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Exercise and diet in the management of nonalcoholic fatty liver disease

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver condition worldwide, and is projected to become the leading cause for liver transplantation in the United States as early as 2020. The mainstay of treatment remains lifestyle modification with diet and exercise recommendations, as although some pharmacological treatments such as glitazones and Vitamin E have shown benefit, there are concerns regarding long term safety. The evidence base for dietary interventions in NAFLD such as the Mediterranean diet, omega-3 polyunsaturated fatty acids and coffee is mainly derived from observational data with questionable validity. Where trials exist, they have shown benefit for surrogate outcomes such as hepatic steatosis and insulin resistance, but no trials have been conducted with salient clinical outcomes such as reduction in progression to chronic liver disease. Benefit in surrogate outcomes has also been seen for aerobic, anaerobic and combined modality exercise but it remains unclear if one type is superior. Furthermore, a reduction in sedentary time appears equally important. To provide a sound evidence base for lifestyle recommendations to people with NAFLD, longer duration trials of standardized dietary or exercise interventions, and testing various doses, types and with liver related outcomes, are essential.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is considered the hepatic manifestation of the metabolic syndrome as it is tightly linked with the global obesity epidemic [1]; indeed, recent data suggest that NAFLD may even precede the development of the metabolic syndrome and type 2 diabetes [2]. NAFLD covers a spectrum of liver histology from bland steatosis to hepatocyte ballooning, inflammation (known as nonalcoholic steatohepatitis, NASH), fibrosis and cirrhosis, with an increased risk of hepatocellular carcinoma. The prevalence of NAFLD is approximately 30% in the United States and Europe [3–5], with a similar prevalence documented in Asian countries [6]. The prevalence of NASH is estimated at 4% [4] and is likely to eclipse other forms of liver disease as the primary indication for liver transplantation in the United States in the next decade [7]. Pharmacological agents for NASH show benefit [8,9], but there are concerns regarding long term safety, and novel insulin sensitizers are not proven for mainstream use [10], thus lifestyle modification with diet and exercise remains first line therapy [11,12]. This review examines the evidence base for dietary and exercise recommendations for people with NAFLD and/or NASH, focusing on trial based data

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CBT, cognitive behavioral therapy; HOMA-IR, homeostasis model assessment of insulin resistance; HCC, hepatocellular carcinoma; IHTG, intrahepatic triglycerides; MR-S, magnetic resonance spectroscopy; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PUFA, polyunsaturated fatty acids.

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where available due to the considerable biases that affect validity of observational studies and diet.

2. Literature Search

A systematic literature search was undertaken to inform this review. The initial literature search was PERFORMED in Medline via the Ovid platform, and the MeSH terms "fatty liver" and text words describing fatty liver (NAFLD, fatty liver, NASH) were combined with MeSH terms and text words for dietary components and exercise. Searches were then filtered for reviews and meta-analyses using the *review.pt* or *meta-analysis.pt* filters. In addition, the Cochrane Database of Systematic Reviews was searched to obtain systematic reviews of dietary or exercise interventions for NAFLD. Reference lists of retrieved articles were perused to obtain additional references. Although a number of well conducted reviews have recently been published [13–15], this review focuses primarily on lifestyle interventions for which there is a high level of evidence, from either trials or systematic reviews thereof. Where the evidence base is low, consisting of observational or animal studies only, this is highlighted to the reader.

3. Dietary Interventions for NAFLD: The Mediterranean diet, Macronutrients and Micronutrients

3.1. *Mediterranean Diet*

In recent years, there has been increasing interest in the Mediterranean diet as an alternative to low fat and calorie-restricted diets because it may offer important benefits for those with dyslipidemia and the metabolic syndrome. The Mediterranean diet incorporates the traditional food of people living in the Mediterranean basin, typified by abundant cereals, vegetables and legumes. An important point of difference between this and typical Western diets is the profile of fats — the Mediterranean diet contains predominantly monounsaturated fats from olive oil with a greater ratio of omega-3 polyunsaturated fatty acids (PUFAs) to omega-6 PUFAs, whereas the reverse is true of Western diets.

Data from randomized trials of the Mediterranean diet have shown benefits in people with type 2 diabetes. In comparison with a person's usual diet, a 12 week trial of Mediterranean diet resulted in lower HbA1C and plasma levels of saturated and trans fatty acids in type 2 diabetics, and did not result in weight gain [16]. Trial based evidence also suggests a reduction in insulin resistance and inflammatory markers in those with metabolic syndrome [17] without associated weight gain [17,18]. More recent trial data examining this diet for those at high risk of cardiovascular events similarly indicate that a Mediterranean diet supplemented with additional olive oil or nuts, in comparison with a traditional low fat diet, resulted in a lower incidence of major cardiovascular events at 5 years [19]. Prevention of cardiovascular events has also been examined in a Cochrane systematic review of 11 trials, which concluded that the Mediterranean diet may modulate important cardiovascular risk factors (such as lower cholesterol and low-density lipoprotein), however meta-analysis was precluded by the vast heterogeneity of the dietary interventions studied [20]; similar conclusions have been drawn by non-Cochrane systematic reviews [21]. Although it is likely that these data can be directly extrapolated to people with NAFLD and metabolic syndrome, there are no randomized trials examining the Mediterranean diet's effect on clinically important liver related outcomes. A small crossover trial (n = 12) in patients with biopsy proven NAFLD of a Mediterranean diet for 6 weeks with crossover to standard diet at 6 weeks, demonstrated reduced insulin resistance and hepatic steatosis, independent of weight loss [22]. Specific criticisms of the Mediterranean diet include its higher cost and a low dairy intake, although as the main dairy is cheese and yogurt, this may have advantages for lactose intolerant people. Ideally, long-term trials with liver related outcomes as the primary endpoint would help to inform whether this diet should be recommended to patients with NAFLD, although such studies are difficult and expensive to conduct.

3.2. *Macronutrients: Omega-3 vs. Omega-6 Polyunsaturated Fatty Acids*

The optimal form of dietary fat that should be recommended to patients with NAFLD has been of intense interest over the last two decades, in particular the role of polyunsaturated fatty acids (PUFAs) and the ratio of omega-3 to omega-6. Polyunsaturated fatty acids include "essential" fatty acids such as omega-3 and omega-6, so called because they cannot be synthesized in humans and must be obtained from diet, and the non-essential fatty acids such as omega-7 and omega-9 fatty acids. Omega-6 fatty acids are derived from seed oils such as canola and cottonseed, and are metabolized to a group of compounds known as the eicosanoids (such as thromboxanes, prostacyclins and leukotrienes) that are involved in inflammatory and thrombotic processes [23]. Omega-3 PUFA has been considered beneficial for health on the basis of promising observational data and has been enthusiastically studied in diverse conditions such as macular degeneration, autism, dementia, intermittent claudication, Crohn's disease, cystic fibrosis, and type 2 diabetes without evidence of benefit for the primary outcomes studied [24–31]. Relevant to cardiovascular disease in particular, a Cochrane review of omega-3 PUFA supplementation for primary prophylaxis in type 2 diabetics with cardiovascular risk factors showed improved dyslipidemia without change in glycemic control, and mortality or cardiovascular endpoints were not studied [32]. Further to this, a large trial of omega-3 supplementation as primary prophylaxis was undertaken in more than 12,000 people, prompted by a previous study showing benefit for omega-3 use as secondary prophylaxis [33]. After 5 years follow-up, this trial concluded that there was no significant reduction in cardiovascular endpoints, although no serious adverse effects were noted [34]. While these data imply that omega-3 PUFA may be preferable to other forms, omega-6 PUFA may themselves be preferable to saturated fat, as a randomized trial of supplementation in 61 obese people with omega-6 PUFA versus saturated fat indicated lower hepatic steatosis, serum insulin and inflammatory markers in the omega-6 group [35].

With respect to NAFLD in particular, a randomized, placebo controlled trial in 60 pediatric patients with ultrasound

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diagnosed NAFLD with supplementation of omega-3 PUFA (500 mg of docosahexaenoic acid) resulted in reduced liver fat and triglycerides and improved insulin sensitivity without weight gain [36], although a similar trial in adults for 18 months did not show any improvement on intention to treat analyses [37]. However, individual studies may be underpowered, and a meta-analysis of omega-3 PUFA supplementation in NAFLD suggested an improvement in liver fat, albeit that small, although substantial heterogeneity was found [38]; this question is to be further addressed in a pending Cochrane review. There are few data on hard endpoints such as histology. A recently published trial of a synthetic omega-3 PUFA, ethyl-eicosapentaenoic acid, in 243 patients with histological improvement as the primary endpoint did not show an improvement, although surrogate outcomes such as triglycerides improved in the intervention group [39]. Currently, there is a lack of evidence to justify routine recommendation of omega-3 PUFA use in patients with NAFLD, and while there does not seem to be any serious adverse effects, further trial based data are needed.

3.3. *Monounsaturated Fats*

Monounsaturated fats are found in avocadoes, olive oil and nuts and are considered preferable to saturated fats in those with metabolic syndrome [40]. A systematic review of trials in type 2 diabetics indicated that monounsaturated fats may improve dyslipidemia but did not improve insulin resistance [41], a finding replicated in trials of healthy male volunteers [42]. However there are no trials of monounsaturated fats in NAFLD patients to inform recommendations, and the current breadth of data, while favorable, is limited to observational human and animal data [43].

3.4. *Trans Fatty Acids*

Trans fatty acids are industrially produced fats that are formed when liquid vegetable oils are hydrogenated to produce a solid fat used for margarines and food manufacturing [44]. They are abundant in fast foods, baked and deep fried goods, crackers and margarine [45] and are estimated to account for 2–3% of dietary calories in the US [46]. Dietary trans fats have been legislated to be removed from food supplies in the US, Denmark and Canada because of their role in promoting dyslipidemia, inflammation and cardiovascular disease. However, while high intake is widely considered harmful, data from studies on whether trans fats promote incidence of diabetes remain inconclusive [44].

The potential role of trans fats in inciting NAFLD has been studied in animal models [47]. In proof of concept studies, mice fed a diet high in trans fats and high fructose corn syrup for 16 weeks developed hyperinsulinemia and severe hepatic necroinflammation [48]; when trans fats were eliminated, steatohepatitis improved [49]. Animal models also suggest a role for HCC development with high intake of dietary trans fats and high fructose corn syrup [50]. Overall, data from human epidemiologic studies and animal models [51] support eliminating trans fats from the human diet, and further data are unlikely to change this recommendation given that randomized trials are unethical. On this basis, patients with NAFLD should be advised to minimize consumption by checking nutritional labels to assess content, which is now mandatory in many countries.

3.5. *Saturated Fats*

Saturated fats derived predominantly from animal sources have also been implicated in the pathogenesis of NASH and may have additive effects on hepatic fat deposition when consumed in parallel with high cholesterol [52]. There are little data on the effect of saturated fats in patients with NASH, although a meta-analysis of 8 randomized trials including 13,614 patients evaluating replacement of saturated fats with PUFA in the general population found a 10% reduction in coronary events for every 5% of energy intake conferred by PUFA, with little evidence for study heterogeneity [53]. Genetic variations may influence risk of high saturated fat intake, as variations in the PNPLA3 gene are associated with susceptibility to NAFLD [54], and the type of dietary fat may influence hepatic steatosis via upregulation of PNPLA3 expression in liver cells. In mice fed a traditional Western diet with saturated fat, the hepatic expression of PNPLA3 was 23 times higher than that seen with regular chow-diet fed mice, and fully reversed with fasting [55]. Other animal data also support upregulation of PNPLA3 expression with a high carbohydrate diet [56]. These data suggest that it may be reasonable to advise reduction of saturated fats in preference of monounsaturated fats, although controlled trials in NAFLD patients are desirable.

3.6. *Macronutrients: Carbohydrates Including High Fructose Corn Syrup*

Excess consumption of carbohydrates, and in particular fructose, should be discouraged in people with NAFLD. The metabolism of fructose differs from that of glucose as it is almost completely extracted by the liver [57] and does not stimulate normal satiety mechanisms as glucose does, thereby promoting overconsumption [58]. The association of dietary fructose and insulin resistance syndrome broadly in epidemiologic studies has been reviewed elsewhere [59]. Cross sectional data in 427 NAFLD patients suggest that daily fructose ingestion from sweetened beverages is associated with more advanced liver fibrosis at biopsy, although paradoxically, no association with hepatic steatosis was seen [60]. Other observational data assessing short term overfeeding with fructose or glucose in humans indicate that even a 1 week high fructose (daily consumption of 4 g/fructose/kg/day) or high glucose (daily consumption of 3 g/glucose/kg/day) diet may cause reduced hepatic insulin sensitivity and increased liver fat content as measured by MR-S [61]. A randomized trial of high sucrose intake (1 liter of sweetened cola per day) *vs.* water, milk or artificially sweetened soft drink in overweight subjects was associated with greater hepatic fat deposition (measured by MR-S), skeletal fat deposition and serum triglycerides in the cola group [62]. Fructose consumption may also promote inflammation in NASH by inducing bacterial overgrowth in the small intestine which increases endotoxin levels in the portal vein [63]. Of interest, a recent trial challenges the assumption that changes are due to fructose only. In this trial, 32 overweight males were randomized to high (25% of daily

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intake) fructose or glucose intake for 4 weeks in total, with a primary outcome of hepatic triacylglycerol content and secondary outcomes of hepatic and systemic insulin resistance, and found no difference between the two groups [64]. This question deserves more interrogation, but currently, it seems prudent to advise limiting excess refined carbohydrate consumption particularly that sourced from soft drinks and fruit juices, in favor of water and non-sweetened beverages.

3.7. Probiotics

Somewhat similar to omega-3, the marketing and use of probiotic agents has preceded firm scientific evidence to support their efficacy [65], and there are currently more than 30 Cochrane systematic reviews addressing effect of probiotics in wide ranging conditions such as eczema, irritable bowel syndrome, pneumonia, urinary tract infections and premature labor with variable results. Probiotics consist of bacteria (e.g. *Lactobacillus*) and/or yeast (e.g. *Saccharomyces boulardii*) that are part of the normal intestinal flora, and although probiotics generally have been promoted to cure a wide range of ailments, the evidence suggests that the efficacy of individual probiotics is specific to the condition and cannot be generalized [65].

There has been increasing interest in whether people with NAFLD/NASH have a dysfunctional microbiome that may promote progression of NAFLD via a breakdown of the normal small intestinal barrier and translocation of bacteria into the systemic circulation [66], leading to systemic inflammation, increased cytokines and insulin resistance [67]. Small bowel bacterial overgrowth is more common in people with NAFLD [68] although the diagnostic test used to verify this is of limited accuracy. In a proof of concept study, a 6 month trial of *Lactobacillus* and *Bifidobacterium* supplementation in NASH patients resulted in significantly less intrahepatic triglyceride (measured by MR-S), although BMI and waist circumference were unchanged [69]. A further trial of supplementation with mixed *Lactobacillus* and *Bifidobacterium* species for 6 months *vs.* placebo indicated a reduction in liver stiffness measured by transient elastography [70], and a meta-analysis of 4 randomized trials (N = 134) suggested that probiotics can reduce insulin resistance [71]. Currently, there is insufficient evidence to recommend probiotics but given their good safety profile (considered safe in most people with the exception of immunocompromised patients where there is a small risk of fungemia), further trials with clinically relevant liver related outcomes, and testing various types, doses and duration of treatment, would be informative.

3.8. Coffee

Coffee and caffeine intake may be inversely associated with liver fibrosis in people with NAFLD, although the evidence base consists of observational, rather than trial based data. The putative beneficial effects of coffee and caffeine in liver disease have been comprehensively reviewed [72] and while the exact hepatoprotective effects have not been elucidated, possible mechanisms are coffee's antioxidant, anti-inflammatory, and antifibrotic effects [73]. In a prospective study, the coffee consumption of patients with NAFLD was recorded at baseline, and 147 patients were followed for 7 years. Those who drank more coffee (3+ cups per day) had a lower fibrosis score measured by a noninvasive fibrosis scoring system [74]. However the strength of these conclusions is tempered by the inherent methodological limitations including change in coffee consumption over time and limited diagnostic accuracy of non-invasive scoring systems. In a further cross sectional study of all-cause liver disease patients with liver biopsy at baseline and data on coffee consumption collected 3 times over a 6 month period, daily coffee consumption was associated with significantly lower odds of liver fibrosis [75]. Similar results have been replicated in a NASH specific cohort [76]. Interestingly, the benefits of coffee may be specific to caffeinated coffee rather than decaffeinated coffee or tea, as some studies have shown a statistically significant relationship for fibrosis reduction for caffeinated coffee only, while other data have shown an independent benefit for coffee in reduction of hepatocellular carcinoma after controlling for tea intake [77]. The exact dose of caffeinated coffee that may be beneficial cannot be determined by the above data, which needs to be addressed by good quality prospective studies, although a statistically significant benefit has generally occurred with higher intake (e.g. 2–3 cups of caffeinated coffee per day, approximately 300 mg caffeine). Overall, current observational data support encouragement of regular caffeinated coffee intake in people with NAFLD who already consume coffee, and provide an attractive therapeutic avenue for further study.

3.9. Nuts

Nuts are known to be high in omega-3 polyunsaturated fatty acids, which have prompted speculation that they may be beneficial in NAFLD. In a cross sectional study of Korean adults with NAFLD, an inverse association was found between nut intake and risk of NAFLD [78]. Walnuts have been of particular interest given their high content of the omega-3 fatty acid, alpha-linolenic acid (ALA), and a high walnut intake is associated with lower prevalence of cardiovascular disease and type 2 diabetes in large epidemiological studies [79]. Further, supplementation with 30 g/day of walnuts in type 2 diabetics indicated reductions in LDL and increases in HDL [80]. These data are insufficient to support recommendations on nut intake in NAFLD patients at present.

3.10. Alcohol Consumption

The evidence base for benefit of alcohol intake in NAFLD is conflicting and limited to observational data only. In a cross sectional study, increased intake was inversely associated with NAFLD, with an odds of having NAFLD of 0.80 for those who drink 1–3 days/week, and odds of 0.52 for those who drink 4–6 days per week [81], although this association may be confounded by other lifestyle factors. Prospective data suggest that fibrosis worsens with heavy alcohol use, defined as heavy episodic alcohol use at least once per month [82]. Contemporary clinical guidelines do not make conclusive recommendations on alcohol use and further prospective data is needed [83].

3.11. Dietary Interventions With Low Levels of Evidence Only: Protein, Choline, Resveratrol, and Fiber

Currently, the evidence base for high protein diets or protein supplements in NAFLD is restricted to observational data

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only. Experimental animal data suggest that dietary protein such as taurine may reduce hepatic inflammation in mice [84], and a small observational study of 11 women indicated that soy protein supplements reduced hepatic lipid content, but no clinical or patient important outcomes were studied [85]. Choline is an essential nutrient found in egg yolks and animal protein and it is speculated that choline deficiency can induce NAFLD. This predisposition is genetically mediated, yet human studies are needed to clarify whether supplementation may be therapeutic in NAFLD patients [86]. Resveratrol, a dietary antioxidant found in red wine appears to improve insulin sensitivity in humans [87], but whether it influences NAFLD has not been studied. Dietary fiber appears to have a positive effect on the microbiome [88] and reduces hepatic steatosis in rodent studies [89,90], but human data are lacking. These interventions remain largely of theoretical interest until trials or well conducted prospective data are available.

3.12. *Potential Adverse Effects of Diets*

Little work has been done to comprehensively examine the adverse effects of dieting. Very low calorie diets (200–800 kcal/day) have been associated with electrolyte disturbance, hypotension and cholelithiasis [91,92], while low carbohydrate diets such as the Atkins diet are associated with ketosis and poor long term compliance [93]. Low carbohydrate diets may also have greater adverse effects on mood than a low fat diet [94]. Diets high in protein may improve satiety compared with low fat diets [95] but are linked with increased gastrointestinal disturbance such as constipation and halitosis [96]. Given the complexity of dieting effects on an individual level, and low adherence that may ensue, clinical monitoring for adverse effects is needed.

3.13. *Summary of Dietary Recommendations (Table 1)*

The major dietary interventions in people with NAFLD and the level of supporting evidence (trial based *vs.* systematic review/meta-analysis *vs.* other) are summarized in Table 1.

4. Exercise Interventions for NAFLD: Aerobic, Anaerobic or Both?

Guidelines from specialty societies on exercise recommendations in NAFLD are variable. The American Association for the Study of Liver Diseases (AASLD) proposes that exercise can reduce hepatic steatosis in NAFLD, but does not make specific recommendations on the amount needed [11]. The European Association for the Study of the Liver (EASL) recommends that guidelines for diabetic patients be followed, namely 150 minutes of moderate intensity exercise per week, 75 minutes of vigorous intensity exercise per week and muscle strengthening exercises twice per week [12]. This is in line with exercise recommendations for the general population (The American College of Sports Medicine recommends 3 to 5 sessions for 40 minutes for at least 8 weeks for a significant improvement in VO_2 max) [97].

In epidemiological studies, levels of physical activity are correlated with the prevalence of metabolic syndrome [98–100] and this relationship is also seen in NAFLD. People with NAFLD are less active than the general population [101], and the amount of activity is inversely associated with levels of intrahepatic fat independent of confounders such as age, sex, BMI and insulin resistance [102]. Krasnoff et al found that >80% of people with NAFLD did not meet recommended physical activity guidelines of 30 minutes of moderate exercise undertaken 3 or more times per week, and this result was true across the histological spectrum of NASH [103]. The largest biopsy-based study of people with NASH and physical activity levels suggests that the more severe the NASH, the lower the physical activity levels [104]. Clearly these data are not necessarily causal, and may even reflect inverse causality, but people who do more vigorous exercise appear to have a lower likelihood of advanced fibrosis [104].

While exercise recommendations form part of standard lifestyle modification advice to patients, whether to advise aerobic, anaerobic or combined modalities are uncertain, with benefits for both seen in prospective studies. In a cohort study of moderate intensity aerobic training, liver enzymes and insulin resistance improved after 3 months of weight training, independently of weight loss [105]. To further test this hypothesis, in a small trial by Bacchi, patients with type 2 diabetes were randomized to aerobic exercise (n = 13) or resistance training (n = 17) and a similar reduction in intrahepatic fat was observed in both groups [106]. However, the interpretation is somewhat limited by small sample size (n = 30) and lack of a control group which precludes assumptions of improvement due to the intervention alone. A trial in 25 obese Japanese patients with NAFLD, randomized to 3 months of walking/jogging and caloric restriction *vs.* standard care, showed that exercise resulted in an improvement in steatosis [107]. Further to this, a meta-analysis of NAFLD patients participating in aerobic exercise programs showed that liver fat was significantly reduced, but substantial heterogeneity existed and the optimal exercise prescription is undetermined [108]. In addition, the important clinical question of whether reduction in liver fat translates to hard endpoints such as reduced progression to chronic liver disease is unknown.

Equally important to increasing exercise seems to be avoiding sedentary time [98]. Data from large population based studies suggest that time spent in sedentary activities is an independent predictor of insulin resistance syndromes, and consistently suggest that this is irrespective of moderate or even vigorous physical activity levels [98,109–112]. There are little data on risk of sedentary time specifically in people with NAFLD, but it seems reasonable to extrapolate these findings given the inextricable relationship of NAFLD to the metabolic syndrome, and recommendations to limit sedentary time are sensible.

4.1. *Special Considerations: Exercise in NAFLD Patients Who are Aged or Morbidly Obese*

Traditional aerobic exercise programs that include walking may be difficult to undertake in elderly, frail patients or those who are morbidly obese, despite the substantial advantages that exercise confers [113]. An alternative is resistance training, as this is low impact and requires less energy expenditure and time compared with aerobic exercise [114]. NAFLD patients undertake lower levels of habitual resistance exercise [115], and resistance training improves insulin resistance in NAFLD patients [116]. Resistance training may also improve autonomic dysfunction seen in NAFLD, thereby

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Table 1 – Nutritional interventions for people with NAFLD/NASH and available evidence from trials or systematic reviews.

Intervention	Description	Level of evidence for people with metabolic syndrome or type 2 diabetes	Level of evidence for people with NAFLD/NASH	Comments
Mediterranean diet	Diet high in monounsaturated fats and omega-3 PUFAs, vegetables, fruits and legumes with less meat and dairy intake	Trial based data show benefits in dyslipidemia outcomes [16] Little evidence from Cochrane review for cardiovascular endpoints [20]	Trial based data for surrogate outcomes of hepatic steatosis and insulin resistance [22]	Reasonable evidence for improvement in surrogate outcomes, but not for hard clinical end points. Further trial based data needed.
Omega-3 PUFAs	Omega-3 polyunsaturated fatty acids supplementation (500 mg to 3 g/day)	Trial based data show benefit as secondary prophylaxis in recent infarct survivors [33] No clear benefit as primary prophylaxis [32]	Improvement in surrogate outcome of liver fat from single pediatric trial [36] and meta-analysis of adult trials [38]	Some evidence for surrogate outcomes but not for hard clinical end points. Minimal side effect profile
Monounsaturated fats	Fats found in olive oil, nuts and avocadoes	Systematic review based data show improvement in dyslipidemia in type 2 diabetics [41]	No trial based data	Insufficient data
Coffee	Caffeinated coffee appears preferable to decaffeinated or tea, 2–3 cups per day (300 mg caffeine)		No trial based data	Insufficient data, but reasonable to encourage ongoing intake in current coffee drinkers
Probiotics	*Lactobacillus* and *Bifidobacterium* species	No Cochrane reviews in metabolic syndrome	Trial based data suggest less liver fat [69] Small trial suggests reduced liver stiffness [70]	Insufficient data. Avoid in immunosuppressed patients
Nuts	High in omega-3 PUFAs; walnuts most studied	A trial of 30 g walnut supplementation improves dyslipidemia [80]	No trial based data	Insufficient data
Olive oil	Dietary olive oil	Cohort studies show reduced incidence of type 2 diabetes	No trial based data	Therapeutic studies in NAFLD are needed

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gradually enabling other forms of more vigorous exercise to be undertaken [117]. Where possible, tailored programs taking into account individual's co-morbidities are desirable to maximize training benefits [118].

4.2. *Summary for Exercise Recommendations*

Based on current data, it is reasonable to recommend exercise guidelines for diabetic patients as outlined above, unless further trial based evidence with liver related outcomes becomes available. Furthermore, advice on limiting sedentary time should also be given. Future research agendas should focus on exercise type, duration and frequency to better inform recommendations.

5. Weight Loss for NAFLD: Do Patients Need to Lose Weight to Achieve Benefits?

A practical question for clinicians is whether patients need to lose weight in order to improve liver specific outcomes. The benefits and harms of weight loss in NAFLD have been the subject of a Cochrane review which included 7 trials — 5 of diet and exercise and 2 of orlistat [119]. The authors concluded that as all trials had a high risk of selection bias due to unclear randomization, allocation techniques and loss to follow-up, it was not possible to make firm recommendations and better quality trials are needed. Individual trials show that aerobic exercise can reduce liver fat without weight loss [120], and recent trial based evidence also suggests that weight loss correlates with histological improvement. A highly cited trial of weight loss in NASH revealed that a 7–10% loss of body weight was directly correlated with histological improvement [121]. More recently, a cohort study of 293 patients prescribed a low fat diet and exercise program with a primary outcome of biopsy-proven resolution of NASH also found that weight loss correlated with histological improvement in a dose dependent fashion [122]. For those who lost 7–10% of body weight, 16/25 (64%) had resolution of steatohepatitis, whereas when weight loss was >10%, 26/29 (90%) had resolution of steatohepatitis, and fibrosis regressed in 45% of participants. Trials of weight loss medications such as orlistat in NASH have also indicated that histological improvement directly correlates with weight loss [123]. These good quality data suggest that where achievable, weight loss should be the primary target of any lifestyle modification program, although exercise alone may still provide benefits in reduction of liver fat. A note of caution however, that rapid weight loss by low carbohydrate ketogenic diets should be avoided, as they may worsen liver disease [124,125].

The benefits of weight loss for lean people, defined as those with a normal or only mildly elevated BMI, have not been studied, and there are scarce data on dietary differences. A retrospective cohort study that compared diets of 431 lean NAFLD patients with lean controls found no difference in dietary intake [126]. In this study, Hispanic ethnicity was a strong predictor of lean NAFLD, and this genetic predisposition is supported by data from an Asian cohort, who were found to develop insulin resistance at a lower BMI [127]. Given the likely central role of insulin resistance in lean NAFLD patients, studies assessing the benefits of dietary manipulation such as reduction in excess carbohydrate, with or without weight loss, would be instructive.

6. Behavioral Strategies for NAFLD: Improving Adherence

The manifold benefits of dietary and exercise regimes for people with NAFLD cannot be realized unless sustained behavioral change is achieved, using behavioral or cognitive behavioral therapies. Cognitive behavioral therapies focus on the interaction between cognition, behaviors and emotions, and propose that maladaptive behaviors can be rectified by focusing on cognitive processes behind them. This differs, at least theoretically, from behavioral therapies where cognition is not considered as important in maladaptive behaviors and is not targeted for intervention. However, the practical applications remain similar [128,129]. Psychological therapies may work because they directly target barriers to lifestyle modification that are not addressed by traditional dietary counseling, such as boredom, stress, loss of motivation and maladaptive thought processes regarding weight loss [130,131]. Other barriers to lifestyle modification cited by NAFLD patients in particular include fatigue [132], lack of confidence and fear of falling [133], which are also amenable to behavioral therapy. Data from large trials in type 2 diabetes clearly illustrate the incremental benefits of behavioral therapies such as individualized counseling and reinforcement measures [134], and they are an integral part of obesity management programs, with clear evidence for their supporting role alongside diet and exercise recommendations [135]. In a cohort study of NAFLD patients, cognitive behavioral therapy in addition to standard dietary prescription resulted in an additional weight loss and improved insulin resistance that was sustained at 2 years [136] and more frequent contact with therapists can result in significantly greater weight loss [105]. Clinicians with no previous experience in CBT techniques should at least aim to use an 'engaging counseling style' and encourage self-empowerment techniques such as self-recording of food intake and physical activity (e.g. with a pedometer), and realistic goal setting [137], and ideally, employ a multidisciplinary approach to patient care.

7. Conclusion

In the absence of effective and acceptable pharmacological therapies, lifestyle modification with diet and exercise advice remains the cornerstone of management of NAFLD. Where available, and as outlined in this review, evidence based dietary recommendations from trials or systematic reviews of trials in NAFLD patients should be followed. Where evidence in NAFLD patients specifically is lacking, we believe that it is reasonable to use good quality evidence from interventions in patients with similar pathophysiology such as metabolic syndrome or type 2 diabetes, given the close relationship between these disorders. For all patients, a multifaceted approach, using a multidisciplinary team is likely to achieve the best outcome.

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