recent prospective cohort study supports a protective role for coffee also in HCC prevention. A US Multiethnic Cohort (MEC), which included 162,022 participants, demonstrated that 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. Compared with non coffee drinkers, participants who consumed 2–3 cups coffee per day had a 46% reduction in risk of death from CLD 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 [Setiawan *et al.* 2015].

Role of physical activity

Several observational studies indicated an inverse association between reported leisure time physical activity or cardiorespiratory fitness and the prevalence of NAFLD or hepatic fat content independently of body mass index [Magkos, 2010; Church *et al.* 2006; Perseghin *et al.* 2007]. Similar results were demonstrated in another study of the general population in which the NAFLD group engaged in less reported leisure time physical activity including total, aerobic and resistance training [Zelber-Sagi *et al.* 2008]. Few studies have tested the association with liver histology. In a small study on 37 NAFLD patients with liver biopsy, there was a lower cardiorespiratory fitness among patients with higher NAFLD activity score and NASH *versus* no NASH [Krasnoff *et al.* 2008]. Self-reported exercise intensity and histological severity of NAFLD was tested in a large cohort of adults with biopsy-proven NAFLD. Vigorous physical activity was associated with decreased BMI adjusted odds of having NASH in both minimum (⩾75 min/week) and extensive time (⩾150 min/week) of physical

activity (35% and 44%, respectively). However, only extensive time spent in vigorous exercise was sufficient to reduce advanced fibrosis in almost 50% [Kistler *et al.* 2011]. In accordance with these findings, a study testing the beneficial effects of a varying volume of moderate to vigorous intensity physical activity among 169 obese men has shown that those enrolled for ⩾250 min/week of such activity (in comparison with <250 min/week) had a greater beneficial effect of reducing liver fat, inflammation and oxidative stress levels, and altering fatty acid metabolism. This was reflected by a greater reduction in levels of ferritin and lipid peroxidation, a significant increase in the adiponectin levels and favorable changes in the expression levels of genes involved in fatty acid synthesis and degradation following the 12-week intervention [Oh *et al.* 2015]. However, it has to be taken into consideration that increasing exercise frequency and dose to ⩾250 min/week may be difficult for most NAFLD patients.

The beneficial effect of exercise is supported by clinical trials and by a recent meta-analysis concluding that there is a clear evidence for a benefit of exercise therapy on liver fat with minimal or no weight loss and at exercise levels below current exercise recommendations for obesity management [Keating *et al.* 2012]. Nevertheless, the ability of exercise alone to improve other aspects of liver histology remains unknown [Chalasani *et al.* 2012].

An RCT assessed the effect of short-term (4 weeks) aerobic exercise training (3 cycle sessions per week of 30–45 min each *versus* stretching) in 19 sedentary obese men and women resulting in a reduction of 21% in hepatic triglyceride concentration with no change in weight or dietary intake [Johnson *et al.* 2009]. Furthermore, two other clinical trials – one in obese adolescents [van der Heijden *et al.* 2010] and the other in healthy elderly [Finucane *et al.* 2010] – support the beneficial effect of aerobic exercise. In both trials, 12-week aerobic exercise led to about 35% reduction in hepatic fat without diet or weight loss. However, the exact intensity and volume which would be optimal to reduce liver fat is unknown. A randomized trial compared different 8-week exercise regiments among inactive obese adults: 50% VO_2 peak, 60 min, 4 days/week; 70% VO_2 peak, 45 min, 3 days/week; 50% VO_2 peak, 45 min, 3 days per week; and placebo. There was no difference in the efficacy of liver fat reduction by either aerobic exercise dose or intensity [Keating *et al.* 2015]. It appears that any reasonable amount of physical activity is better than nothing, since prolonged sitting time by itself was demonstrated to be positively associated with the prevalence of NAFLD in a large sample of Korean adults [Ryu *et al.* 2015].

Resistance training, without a concomitant weight loss diet, improves insulin sensitivity and fasting glycaemia and decreases abdominal fat [Ibanez *et al.* 2005]. In a small RCT including 19 sedentary adult NAFLD patients, 8 weeks of resistance training consisting of 45-minute sessions trice weekly, led to a reduction in liver fat without weight loss [Hallsworth *et al.* 2011]. In another RCT, patients were randomized to either resistance training ($n = 33$) or stretching arm ($n = 31$); 3-month resistance training improved hepatic fat content as tested by the hepatorenal-ultrasound index accompanied by favorable changes in body composition and ferritin [Zelber-Sagi *et al.* 2014a].

In a larger RCT that compared the effect of 8-month aerobic training *versus* resistance training and *versus* the combination of both, only aerobic training led to significant reductions in liver fat and serum ALT levels; moreover the effect of the combined training was indistinguishable from the effect of aerobic training alone [Slentz *et al.* 2011]. However, the aerobic training and combined training groups lost a small but significant body weight (2 kg) whereas the resistance training group did not, a difference that may partially explain the difference in outcomes. In contrast, in an RCT among 31 sedentary adults with type 2 diabetes and NAFLD, 4-month aerobic *versus* resistance training 3 times per week led to reduction in hepatic fat content to a similar extent in both training groups (mean relative reduction from baseline −32.8% *versus* −25.9%, respectively). Additionally, hepatic steatosis (defined as hepatic fat content >5.56%) regressed in almost one-quarter of the patients in each intervention group [Bacchi *et al.* 2013]. The combination of both types of activities may be best as demonstrated in a recent large RCT among 304 adolescents, in which 22-week combined aerobic and resistance training was superior to aerobic training alone in decreasing percentage body fat and waist circumference [Sigal *et al.* 2014].

Until more studies in large samples of NAFLD patients are performed, we can adopt the 2013 American College of Cardiology/American Heart Association guideline on lifestyle management to reduce cardiovascular risk, advising healthy adults

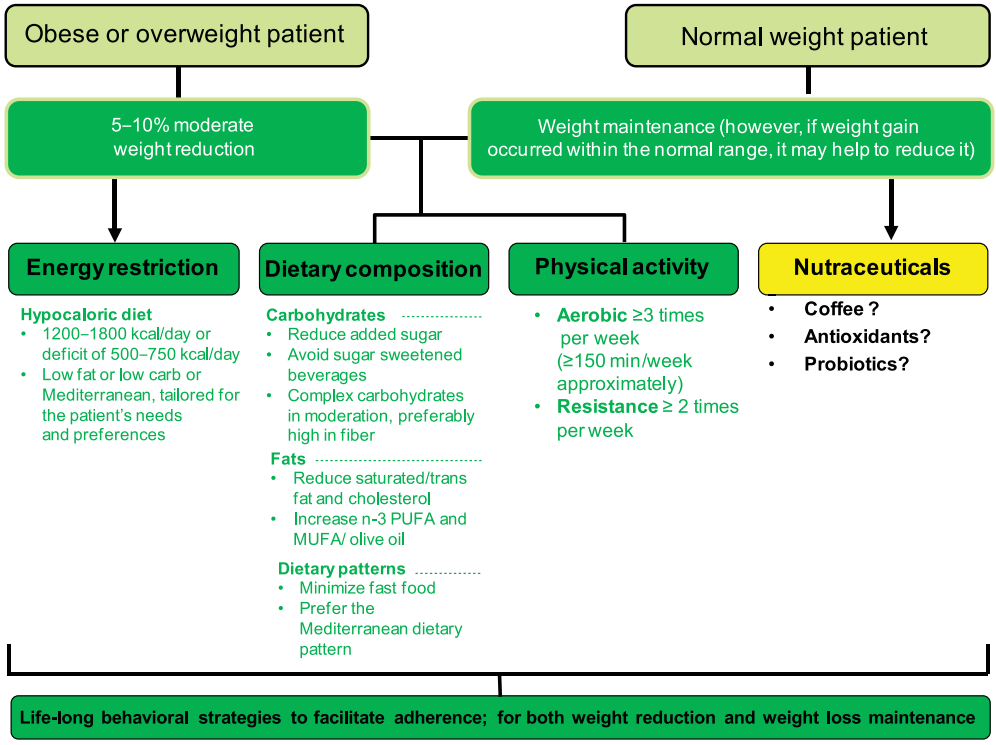

Figure 1. Algorithm for lifestyle changes in nonalcoholic fatty liver disease (NAFLD).
MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

to engage in aerobic physical activity 3–4 sessions a week, lasting on average 40 minutes per session, and involving moderate-to-vigorous intensity physical activity [Eckel *et al.* 2014]. The European guidelines on cardiovascular disease prevention recommend 2.5–5 hours a week of aerobic exercise training of at least moderate intensity, or 1–2.5 hours a week on vigorous intense exercise [Perk *et al.* 2012]. However, no specific recommendations were provided for resistance training or the combination of both aerobic and resistance training due to limited data [Eckel *et al.* 2014].

Conclusion

Lifestyle changes are crucial for the treatment of NAFLD. The position statement by the European Association for the Study of the Liver (EASL) on NAFLD/NASH [Ratziu *et al.* 2010] recommends a weight loss of 7% on the basis of an extensive body of literature. The American Association for the Study of Liver Diseases (AASLD) practice guideline indicates that loss of at least 3–5% of body weight appears necessary to improve steatosis, but a greater weight loss (up to 10%) may be needed to improve necroinflammation [Chalasani *et al.* 2012]. There is presently no convincing evidence that long-term low carbohydrate diets are better than low fat diets, and the diet of choice should be the one which individuals are able to adhere for years rather than weeks. Studies performed so far identified soft drinks as an important modifiable risk factor. Physicians and dietitians should routinely include questions regarding soft drink consumption as part of the patient's history and advise patients to minimize its consumption. Reducing the consumption of fast food would be wise since it is served in large energy dense portions and combines several potential hepatotoxic nutrients, i.e. saturated fat, refined carbohydrates, fructose, caramel coloring, industrially produced trans fatty acids, and is low in fiber [Kechagias *et al.* 2008; Marchesini *et al.* 2008; Sobrecases *et al.* 2010]. Physical activity should be integrated into behavioral therapy in NAFLD, as even small gains in physical activity and fitness may have significant health benefits.

The suggested NAFLD's lifestyle therapeutic algorithm is depicted in Figure 1 and represents the importance of all components in the treatment of NAFLD. Table 1 summarizes the main features and results of lifestyle intervention trials conducted so far.

Table 1. Lifestyle intervention trials for nonalcoholic fatty liver disease (NAFLD) treatment.

Reference	Country	Study design	Patients, (% men)	Liver fat content evaluation	Intervention (type, time)	Effects on liver fat content	Effects on liver histological endpoints
DIET INTERVENTIONS							
Huang *et al.* [2005]	USA	Intervention without control arm	16 obese, (50)	Liver biopsy	NC, 12 months	No effect	Decreased ballooning/ inflammation
Kirk *et al.* [2009]	USA	RCT	22 obese, (18)	MRS	Low calorie HCD *versus* LCD, 11 weeks	Decreased in HCD and LCD	NP
Haufe *et al.* [2011]	Germany	RCT	102 obese, (18)	MRS	Low calorie LCD *versus* LFD, 6 months	Decreased in LCD and LFD	NP
Bozzetto *et al.* [2012]	Italy	RCT	36 diabetic, (81)	MRS	CHO/fiber *versus* MUFA, CHO/fiber+ exercise, *versus* MUFA + exercise, 8 weeks	Decreased in MUFA and MUFA + exercise	NP
Ryan *et al.* [2013]	Australia	RCT	12 obese, (50)	MRS	MD *versus* LF/HCD	Decreased	NP
Trovato *et al.* [2015]	Italy	Intervention without control arm	90 obese, (49)	US	MD, 6 months	Decreased	NP
EXERCISE INTERVENTIONS							
Johnson *et al.* [2009]	Australia	RCT	19 obese, (NA)	MRS	Aerobic training *versus* regular stretching, 4 weeks	Decreased	NP
Van der Heijden *et al.* [2010]	USA	Intervention without control arm	15 obese and 14 lean (58)	MRS	Aerobic training obese *versus* lean, 12 weeks	Decreased	NP
Slentz *et al.* [2011]	USA	RCT	144 obese, (44)	CT	Resistance training *versus* aerobic training *versus* combined, 8 months	Decreased in aerobic arm and aerobic + resistance training	NP
Hallsworth *et al.* [2011]	UK	RCT	19 obese, (NA)	MRS	Resistance training *versus* SC, 8 weeks	Decreased	NP
Bacchi *et al.* [2013]	Italy	RCT	30 obese, (73.3)	MRS	Aerobic training *versus* resistance training, 4 months	Decreased	NP
Zelber-Sagi *et al.* [2014a]	Israel	RCT	64 obese, (53.1)	US	Resistance training *versus* home stretching, 3 months	Decreased	NP
DIET AND EXERCISE INTERVENTIONS							
Ueno *et al.* [1997]	Japan	Intervention without control arm	25 obese, (52)	Liver biopsy	Restricted diet and exercise *versus* control, 3 months	Decreased	Decreased steatosis
Shah *et al.* [2009]	USA	RCT	18 obese, (28)	MRS	Diet *versus* diet with exercises, 6 months	Decreased in both arms	NP
Oza *et al.* [2009]	Japan	Intervention without control arm	22 overweight (54.5)	CT	Weight loss (caloric restriction), 3 or 6 months	Decreased	NP

(Continued)

Table 1. (Continued)

Reference	Country	Study design	Patients, (% men)	Liver fat content evaluation	Intervention (type, time)	Effects on liver fat content	Effects on liver histological endpoints
Lazo *et al.* [2010]	USA	RCT	96 obese, (51)	MRS	Weight loss (caloric restriction, increased physical activity) *versus* DSE, 12 months	Decreased	NP
Promrat *et al.* [2010]	USA	RCT	31 obese, (71)	Liver biopsy	Weight loss (caloric restriction, increased physical activity) *versus* control, 48 weeks	Decreased	Decreased steatosis and ballooning, no change in fibrosis score
Browning *et al.* [2011]	USA	Intervention without control arm	18 obese, (68)	MRS	Low calorie *versus* low carbohydrate, 2 weeks	Decreased in both arms	NP
Wong *et al.* [2013]	Hong-Kong	RCT	154 normal weight, (25)	MRS	Weight loss (caloric restriction, increased physical activity) *versus* SC, 12 months	Decreased	NP
Vilar-Gomez *et al.* [2015]	Cuba	Intervention without control arm	261 obese, (25)	Liver biopsy	Weight loss (caloric restriction, increased physical activity) *versus* SC, 52 weeks	Decreased	Decreased steatosis, ballooning and fibrosis

CHO/fiber, high carbohydrate/high fiber/low glycemic index; CT, computed tomography; DSE, diabetes support and education; HCD, high carbohydrate diet; LCD, low carbohydrate diet; LFD, low fat diet; LF/HCD, low fat/high carbohydrate diet; MD, Mediterranean diet; MRS, magnetic resonance spectroscopy; MUFA, monounsaturated fatty acids; NA, not available; NC, nutritional counseling,; NP, not pertinent; RCT, randomized trial; SC, standard counseling; US, ultrasonography.

In the future, one of the treatment goals would be to establish a tailored treatment approach for NAFLD according to diet and genotype interactions.

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