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REVIEW ARTICLE

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Non-pharmacological interventions in non-alcoholic fatty liver disease patients

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Abstract

Patients with non-alcoholic fatty liver disease have unhealthy diets, sedentary behaviour and not enough physical activity. This lifestyle triggers liver disease and probably favours its progression. It also has significant deleterious effects on health and longevity and should therefore be corrected by first-line therapy at all stages of the disease. However, important questions remain: is weight loss alone beneficial or do particular diets have beneficial effects beyond weight loss? Which specific micro- or macronutrients are clearly harmful? Does exercise without weight loss improve hepatic histology and what type of exercise is optimal? Does moderate or only vigorous exercise have metabolic and hepatic benefits? What is the efficacy of lifestyle measures outside of clinical trials? And most importantly, what is the turning point in the natural history of liver disease when non-pharmacological measures should be combined with drug therapy?

KEYWORDS
diet, exercise, fibrosis, non-alcoholic steatohepatitis, steatosis

1 | INTRODUCTION

Currently the prevalence of non-alcoholic fatty liver disease (NAFLD) is 25% worldwide[1] which makes it a global non-communicable disease and no longer a disease of affluence. It is now the most common chronic liver disease as well as a significant cause of end-stage liver disease[2] and hepatocellular carcinoma. It has been calculated that 20 million patients with NAFLD worldwide will eventually die of liver disease.[3] The reason for the rising prevalence of NAFLD is the strong association with excess weight and type 2 diabetes. Diet and lifestyle changes to correct unhealthy habits are the first-line therapy for this condition and they should be directed to all patients with NAFLD including those with steatohepatitis (non-alcoholic steatohepatitis, NASH) and advanced fibrosis.[4] Many excellent reviews have provided detailed insights into the non-pharmacological interventions in NAFLD/NASH patients.[5–7] Recommendations from scientific societies are also available.[8–10] In this paper, we will report some of the salient findings, controversial issues and unresolved questions.

2 | EFFICACY OF WEIGHT LOSS IN IMPROVING LIVER HISTOLOGY

Weight loss is one of the cornerstones of treatment of NAFLD/NASH. This was first shown by the remarkable histological improvement, including the reversal of fibrosis and cirrhosis in patients undergoing massive weight loss following bariatric surgery. Natural history studies with repeat biopsies have confirmed a higher proportion of fibrosis reversal in patients with weight loss >10%.[11] Although available data are limited, this histological benefit may occur regardless of the method used to achieve weight loss, as long as it is gradual and lasting.

The amount of weight loss necessary to improve the different histological lesions of NASH has been determined from limited data in

Abbreviations: NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; RCT, randomized controlled trials.

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interventional studies with histological follow-up[8,12]: 3-5% of body weight loss to improve steatosis, more than 5% to improve liver cell injury and inflammation, more than 7% for the resolution of steatohepatitis and 10% or more to improve fibrosis. This weight-dependent relationship is supported by the sequence of events in the natural history of NASH. However, sampling variability in liver biopsies and the natural fluctuations in the disease mean that reliable data can mostly be obtained from randomized controlled trials (RCT). Although several studies are available, the sample populations are limited. One well designed but small randomized study in 30 patients[13] has shown that the percent of weight reduction is correlated with the reduction in NAS score, a composite histological score that sums up steatosis, liver cell injury (ballooning) and hepatic inflammation. Steatosis, liver cell injury and inflammation clearly improved more often in participants who lost ≥7% of body weight. This has been confirmed in uncontrolled studies[14] as well as in an RCT with orlistat, a drug acting through weight loss without a direct hepatic effect.[15] The largest series so far to look into the relationship between weight loss and histological improvement was an open label uncontrolled study performed in 293 patients with histologically confirmed NASH who received intensive lifestyle and diet intervention (low fat hypocaloric diet and exercise).[16] Data show a strong correlation between weight loss and NASH resolution and weaker (but significant) correlations with the reversal of fibrosis. Remarkably, a ≥5% weight loss resulted in resolution of steatohepatitis in 58% of patients; a ≥10% weight loss resulted in a resolution of NASH in 90% of patients and regression of fibrosis in 45% of patients.[16] Somewhat surprisingly, in this series even a <5% weight loss resulted in an improvement in fibrosis in a large proportion of patients, (45%) which is much higher than that in available RCTs.[17] Nevertheless, it is clear that: (i) moderate weight loss is associated with histological improvement of NASH and fibrosis; (ii) a higher rate of weight loss is necessary for the reversal of fibrosis than for improvement of other NAFLD histological lesions.

3 | HOW EFFECTIVE IS WEIGHT LOSS AS A THERAPEUTIC INTERVENTION?

Two separate issues need to be considered for non-pharmacological, non-surgical weight loss programmes. First, are weight loss interventions successful and sustainable? Second, does improvement in histology occur whatever the severity of liver disease?

Most interventions only successfully achieve target weight loss in a small minority of patients. In patients with NAFLD, only 12% of patients lost between 5 and 7% of their initial weight and 8.5% lost between 7% and 10% even during clinical trials.[16] This explains why real-life clinical experience has been so frustrating, thus far. Moreover, it is important to remember that weight-loss interventions range from minimal dietary advice, to changing dietary patterns, or active, intensive, interventions involving multiple professionals (psychologists, dieticians, health educators, physical therapists, physical coaches and complex behavioural therapies, and frequent meeting groups). Although it is clear that more multidisciplinary and elaborate interventions result in greater weight loss, it is also true that no existing hepatology department can implement these intensive interventions in real life (except for very few multidisciplinary NASH clinics). Even when these programmes can be put into clinical practice the results are not expected to be impressive. A meta-analysis concluded that compared to usual care, weight-loss interventions result in only modest weight loss that diminishes over time. Weight loss is usually maximum in the first 6 months (and approximately 6% or 5 kg of the initial body weight at 1 year) and half of the initial weight loss has usually been regained after 3 years.[18] Whether weight loss is rapid or gradual, initial weight loss is followed by a 71% weight regain during a 3 year maintenance phase of the diet.[19] It is more worrisome that this weight regain is at least partly dictated by physiological adaptations, such as an increase in serum ghrelin concentrations and other numerous hormonal adaptations[19,20] and by a permanent increase in the sensation of hunger.[19] Unfortunately, with both low-key weight maintenance interventions[21] and intensive lifestyle interventions combining diet, exercise and behavioural therapy,[22] weight regain is inevitable. Nevertheless, some studies have shown that modest weight loss still substantially reduces cardiovascular risk factors such as hyperglycaemia, hypercholesterolaemia and hypertension[23] and could reduce the risk of and delay the progression to diabetes.[24] However, in the long-term results are less conclusive. The Look AHEAD trial randomized more than 5000 overweight or obese patients with type 2 diabetes to receive intensive lifestyle intervention or diabetes support and education. The intensive lifestyle intervention group had greater weight loss and greater initial improvement in most cardiovascular risk factors (except for LDL-cholesterol levels). However, this did not translate into clinical outcomes: after a 9.6 year follow-up, the study was stopped for futility because of the inability of a 6% weight loss to reduce death from cardiovascular causes or to reduce myocardial infarction, stroke or hospitalization for coronary artery disease.

It is also questionable whether weight loss interventions induce hepatic histological improvement in patients with advanced liver disease. Data from the few RCTs in NASH published to date are not

Key points

- A 7%-10% weight loss should be the goal in all overweight/obese NAFLD or NASH patients. No particular diet seems to be clearly beneficial beyond weight loss.
- Weight loss improves liver histology including hepatic fibrosis if ≥10%. However, improvement of histologically advanced NASH by weight loss interventions is significantly decreased.
- Physical activity should be implemented because it improves metabolism, has protective effects on cardiovascular disease and the risk of cancer. Vigorous rather than moderate activity and resistance training should be encouraged.
- A sedentary lifestyle should be strongly discouraged.

sufficient. For instance, the Promrat article does not provide information on the histological severity of steatohepatitis and fibrosis in their participants and whether this influenced the therapeutic response.[13] An interesting evaluation was performed of the above-mentioned open-label study by Vilar-Gomez et al.[25] The authors identified independent negative predictive factors of histological improvement in their intensive diet and lifestyle intervention : these were older age, type 2 diabetes and more severe NASH histological activity.[25] It is interesting that both the histological severity of NASH and the presence of cofactors that aggravate NASH liver injury (older age and type 2 diabetes) significantly reduced the chances that diet and lifestyle interventions improve hepatic histology. This suggests that patients with more severe NASH are less susceptible to improvement in their liver disease with non-pharmacological, non-surgical weight loss interventions.

4 | WHAT TYPE OF DIET IS MOST APPROPRIATE FOR NAFLD/NASH PATIENTS?

The most important factor in dietary interventions seems to be calorie restriction. It is the main driver of weight loss and visceral adiposity, subcutaneous fat and liver fat reduction.[26] Relatively small amounts of weight loss result in significant reductions in liver fat and improvement in hepatic insulin resistance[27] although there are no data on other histological end-points. The macronutrient composition of the diet does not matter for the outcome as long as weight loss is achieved.[26,28] Certain data suggest that carbohydrate-deficient diets have an early beneficial effect on hepatic fat and insulin sensitivity.[29,30] However, this might not make a difference, in the long term when overall weight loss is obtained and insulin-resistant sites other than the liver are studied.[29] Other studies did not confirm differences between low carbohydrate and low fat diets as long as they are both calorie restricted.[31] Needless to say, there are almost no studies comparing different diets and evaluating hepatic endpoints. A recent randomized trial compared a low carbohydrate diet with a low fat diet for 1 year in overweight/obese individuals without other comorbidities.[32] The low carbohydrate diet resulted in greater weight loss (a modest 3.5 kg mean reduction from baseline) as well as a greater increase in HDL and decrease in triglycerides than the low fat diet. This resulted in greater reduction in the 10-year Framingham risk score for cardiovascular disease. The weight loss was explained by a greater proportional reduction in fat mass, although no differences were seen for improvement in serum glucose or insulin between diets.[32] It must still be shown whether greater improvement in insulin sensitivity can be obtained. Although a meta-analysis also showed greater improvement in HDL and triglyceride levels for low carbohydrate diets,[33] many of these studies have significant limitations including imprecise outpatient food-intake monitoring, suboptimal body composition techniques to measure fat balance and short-term follow-up. A recent study comparing low carbohydrate and low fat diets in a rigorous crossover design and using inpatient food-intake monitoring and indirect calorimetry has shown that unlike commonly held beliefs, calorie for calorie restriction of dietary fat led to greater body fat loss than restriction of dietary carbohydrates.[34] More studies are needed but there is probably very little long-term difference in fat loss between isocaloric weight loss diets that mainly restrict carbohydrate or fat.[35]

The Mediterranean diet is a dietary pattern characterized by high consumption of monounsaturated fatty acids primarily from olives and olive oil, fruit, cereals, whole grain cereals, and low fat dairy products with infrequent consumption of red meat. It has been shown to play a beneficial role in mortality from all causes, cardiovascular disease, cancer, obesity and type 2 diabetes.[36,37] A meta-analysis has shown that following the Mediterranean diet was associated with a reduced risk of developing the metabolic syndrome and a protective role from each of its components.[38] It might therefore play a role in the primary and secondary prevention of the metabolic syndrome and its individual components. When supplemented with extra-virgin olive oil or nuts it prevents major cardiovascular events and cardiovascular death in patients with high cardiovascular risks.[39] The effect was highest for stroke. The beneficial effect of the Mediterranean diet for central obesity[38] is particularly relevant to NASH, a condition that is closely linked to excess truncal fat. Recently, an RCT suggested that the Mediterranean diet could reduce liver fat and improve hepatic insulin resistance, even without weight loss.[40] One study performed in Greece and Italy in patients with newly diagnosed hepatocellular carcinoma has shown that close adherence to the Mediterranean diet reduces the risk of developing this neoplasm by a third. [41]The inverse relationship was roughly monotonic and individuals with the highest adherence had a 50% risk reduction. Most patients in this study had hepatitis B or C, so we lack specific data for NASH. There are numerous reports of an inverse relationship between this diet and numerous other forms of cancer. [42,43]

5 | UNHEALTHY DIET AND NAFLD

NAFLD patients have unhealthy diets characterized by overconsumption of fructose and soft drinks, lower consumption of fibre, overconsumption of meat, saturated fat and cholesterol, lower consumption of fish or omega-3 fatty acids or PUFA, and lower consumption of certain vitamins.[44–46] Animal data suggest that, independent of weight loss, switching from a high fat to a healthy diet lowers liver fat content, improves hepatic inflammation and arrests liver fibrosis. Cellular mechanisms include a change from the M1 to the M2, anti-inflammatory phenotype of macrophages, an inhibition of stellate cell activation and a reduction in NF-kB induction. This attenuates the severity of NASH and fibrotic progression but weight loss is necessary for a total reversal of steatosis and hepatic apoptosis. Nonetheless these data give biological support to the beneficial effects of a healthy, physiological diet for NASH patients. Overconsumption of meat and insufficient intake of vegetables

could also contribute to an increased risk of liver cancer[47,48] Many studies have concentrated on the deleterious hepatic and metabolic effects of fructose which is excessively consumed in NASH patients.[46] Some data have shown that high fructose consumption, possibly industrial fructose only (not fruit fructose)[49] increases the risk of fibrosis in NASH patients.[50] In overweight/obese individuals dietary fructose specifically increases de novo lipogenesis, promotes dyslipidaemia, increases visceral adiposity and insulin resistance.[51] It is not entirely clear, however, whether the excess risk is not in fact because of excess calorie intake (whatever the type of sugar)[52] or if it is not confounded by an overall unhealthy lifestyle pattern that includes smoking, lack of exercise, diets rich in fat, poor in fibre, etc.[53] Well designed, prospective studies that take into account multiple confounders are needed to more clearly establish the epidemiological basis of this association. Nevertheless, experimental studies have shown that while HFD alone only induces steatosis, HFD + high sucrose diets induce steatohepatitis, inflammation oxidative stress and fibrosis.[54]

6 | LACK OF EXERCISE IS A MAJOR CAUSE OF CHRONIC DISEASES

It has been estimated that physical inactivity causes 6% of the burden of disease from coronary heart disease, 7% of type 2 diabetes and 10% of breast and colon cancer.[55] Nine percent of the premature deaths worldwide may be caused by the lack of physical activity.[50] Regular exercise reduces the risk of many chronic metabolic and cardiorespiratory diseases through multiple cellular mechanisms resulting in anti-inflammatory effects: reduction in visceral fat mass with inhibition of monocyte and macrophage infiltration into adipose tissue, release of anti-inflammatory cytokines from contracting skeletal muscle, reduced expression of toll like receptors on monocytes and macrophages and increase in the circulating number of T regulatory cells (reviewed in 56).

The relationship between physical exercise and cancer is particularly intriguing. A prospective study with an average follow-up of 8.3 years in more than 416 000 individuals from the general Taiwanese population has shown an almost monotonic relationship between physical exercise and overall and cancer-related mortality.[52] Compared to low-volume activity, inactive individuals had a 17% increase in the risk of mortality from all-causes and an 11% increase in the risk of cancer mortality. Every additional 15 minutes of daily exercise (above the minimum 15 minutes daily and up to 100 minutes daily) is expected to generate an additional reduction in 4% all-cause and 1% all-cancer mortality. Vigorous exercise has a much greater beneficial effect than moderate exercise.[52] Myokines released by contracting muscle fibres such as oncostatin M[53] or osteonectin[54] have anti-proliferative properties resulting in apoptosis of colon or breast cancer cells. In liver, melanoma and lung cancers, after exercise another myokine, interleukin 6 is increased, mobilizing natural killer cells which migrate into tumours and destroy tumour cells.[55]

7 | PHYSICAL ACTIVITY AND SEDENTARITY IN NAFLD PATIENTS AND ITS CONSEQUENCES

Half of NAFLD patients are inactive including almost a third that do virtually no physical exercise[56,57] Physical inactivity has been associated with increased body weight, central adiposity, and insulin resistance as well as an increased risk of the metabolic syndrome. [58,59]It has long been recognized that physical activity is inversely related to the amount of liver fat, but this seems to be especially true for high levels of physical activity.[60] Data from animal models further support the association between exercise and fatty liver.[61,62] In a large cross-sectional cohort of 813 patients from the NASH-CRN, patients who declared that they regularly engaged in vigorous physical exercise (26% of the total) had a significant reduction in the adjusted odds of having steatohepatitis and advanced fibrosis.[56] Interestingly, patients who engaged in moderate physical activity did not have this significant reduction.[56] Large cross-sectional studies in Asians have shown similar results: patients who engaged in regular exercise (>3 times per week, 30 minutes each time) had a reduced risk of being diagnosed with NAFLD; in patients with NAFLD, regular exercise was associated with a reduced risk of elevated aminotransferases.[63]

The impact of physical exercise in NAFLD patients has been reported in a few studies. Moderately intense physical activity (60-150 min per week) in three sessions resulted in biochemical (ALT) and in metabolic improvement (mainly glucose and HOMA) even in the absence of weight loss.[64] Uncontrolled interventional studies have confirmed that insulin resistance and ALT are reduced in patients who are compliant for exercise have a reduction in compared to non-compliant patients.[65] Two important issues must still be clarified. One of them is to understand the benefits of exercise *per se*, independent of dietary changes and weight loss. The other is to determine whether there are differential benefits between resistance exercise (anaerobic, muscle strengthening) and aerobic exercise.

A randomized study compared these two types of exercise and showed that both of them reduce hepatic fat content, visceral and subcutaneous fat and improved insulin sensitivity and the lipid profile comparably. Although weight was also reduced in both arms of the study there was no concomitant reduction in ALT.[66] In contrast, another controlled study[67] showed only a modest reduction in liver fat and no improvement in lipoprotein metabolism with exercise, in the absence of weight loss. A meta-analysis has shown that exercise alone significantly reduces hepatic fat content, a benefit occurring with minimal or no weight loss.[68] The effect on the other histological lesions of NASH remains unknown. Unfortunately, all of methodologies in these studies did not take into account the numerous confounders. One study concluded that resistance exercise reduces liver fat (with the resolution of NAFLD in some cases), improves glucose control and insulin sensitivity and promotes fat oxidation, even without weight loss or impact on visceral fat.[69] However, patients that benefit most from exercise interventions are those that have a certain level of cardiorespiratory fitness at baseline,[70] which represents only a minority

of NAFLD patients.[59] Another major limitation, which is a real-life problem, is that most NAFLD patients have high levels of fatigue, associated with inactivity and daytime sleepiness,[71] thus reducing compliance to physical exercise.

While engaging in physical exercise is beneficial, avoiding sedentarity is equally important. Sedentarity increases all-cause mortality independent of physical activity[72] and is predictive of higher levels of insulin resistance[73] and reducing sitting time improves insulin sensitivity.[74] No specific studies are available in NAFLD, but since this only requires minimal disruption of daily activities by short bouts of walking, it should be part of lifestyle changes in all NAFLD patients.[75]

8 | CONCLUSION

NAFLD patients have unhealthy dietary intakes that should be quantitatively and qualitatively optimized. Although the best diet for treating NAFLD/NASH patients has not been established, whatever the diet, weight loss is the cause of most of the benefits. Physical activity has a dose-effect relationship and vigorous (running) rather than moderate exercise provides the full benefit for metabolic and biochemical improvement as well as histological improvement as well. Resistance training that promotes musculoskeletal fitness rather than cardiovascular fitness should be implemented. Long-term compliance is key to the success of dietary and lifestyle interventions and therefore a more holistic approach including behavioural changes is needed. While diet and lifestyle measures should always be implemented because of systemic as well as hepatic benefits, a key question is whether advanced liver disease in NASH is still amenable to substantial improvement with non-pharmacological interventions.

CONFLICTS OF INTEREST

The author is a consultant for Boehringer, Bristol Myers Squibb, Galmed, Genfit, Intercept, Pfizer and Tobira.

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