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REVIEWS

Opinion

Are Lifestyle Therapies Effective for NAFLD Treatment?

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Nonalcoholic fatty liver disease (NAFLD) is becoming the most common liver disorder worldwide. Specifically, nonalcoholic steatohepatitis (NASH) and fibrosis pose an enormous burden for patients and health-care systems. In the absence of approved pharmacological therapies, effective lifestyle interventions for NAFLD, such as dietary strategies and exercise training, are currently the therapeutic strategies of choice. This review covers the influence of macronutrient quality and quantity (i.e., low-carbohydrate and high-protein diets), for successful reduction of intrahepatocellular lipids (IHL). Moreover, we discuss the effectiveness of different modalities of physical exercising with and without weight loss. These lifestyle modifications not only provide strategies to reduce IHL but may also hold a still underestimated potential to induce improvement and/or even remission of NAFLD.

Highlights

Due to its high prevalence, nonalcoholic fatty liver disease (NAFLD) is becoming an increasingly important health issue. In the absence of an established pharmacological therapy, lifestyle therapies, including dietary modifications and physical activity, are of increasing clinical significance.

Although weight loss can improve IHL, distribution of macro- and micronutrients, the role of total calories, type of diet, and physical activity is less clear. Some evidence suggests consumption of a Mediterranean diet, high fiber and protein intake, as well as physical activity, regardless of modality or intensity, have beneficial effects on intrahepatic lipids.

Recent advances also indicate that meal timing, such as shifting a higher number of daily calorie intake to the morning, can benefit NAFLD.

Nonalcoholic Fatty Liver Disease: The Challenge

The global burden of nonalcoholic fatty liver disease (**NAFLD**) (see Glossary), which ranges from steatosis to nonalcoholic steatohepatitis (**NASH**) to **fibrosis** and hepatocellular carcinoma, is rapidly rising [1]. Recent data reveal a world-wide prevalence of 24% among the adult population [2]. The etiology is multifactorial and yet incompletely understood, but involves accumulation of intrahepatic lipids (IHL), alterations of energy metabolism, **insulin resistance**, and inflammatory processes [3]. Besides genetic predisposition, unhealthy dietary habits and low levels of physical activity and regular exercising are the main modifiable risk factors for NAFLD. In the absence of approved pharmacological agents for the treatment of NAFLD, the current European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), and European Association for the Study of Obesity (EASO) Clinical Practice Guidelines for the management of NAFLD recommend lifestyle modification as the strategy of choice for preventing and improving NALFD [1]. They suggest to induce an energy deficit of 500–1000 kcal, leading to an associated weight loss of 7–10% by low-to-moderate fat, low-carbohydrate ketogenic or high-protein diets, and moderate-intensity aerobic exercise training with additional resistance training [1]. However, while there is clear evidence that weight loss improves IHL, only few people achieve the required 10% minimum weight loss required for clinically meaningful improvement or resolution of NASH and fibrosis [4]. Here, we discuss the recent evidence supporting or challenging this view.

Is Nutritional Quality or Quantity More Important to Reduce IHL?

Effect of Body Weight Reduction

A surplus of 1000 kcal for 12 weeks in obese people, leading to a weight gain of 6% body weight, increases IHL by ~50%, mainly through increased ***de novo* lipogenesis** together with reduced intrahepatic fatty acid oxidation [5], while fatty acid availability is less relevant in this setting [6,7]. Moreover, a single oral saturated fat load increases IHL, reduces hepatic insulin sensitivity in humans, and induces an inflammatory phenotype in mice, independent of body weight [8]. However, progressive weight loss by hypocaloric diet (50–55% of energy as carbohydrate, ~30% fat, and 15–20% protein) gradually reduces IHL in obese, insulin-resistant humans [9,10]. The effect is mediated at least in part through reduced fatty acid availability by improved adipose tissue insulin sensitivity [11]. In addition, a caloric deficit of ~400 kcal/day with ~5-kg weight loss improves histological features of NASH (i.e., portal and lobular inflammation, ballooning, apoptotic hepatocellular injury, **Mallory-Denk bodies**, as well as fibrosis) [12]. In morbidly obese patients undergoing bariatric surgery, a reduction of body mass index (BMI) by ~15% leads to a resolution of hepatic steatosis and NASH in ~85% of patients and an improvement in fibrosis in 34% of patients [12]. Taken together, these data show that the

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degree of weight loss is strongly associated with IHL improvements [4]. It remains a matter of debate, whether or not macronutrient composition or meal timing can drive reductions in IHL, or if the caloric deficit by itself is more critical.

Effect of Macronutrients on IHL Content

Hypocaloric low-carbohydrate diets as well as low-fat diets clearly reduce IHL measured by **proton magnetic resonance spectroscopy (^{1}H-MRS)**, without significant differences between these diets [13,14]. Yet, several studies indicate that hypocaloric low-carbohydrate strategies result in faster and more pronounced IHL reductions within 48 h [15], suggesting that at least initially, a low-carbohydrate diet could be more effective than a low-fat diet to rapidly improve IHL. These studies do not allow differentiating between the effect of the calorie deficit and a specific macronutrient action. More recent studies examined the effect of isocaloric diets with different macronutrient compositions. An isocaloric, carbohydrate-restricted (<4%; 23–30 g/day), protein-rich diet (average of 3115 kcal/day), leading to a moderate weight loss of 1.8%, reduces IHL by 43% within 2 weeks. The decrease in IHL assessed by ^{1}H-MRS is mediated by a 73% reduction in *de novo* lipogenesis, an increase in hepatic lipid oxidation, as well as an increase in folate-dependent one-carbon metabolism [16]. While this study could not completely exclude that the effect was at least in part mediated by weight loss *per se*, it suggests that reducing dietary carbohydrates has a beneficial effect on IHL, even in an isocaloric setting. Interestingly, isocaloric reduction of fructose consumption for 9–10 days also reduces liver fat and *de novo* lipogenesis independent of body weight changes [17,18]. Although there is some controversy in carbohydrate research due to inconsistencies of metabolic data from studies on isocaloric replacement of fructose with other carbohydrates, the majority of evidence from human and animal studies has shown that intake of excess energy from fructose-containing sugars leads to obesity, **dyslipidemia**, steatosis, and insulin resistance [19–22]. Along these lines, isocaloric reduction of fructose consumption for 9–10 days has been shown to reduce IHL and *de novo* lipogenesis, independent of body weight changes [17]. Moreover, restriction of fructose consumption to <20 g/day for 6 weeks significantly reduced the severity of hepatic steatosis and triglyceride levels, without altering body weight [23]. Of note, while fructose from calorically sweetened drinks had detrimental effects, fruit-derived fructose ingestion may favorably affect liver fat content [24]. While data in rodents suggest that isocaloric replacement of glucose by fructose increases *de novo* lipogenesis by activating sterol regulatory element-binding protein (**SREBP**)**-1c** and carbohydrate responsive element binding protein beta (**ChREBP-β**) signaling with subsequently higher expression of enzymes involved in fatty acid synthesis [25], clinical data comparing both macronutrients are contradictory [26–28]. The discrepancy might be partly due to different patient groups examined. An alternative explanation may be offered by the recent finding that fructose in low doses is nearly entirely cleared by the intestine, while doses of fructose exceeding 1 g/kg overwhelm intestinal fructose absorption and clearance, resulting in fructose reaching both the liver and colonic microbiota [29]. Taking these findings into account, randomized, double-blind, controlled trials in patients with NAFLD and isocaloric replacement of glucose by fructose are still warranted to better understand the effect of different doses of fructose versus glucose.

Only few studies focused on the effect of protein intake on IHL. Since, in some studies, protein intake is increased when carbohydrate intake is reduced, it cannot be excluded that effects thought to be mediated by the reduction of carbohydrates are at least in part mediated by increased protein content. Recent studies assessed the effect of isocaloric high-protein diets (30% of energy from protein, 40% from carbohydrates, and 30% from fat) in patients with NALFD and type 2 diabetes (T2D) and controlled for the quality of dietary fatty acids. These groups were randomized to receive either plant protein or animal protein for 6 weeks. This elegant study shows that a high-protein diet, independent of the source of protein, causes significant reductions in IHL by 36–48%. Moreover, serum levels of **FGF21** decreased by 50% in each group, and the decrease in FGF21 correlated with loss of IHL as assessed by ^{1}H-MRS [30]. Serum transaminases and markers of inflammation also decreased. However, this study has limitations. First, patients also slightly lost body weight in both groups. Second, in order to increase protein content, carbohydrate content of the diet was relatively low (40% of energy intake). These limitations illustrate the general challenges of diet intervention studies. So far,

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the existing data indicates a beneficial effect of reduced caloric intake on IHL, while reduced carbohydrate intake together with increased protein intake seems to affect IHL, also independently of a major caloric deficit (Figure 1).

Mediterranean Diet

The so-called Mediterranean diet is a promising dietary regimen as it can lower the incidence of several chronic diseases (e.g., cardiovascular disease, cancer, and obesity) [31,32], even without effects on markers of inflammation in patients with coronary artery disease [33].

The Mediterranean diet is traditionally consumed by populations living in regions nearby the Mediterranean Sea. Although it is difficult to precisely define the Mediterranean diet due to regional differences in culture, agricultural conventions, and lifestyles, it is typically rich in vegetables and fruits, legumes, potatoes, nonrefined cereals, and rice, with fish and white meat as predominant protein sources and red wine in moderation. Red meat and unskimmed dairy products are consumed in low amounts. The main source of fat is (extra virgin) olive oil but also nuts providing healthy fats [32,34]. As a result, this diet has a beneficial fatty acid profile as it is low in saturated fatty acids and rich in unsaturated fatty acids as well as **fibers**, carbohydrates, and antioxidants [34]. The Mediterranean diet appears to be a promising dietary option to induce metabolic benefits for patients with NAFLD.

Mediterranean diets are also effective for treating NAFLD. Following a 6-week randomized, controlled cross-over trial, patients with biopsy-proven NAFLD (> grade steatosis) following an *ad libitum* Mediterranean diet showed a significantly higher reduction of both IHL measured by ultrasound and insulin sensitivity compared with an *ad libitum* low-fat, high-carbohydrate diet, despite similar weight loss [35]. These results were confirmed by other groups [34,35]. The grade of improvement of ultrasound-assessed hepatic steatosis is significantly and inversely correlated with adherence to the Mediterranean diet [32]. Unfortunately, also in these studies, the effect of the higher intake of carbohydrates in the control group cannot be separated from effects of the Mediterranean diet itself. Overall, it is difficult to differentiate between the effects of Mediterranean diets *per se* and those of control diets. Therefore, it seems premature to draw final conclusions from the existing data.

Does It Matter When We Eat?

Recently, it has become of interest not only 'what' to eat for the treatment of NAFLD but also 'when' and 'how often'. Data suggest that eating before bedtime and consuming most of the calories at dinner time is associated with a higher risk of NAFLD based on the NAFLD liver fat score [36,37]. Furthermore, shifting most of the daily calorie intake to the morning seems to be beneficial for weight loss. The same is true for fasting periods of 12–16 h (intermittent fasting) [38]. Regarding eating frequency, it was reported to be rather beneficial to eat more meals per day as it lowers the odds of severe steatosis, whereas skipping meals in the morning and at midday was associated with 20% and 73% increase in odds for steatosis, respectively. Also, this study suggests to consume the majority of daily calories at breakfast, as this was associated with decreased probability of steatosis, but not fibrosis [39]. The mechanism underlying these effects seems to involve adenosine monophosphate-activated protein kinase (**AMPK**) activation in the liver [38]. Thus, it may be beneficial to switch from high-calorie meals in the evening to the consumption of a greater number of daily calories in the morning. The influence of other eating patterns, such as intermittent fasting, on NAFLD remains still unclear.

The Fiber Intake Gap: 'A Nutrient of Concern'

Reduced fiber intake or a 'fiber gap' by NAFLD/NASH patients may contribute to disease progression through promoting microbiome depletion and increased gut permeability with subsequent intestinal translocation of bacterial lipopolysaccharide [40]. The later induces insulin resistance, inflammation, and oxidative stress [40]. Nondigestible fibers, also known as 'prebiotics', beneficially modulate the composition and activity of gut microbiota. Prebiotics undergo fermentation by microbiota releasing

Glossary

^{1}H-MRS: proton magnetic resonance spectroscopy is a gold-standard non-invasive method to assess the amount of liver fat from a spectrum. It is precise, reproducible and applicable for almost all groups of patients.
AMPK: the 5′ AMP-activated protein kinase plays an important role in cellular energy homeostasis and is activated upon dropping energy levels (ATP). The kinase promotes glucose and fatty acid uptake and oxidation. Increased AMPK levels in the liver have been associated with lower hepatic lipid content, improved mitochondrial function, and better glucose tolerance.
ChREBP-β: isoform of the lipogenic transcription factor carbohydrate responsive element binding protein (ChREBP). Little is known about ChREBP-β, however, it is highly expressed in response to glucose uptake.
***De novo* lipogenesis**: a metabolic process that mainly takes place in liver and adipose tissue. It converts excess carbohydrates into fatty acids, which are then esterified and stored as triglyceride.
Dyslipidemia: disorder of lipoprotein metabolism, mostly hyperlipidemia or elevated plasma lipids (cholesterol or triglyceride).
FGF21: fibroblast growth factor 21 is a protein expressed in the liver, released in response to peroxisome proliferator-activated receptor α nuclear receptor (PPAR-α) activation by fatty acids, and is involved in glucose homeostasis, lipid metabolism, and energy balance.
Fiber: primarily plant-based carbohydrate polymers that are largely nondigestible. Important for human nutrition as they lower the glycemic load, which leads to slower increase in blood glucose levels after food ingestion. Fibers positively influence gut microbiota and may have the potential to lower lipid derivatives in the blood.
Fibrosis: a process which involves accumulation of extracellular matrix proteins and fibrous connective tissue, leading to thickening or scarring of the tissue.
Insulin resistance: a state in which cells fail to properly respond to the hormone insulin.

short-chain fatty acids, which are well known for their beneficial effects on body weight, energy expenditure, and insulin sensitivity, in addition to their lipid lowering, anti-inflammatory, and anti-tumor effects [41,42]. Previous studies suggest that increased fiber intake is inversely correlated with low-density lipoprotein, cholesterol, hepatic lipid accumulation, insulin resistance, as well as risk for metabolic syndrome [43]. Recent clinical trials showed that NAFLD patients on high-fiber diets had lower transaminases and cholesterol levels, together with decreased hepatic steatosis and NAFLD fibrosis score [44,45]. Although most studies recommend a total daily fiber intake of 20–30 g with maximum intake of 35 g, recent reviews highlight that this may still be too low compared with the amount present in African diet (>50 g/day), whose consumers are protected from chronic inflammatory diseases. Concerns were raised about the tolerability of such high amounts of fibers due to gastrointestinal problems in Western populations. However, tolerability issues usually improve over time as microbiota adapts to high fiber intake [40]. Accordingly, it seems to be beneficial for patients with NAFLD to close their fiber gap and increase fiber-rich food consumption (fruits, vegetables, cereals, and whole grain food) as much as tolerated, with a minimum intake of 25 g/day and maximum intake of 55 g/day.

Can Exercise Training Improve IHL?

Regular exercise training not only decreases IHL, but also improves comorbidities associated with NAFLD, such as insulin resistance and cardiovascular diseases [46]. The current EASL-EASD-EASO guidelines suggest 3–5 sessions per week, with a total duration of 150–200 min of moderate intensity aerobic activities, and also accentuate the direct dose-effect relationship with regard to exercise intensity [1]. These guidelines also recommend additional resistance exercise training, but are less specific on overall exercise intensity and efficacy of exercise modalities.

Aerobic and High-Intensity Interval Training (HIIT)

Along these lines, supervised community-based aerobic exercise training at 60–75% of **maximal oxidative capacity** (VO_2max), 2–3 times/week for 30–60 min over about 8 months led to a 25% reduction in IHL combined with significant loss of fat mass in individuals with HbA1c of 5.7−6.4% and NAFLD, who are at increased risk for T2D [47]. A modified HIIT protocol thrice weekly for 12 weeks at an intensity perceived as between 'light' and 'very hard' reduced IHL by ~27% in participants with NAFLD (liver fat >5%) as compared with individuals on standard care and regular monitoring by their general practitioner [48]. In addition, the HIIT group also decreased their whole-body fat mass by ~2 kg.

The relevant question is whether exercise training *per se* – without any clinically meaningful caloric deficit and weight loss – is sufficient to reduce IHL (Figure 2). In this context, a partly supervised, mild aerobic exercise training in the form of brisk walking five times weekly for 16 weeks reduced IHL by 10% in obese individuals, without changes in body weight or percent body fat content [49]. Likewise, progressive, supervised aerobic cycling exercise training over 4 weeks reduced IHL by 21% in obese men and women, along with decreased visceral adipose tissue volume, again despite unchanged body weight [50]. Another 12-week supervised endurance training study reported neither changes in body weight nor in IHL, which, however, was assessed only by semiquantitative computed tomography [51]. Nevertheless, exercise training may exert beneficial effects on IHL even without significant weight loss, which is difficult to achieve. In this context, 12 weeks of supervised high-intensity aerobic exercise training, thrice weekly, reduced both IHL, as measured by ^{1}H-MRS, and hepatic stiffness, as assessed by **transient elastography**, by ~17% [52]. Despite unchanged body weight, participants slightly but significantly increased their lean mass with training. This exercise modality further restored the phagocytic function of **Kupffer cells**, measured by contrast-enhanced ultrasonography, and led to reduced expression of receptors TLR4/CD14 involved in inflammatory processes in these obese adult males with NAFLD. In obese diabetes patients with NAFLD, 8 weeks of HIIT not only improved IHL by ~20%, but also increased VO_2max and health-related quality of life compared with a group on pharmacotherapy only [53]. Although the question remains whether exercise directly impacts IHL or whether the variations are due to

Consequently, blood glucose levels raise as glucose uptake into insulin-sensitive tissues (muscle and adipose) is impaired and hepatic glucose production is elevated. Due to impaired inhibition of lipolysis, insulin resistance is associated with increased circulating fatty acids, which promotes development of NAFLD.
Kupffer cells: these are the liver resident macrophages. Upon liver injury, Kupffer cells are activated, releasing different inflammatory and fibrogenic mediators, eliciting an uncontrolled inflammatory state in the liver.
Mallory-Denk bodies: inclusion bodies of damaged intermediate filaments in the cytoplasm of hepatocytes that consist of cytokeratin and protein and are mainly found in alcoholic liver disease. However, to a lesser degree, they are also found in nonalcoholic liver cirrhosis and several other pathophysiological states of the liver.
Maximal oxidative capacity: The maximum amount of oxygen that the body can take up during maximum exertion. The oxygen uptake capacity is measured by respiratory gas analysis during a gradually increasing exercise load.
Maximal voluntary contraction: the maximum weight that a person can move once in a defined range of motion.
NAFLD: the most common liver disease in developed countries, NAFLD encompasses a disease spectrum, ranging from simple steatosis characterized by excessive fat accumulation in the absence of excessive alcohol consumption and inflammation to NASH, liver cirrhosis, and hepatocellular carcinoma. Insulin resistance and obesity are risk factors for the development of NAFLD.
NASH: nonalcoholic steatohepatitis is the progressive state of NAFLD, characterized by steatosis and liver inflammation.
SREBP-1c: sterol-regulatory element-binding protein 1c transduces the insulin signal and induces genes involved in glucose utilization and fatty acid synthesis.
Transient elastography: an ultrasound imaging technique that measures liver stiffness as a surrogate for liver fibrosis.

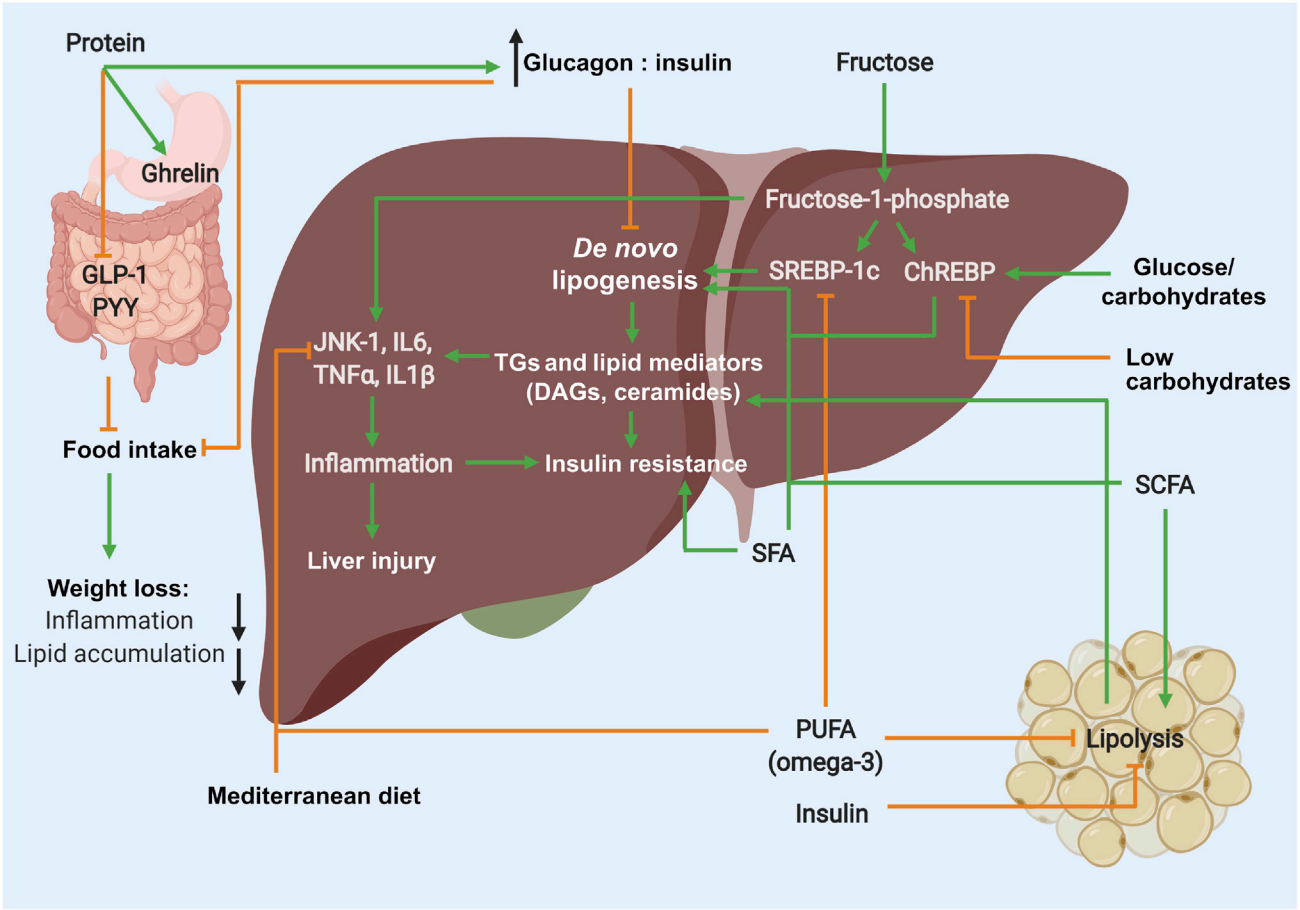

Figure 1. Influence of Different Nutrients on Hepatic Energy Metabolism.

Protein ingestion stimulates ghrelin release and inhibits the synthesis of glucagon-like peptide 1 (GLP-1) and peptide YY (PYY). Moreover, this macronutrient increases the glucagon-to-insulin ratio. Taken together, this leads to reduced food intake and, consequently, weight loss. The increment in glucagon inhibits *de novo* lipogenesis. Fructose intake promotes the activity of fructose-1-phosphate, which activates sterol-regulatory element-binding protein 1c (SREBP-1c), thereby leading to *de novo* lipogenesis. Fructose-1-phosphate also positively regulates cytokines, such as janus kinase 1 (JNK), promoting inflammation. The increase in fatty acids due to *de novo* lipogenesis and the stimulation of inflammation promotes liver injury and contributes to the development of insulin resistance [63]. Short-chain fatty acids (SCFA) promote adipose tissue lipolysis, whereas polyunsaturated fatty acids (PUFA), mainly omega-3 fatty acids, inhibit adipose tissue lipolysis, hepatic SREBP-1c activation, and cytokines, thereby preventing *de novo* lipogenesis, insulin resistance, and inflammation. Mediterranean diets were also shown to have an anti-inflammatory effect. Abbreviations: ChREBP, carbohydrate responsive element binding protein; DAGs, diacylglycerides; IL6, interleukin 6; IL1β: interleukin 1 beta; TG, triglycerides; TNFα, tumor necrosis factor alpha. Green arrows: stimulation; orange lines: inhibition. Created with Biorender.com.

the negative energy balance in response to exercise, these studies suggest that mild- and high-intensity aerobic exercise training can provide a promising therapeutic option (Figure 2).

Resistance Exercise

Only few studies have looked at the effect of resistance training on IHL. One study elucidated the effects of 8 weeks of whole-body resistance exercise, three times a week in sedentary adults with NAFLD (liver fat >5%). The authors report a ~13% reduction in IHL, which was associated with increased insulin sensitivity despite no change in body weight [54]. Another study compared the effects of aerobic and resistance training on IHL in individuals with T2D and NAFLD [55]. Participants

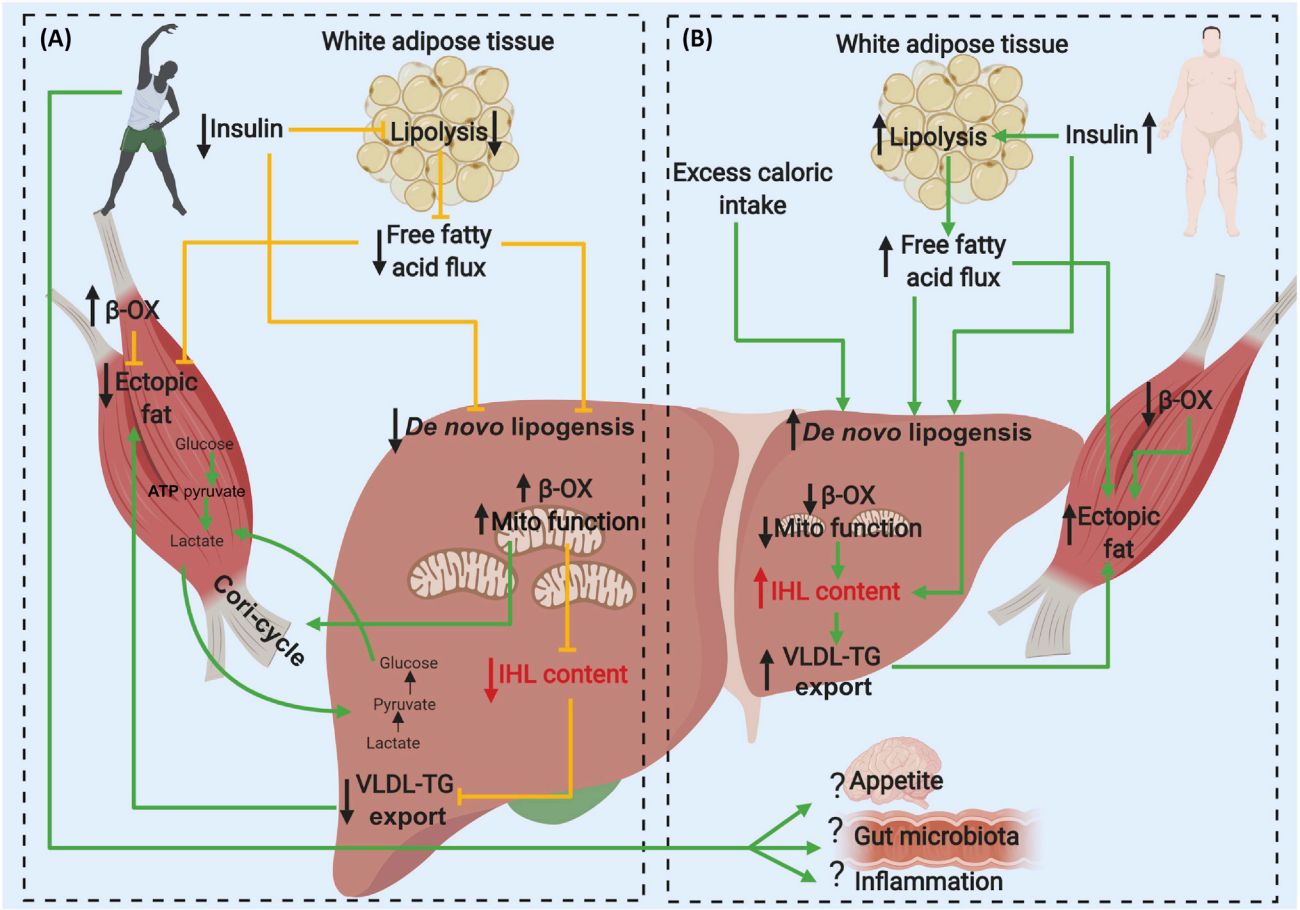

Figure 2. (A) Exercise Training Increases Insulin Sensitivity and Suppresses Adipose Tissue Lipolysis, Which Leads to Reduced Plasma Free-Fatty Acid Flux and Ectopic Fat Storage.

De novo lipogenesis is low when insulin levels are physiological. Due to high muscular demand during contraction, VLDL uptake and chylomicron clearance by muscle is high. The Cori-cycle is another energetically demanding process requiring energy derived from hepatic beta-oxidation. Low levels of inflammation and proper mitochondrial function keep IHL levels low, which in turn leads to reduced VLDL-secretion by the liver. (B) In the sedentary, insulin-resistant individual, elevated lipolysis leads to increased plasma free fatty acid flux, which is mainly directed to the liver but may also increase ectopic fat deposition in the muscle. Hyperinsulinemia in these individuals contributes to increased hepatic *de novo* lipogenesis. Due to the low energy expenditure and reduced muscular demand, muscle substrate utilization is low and VLDL uptake as well as chylomicron clearance is low. Inflammatory processes and altered mitochondrial function will further contribute to accumulation of IHL, which further promotes VLDL secretion by the liver and ectopic fat storage in the muscle. Excess caloric intake can exacerbate these processes. Abbreviations: β-OX, beta-oxidation; IHL, intrahepatic lipids; TG, triglycerides; VLDL, very low-density lipoproteins. Created with Biorender.com.

either performed resistance exercise for all major muscle groups thrice weekly for 12 weeks or aerobic exercise training. Aerobic and resistance training led to a prominent 33% and 26% reduction in IHL, while about 25% of patients with T2D and NAFLD in both groups showed a remission of hepatic steatosis [55]. These changes were accompanied by improved glycemic control in both intervention groups. In patients with NAFLD, 3 months of classical resistance training for the large muscle groups, three times a week for 40 min, significantly reduced IHL, as assessed by the hepatorenal-ultrasound index, compared with a control group performing only home stretching [56]. The exercise training group also lost body fat and improved their lean mass, in addition to reductions in serum ferritin and total cholesterol levels. Although only few studies are currently available, resistance

training seems to be effective for reducing IHL in obese individuals with NAFLD and also preserves or even improves lean body mass in exercising individuals.

Combined Training

Combined aerobic and resistance exercise training for 12 weeks comprising two aerobic training sessions at 70% maximal power output and one resistance training session at 60% **maximal voluntary contraction** (1-RM) reduced IHL not only in overweight/obese people with NAFL by ~35%, but to a similar degree (~28%) in age- and BMI-matched healthy humans without NAFL [57]. In addition, individuals improved their maximal aerobic capacity, skeletal muscle strength, and insulin sensitivity. Although body weight and food intake did not change and fat mass was slightly reduced, changes in IHL were associated with changes in body weight but not changes in fat mass. Another study using a similar combined training program for 8 weeks also demonstrated an equal reduction of IHL in men with NAFLD of both intervention groups [58]. These studies show that combined training is highly effective in improving functional performance (i.e., aerobic capacity and strength), as well as IHL.

IHL Reduction; A Matter of Exercise Intensity and Modality?

There is some evidence that more vigorous, high-intensity forms of exercise (with lower volume) appear to be similarly effective in reducing IHL than higher volume, aerobic forms of exercise with lower intensity. A recent randomized controlled trial including individuals with central obesity and NAFLD failed to confirm this concept [59]. Participants performed either: (i) 12 months of moderate walking (150 min per week at 45–55% of maximum heart rate); (ii) 6 months of vigorous jogging (150 min per week at 65–80% of maximum heart rate) followed by 6 months of moderate walking; or (iii) no exercise [59]. At 6 and 12 months, the authors report similar reductions in IHL in the vigorous-moderate and moderate exercise groups and hence the authors conclude that both exercise intensities are equally effective in reducing IHL. This study, however, is limited by estimating the training intensity from the calculated maximal heart rate of the participants and not by the gold standard of cardio-pulmonary exercise testing [60]. Similar results were obtained in a study subjecting inactive and overweight/obese adults with NAFLD to 8 weeks of different training regimes comprising either: (i) low to moderate intensity, high volume aerobic exercise; (ii) high intensity, low volume aerobic exercise; (iii) low-to-moderate intensity, low volume aerobic exercise; or (iv) stretching exercises not intended to induce cardiometabolic adaptations. While all regimes resulted in reductions of IHL, no difference was observed between the regimes with regard to effectiveness of IHL reduction [61]. Only 4 weeks of HIIT and energy-matched moderate intensity exercise training were sufficient to induce similar reductions of IHL, independent of alterations in abdominal adiposity or body mass [62]. Current evidence suggests that any form of structured aerobic exercise is effective in reducing IHL and that exercise intensity seems to have a subordinate influence on this endpoint. There is also evidence that resistance training, HIIT, as well as aerobic training over a 12-week period all lead to similar reductions in liver fat of about 14%, assessed by transient elastography, indicating that different training modalities seem to be equally effective when it comes to beneficial effects on liver fat content [52]. Hepatic stiffness, phagocytic function of Kupffer cells, and inflammation, however, were only improved by HIIT, indicating a superiority regarding this training modality when inflammatory conditions also play a role.

Concluding Remarks

The available data and current guidelines suggest that overweight-to-obese patients with NAFLD should reduce their body weight by 0.5–1.0 kg per week, independent of dietary macronutrient composition. This recommendation is incomplete, as macronutrient composition does modulate the success of IHL loss. While it is clear that progressive weight loss leads to continuous IHL reductions, some studies also suggest that a low-carbohydrate, high-fiber, and high-protein diet, as well as a Mediterranean diet, have at least some additional effects on reducing IHL. Physical exercise provides another relevant tool for improving IHL, independent of change of body fat or composition. Combined aerobic and resistance training has proven to be very effective in NAFLD, while different exercise modalities (aerobic exercise, resistance exercise, or HIIT) seem to have similar effects on IHL. It is most important to engage in physical exercise, as it can improve the outcome of NAFLD, or at

least its progression. However, HIIT may be superior to other training modalities under certain conditions.

Nevertheless, the evidence from both dietary and exercise interventions is limited regarding the effectiveness in more advanced NAFLD, such as NASH (see Outstanding Questions). A combination of intensified diet and physical exercise is likely to be the most promising nonpharmaceutical approach for improving NAFLD.

Outstanding Questions

Which mix of macronutrients, such as carbohydrates and proteins, is most beneficial for NAFLD?

Does the composition of macronutrients also have an effect on the resolution of NASH and fibrosis?

How do macronutrients influence the progression of NASH from NAFL?

Do increasing breaks of sedentary time, independent of physical exercise, impact intrahepatic lipids?

Are clinically relevant improvements of metabolic health and NAFLD associated with improvements of objectively assessed physical activity parameters?

Based on large-scale physical activity and exercise intervention studies, what is the best regimen and modality to form a basis for guidelines as part of optimized NAFLD treatment?

How does long-term exercising and deconditioning/sedentary behavior affect treatment and progression of NAFLD?

How do exercise and physical activity impact the more progressive forms of NAFLD, such as NASH and inflammatory conditions?

Can we prevent a nonresponse with regard to exercise-mediated improvements in NAFLD by considering the genetic background of individuals?

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