Diet and exercise in NAFLD/NASH: Beyond the obvious

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Abstract Lifestyle represents the most relevant factor for non-alcoholic fatty liver disease (NAFLD) as the hepatic manifestation of the metabolic syndrome. Although a tremendous body of clinical and preclinical data on the effectiveness of dietary and lifestyle interventions exist, the complexity of this topic makes firm and evidence-based clinical recommendations for nutrition and exercise in NAFLD difficult. The aim of this review is to guide readers through the labyrinth of recent scientific findings on diet and exercise in NAFLD and non-alcoholic steatohepatitis (NASH), summarizing "obvious" findings in a holistic manner and simultaneously highlighting stimulating aspects of clinical and translational research "beyond the obvious". Specifically, the importance of calorie restriction regardless of dietary composition and evidence from low-carbohydrate diets to target the incidence and severity of NAFLD are discussed. The aspect of ketogenesis—potentially achieved via intermittent calorie restriction—seems to be a central aspect of these diets warranting further investigation. Interactions of diet and exercise with the gut microbiota and the individual genetic background need to be comprehensively understood in order to develop personalized dietary concepts and exercise strategies for patients with NAFLD/NASH.

Keywords diet, lifestyle, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, nutrition, physical activity

1 | INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) may present as "simple" steatosis or with a potentially progressive inflammatory phenotype of non-alcoholic steatohepatitis (NASH) that can progress to cirrhosis and/or hepatocellular cancer, thus being expected to become the leading cause of liver-related morbidity and mortality. Since no drug has yet been approved specifically for the treatment of NASH and/or associated cirrhosis, dietary interventions and physical activity (PA) and exercise are generally regarded the cornerstones of NAFLD/NASH treatment. These interventions might be specifically effective to target the "triple hit" of modern-day lifestyle

Abbreviations: β-OHB, β-hydroxybutyrate; AcAc, acetoacetate; ADF, alternate day fasting; BW, body weight; DNL, de-novo lipogenesis; FA, fatty acid; FGF-21, fibroblast growth factor 21; HCC, hepatocellular carcinoma; HCD, high-carbohydrate diet; HFCs, high-fructose corn syrup; HFD, high-fat diet; ICR, intermittent calorie restriction; IHLC, intrahepatic lipid content; IR, insulin resistance; KD, ketogenic diet; LCD, low-carbohydrate diet; LFD, low-fat diet; LSM, liver stiffness measurement; MED, Mediterranean diet; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NEFA, non-esterified fatty acids; PA, physical activity; PPARα, peroxisome proliferator-activated receptor α; PUFA, polyunsaturated fatty acid; RCT, randomized controlled diet; SSB, sugar-sweetened beverages; TCA, tricarboxylic acid-cycle; VLCD, very-low carbohydrate diet; WD, Western diet; WL, weight loss.

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(ie sedentary behaviour, low PA and poor diet) that contributes to the “multiple-hit” pathogenesis of NAFLD. The aim of this review is to provide an overview of recent research findings covering diet and PA “beyond the obvious”, thereby presenting stimulating aspects of this topic complimentary to state-of-the-art reviews (eg Refs. [5-7]).

2 | THE OBVIOUS – GUIDELINE RECOMMENDATIONS

Although being regarded as the key component to tackle the NAFLD epidemic, guidelines are rather unspecific and vague regarding recommendations for diet and exercise in NAFLD patients (Table 1, reviewed in 12). Several scientific associations (EASL-EASD-EASO 2016, AASLD 2018, ESPEN 2019 and APASL 2020) highlight the low evidence supporting any dietary composition (eg low-carbohydrate/low-fat diets), EASL-EASD-EASO, ESPEN and APASL do not provide such recommendations. Although all guidelines, but no recommendations exist for a specific type or amount of PA and/or duration. Importantly, recommendations on diet and PA are similar in NAFLD patients with type-2 diabetes mellitus emphasizing an individual approach aiming at calorie-restriction and MED diet. However, specific recommendations are divergent. While the EASL-EASD-EASO and APASL recommend the exclusion of processed food and any beverages/food high in added fructose, AASLD and ESPEN do not provide such recommendations. Although all guidelines highlight the low evidence supporting any dietary composition (eg low-carbohydrate/low-fat diets), EASL-EASD-EASO, ESPEN and APASL specifically mention the Mediterranean diet (MED) as beneficial in patients with NAFLD. While EASL-EASD-EASO and AASLD discussed beneficial effects of light (<1 drink/d) or moderate alcohol consumption (<20 g/d for ♀ and <30 g/d for ♂), more recent ESPEN and APASL guidelines recommend complete abstinence. No recommendations are given for coffee consumption or other macronutrients. Finally, an increase in PA is generally recommended in all guidelines, but no recommendations exist for a specific type or amount of PA and/or duration. Importantly, recommendations on diet and PA are similar in NAFLD patients with type-2 diabetes mellitus emphasizing an individual approach aiming at calorie-restriction and MED diet. However, dietary recommendations for cirrhotic patients avoiding malnutrition, sarcopenia and a low-protein diet need specific attention, and are not covered in this review.

3 | TYPES OF DIET

Apart from a MED, several types of diet have been proposed to tackle NAFLD (interventional studies are summarized in Table 2).

3.1 | Mediterranean diet

In contrast to the Western diet (WD) rich in animal products including red and processed meat, refined grains, potatoes and sugar sweetened beverages (SSB), the MED containing vegetables, fruits, whole grains, nuts and legumes, olive oil, and fish, and has been promoted for WL and improvement of metabolic parameters. Also, the MED has been reported to prevent cardiovascular disease. Since most of its components have either been (inversely) associated with the prevalence, severity or regression of NAFLD (see chapter 4), it is not surprising that the MED is recommended over the WD for individuals with NAFLD. Generally speaking, studies have shown that adherence to a MED is inversely associated with NAFLD prevalence and severity, and reduces hepatic steatosis and liver stiffness measurement (LSM). In addition, MED might even be associated with a reduced risk of HCC or liver-related death.

3.2 | High-protein diet

Studies investigating an increase in dietary protein content are less common given the data on the potentially negative effects of red meat on NAFLD (see chapter 4.1). A RCT by Markova et al (2017) showed that two isocaloric diets rich in animal or plant protein (30% protein, 40% carbohydrates and 30% fat) were both able to reduce IHLC by 36%-48% in individuals with type-2 diabetes mellitus. Another study by Xu et al found different decreases in IHLC among three hypocaloric diets: Subjects consuming a high-protein diet (~40% carbohydrates, ~30% protein, ~30% fat) had a 43% decrease in IHLC, subjects with a normal-protein diet (~20% protein) had a 37% decrease while those with a low-protein/high-carbohydrate diet (HCD; ~10% protein, ~60% carbohydrates, ~30% fat) had no reduction despite similar WL. Nevertheless, these differences might also be attributed to the differences in carbohydrates (see chapter 3.4 and 3.5).

3.3 | Hypocaloric diet

Another more general approach to achieve caloric deficit and consecutive WL is a hypocaloric diet regardless of its dietary composition. Several studies have shown that a total energy deficiency leads to a decrease in BW, transaminase levels, total body fat, visceral fat and IHLC, regardless of how it is achieved. This is supported by similar long-term outcomes after 7% WL following a low-carbohydrate-diet (LCD) vs a HCD despite short-term effects in favour of a LCD.

With this regard, an important study was done by Vilar-Gomez et al who reported a strong correlation of the degree of WL following a hypocaloric diet with the degree of histological NAFLD improvement including NASH resolution and fibrosis regression in NASH patients. This correlation was recently confirmed by a meta-analysis.
**TABLE 1** Comparison of guideline recommendations of the EASL-EASD-EASO guideline 2016, AASLD guidance 2018, ESPEN guideline 2019 and APASL guideline 2020. Modified after Miller (2020)\(^1\)

| Recommendations |
|-----------------|-----------------|-----------------|-----------------|
| **EASL-EASD-EASO 2016\(^8\)** | **AASLD 2018\(^9\)** | **ESPEN 2019\(^10\)** | **APASL 2020\(^11\)** |
| - In overweight/obese NAFLD, a 7%-10% weight loss is the target of most lifestyle interventions, and results in improvement of liver enzymes and histology (B1). | - Weight loss generally reduces hepatic steatosis, achieved either by hypocaloric diet alone or in conjunction with increased physical activity. A combination of a hypocaloric diet (daily reduction by 500-1,000 kcal) and moderate-intensity exercise is likely to provide the best likelihood of sustaining weight loss over time. | - In overweight/obese NAFL/NASH patients a 7%-10% weight loss shall be aimed for to improve steatosis and liver biochemistry; a weight loss of >10% shall be aimed for in order to improve fibrosis. (A) | - Lifestyle change towards a healthy diet and physical activity norms via structured programs are recommended for MAFLD (C2). |
| - Dietary recommendations should consider energy restriction and exclusion of NAFLD-promoting components (processed food, and food and beverages high in added fructose). The macronutrient composition should be adjusted according to the Mediterranean diet (B1). | - Weight loss of at least 3%-5% of body weight appears necessary to improve steatosis, but a greater weight loss (7%-10%) is needed to improve the majority of the histopathological features of NASH, including fibrosis. | - In overweight/obese NASH patients, intensive lifestyle intervention leading to weight loss in conjunction with increased physical activity shall be used as first-line treatment. (A). | - Patients without steatohepatitis or fibrosis should receive counselling for a healthy diet and physical activity and no pharmacotherapy for their liver disease (B2). |
| - Both aerobic exercise and resistance training effectively reduce liver fat. The choice of training should be tailored based on patients’ preferences to be maintained in the long-term (B2). | - Exercise alone in adults with NAFLD may prevent or reduce hepatic steatosis, but its ability to improve other aspects of liver histology remains unknown. | - In normal weight NAFL/NASH patients, increased physical activity to improve insulin resistance and steatosis can be recommended (GPP). | - Both overweight/obese and nonobese MAFLD can benefit from weight loss. In the former, a 7%-10% weight loss is the target of most lifestyle interventions and results in improvement of liver enzymes and histology (B1). |
| - There are insufficient data to make recommendations with regard to nonheavy consumption of alcohol by individuals with NAFLD. | - Patients with NAFLD should not consume heavy amounts of alcohol. | - Overweight and obese NAFL/NASH patients shall follow a weight reducing diet to reduce the risk of comorbidity and to improve liver enzymes and histology (necroinflammation) (A) | - Dietary recommendations should consider energy restriction and exclusion of MAFLD-mediating components (processed food, food and beverages high in added fructose). A Mediterranean type diet is advisable (B1). |
| - There are insufficient data to make recommendations with regard to nonheavy consumption of alcohol by individuals with NAFLD. | | - In order to achieve weight loss, a hypocaloric diet shall be followed according to current obesity guidelines irrespective of the macronutrient composition (A) | - Combined diet/exercise strategies are more effective in normalization of liver enzymes levels and reducing liver fat and improving histology (B1). |
| - Both aerobic exercise and resistance training effectively reduce liver fat and should be tailored based on patient preferences to ensure long-term adherence. Resistance exercise may be more feasible than aerobic exercise for MAFLD patients with poor fitness (B2). | | - A Mediterranean diet should be advised to improve steatosis and insulin sensitivity, (B) | - Both aerobic exercise and resistance training effectively reduce liver fat and should be tailored based on patient preferences to ensure long-term adherence. Resistance exercise may be more feasible than aerobic exercise for MAFLD patients with poor fitness (B2). |

(Continues)
| Table 1 (Continued) |
|---------------------|
| **Energy restriction** | EASL-EASD-EASO 2016 | AASLD 2018 | ESPEN 2019 | APASL 2020 |
| Energy restriction | 500-1000 kcal energy deficit/day to induce a weight loss of 500-1000 g/week | Decrease caloric intake by at least 30% or by approximately 750-1000 kcal/day | Hypocaloric diet | Hypocaloric diet (500-1000 kcal deficit/day) |
| Weight loss | 7%-10% total weight loss target | ≥5% for steatosis improvement, ≥7% for histological improvement | 7%-10% in overweight/obese patients >10% to improve fibrosis | 7%-10% weight loss, gradual weight loss (up to 1 kg/week) |
| Macronutrient composition | • Low-to-moderate fat and moderate-to-high carbohydrate intake | NS | • Irrespective of macronutrient composition | • No strong evidence to support a particular dietary approach. |
| | • Low-carbohydrate ketogenic diets or high-protein diet | NS | • Mediterranean diet to improve steatosis and insulin sensitivity | Plans should encourage low-carbohydrate, low-fat and Mediterranean-type diets |
| Fructose | Avoid fructose-containing beverages and foods | NS | NS | Exclusion of beverages high in added fructose |
| Alcohol | • Strictly keep alcohol below the risk threshold (30 g, men; 20 g, women) | • Should not consume heavy amounts of alcohol. | Abstain | • The “cut-off” values of alcohol intake in MAFLD should be set lower than the apparent “threshold levels”. |
| | • Moderate alcohol intake (namely, wine) below the risk threshold is associated with lower prevalence of NAFLD, NASH and even lower fibrosis | • Insufficient data on non-heavy consumption of alcohol | • Insufficient data on non-heavy consumption of alcohol | • Patients with MAFLD should be advised to avoid alcohol and if that is not possible, to consume the lowest amount possible. |
| Coffee | No liver-related limitations. | NS | More likely to benefit health than harm | NS |
| Physical activity | • 150-200 min/week of moderate intensity aerobic physical activities in 3-5 sessions are generally preferred (brisk walking, stationary cycling) | • Physical activity more than 150 minutes/week | Increase physical activity | • Aerobic exercise and resistance training effectively should be tailored based on patient preferences to ensure long-term adherence. |
| | • Resistance training is also effective and promotes musculoskeletal fitness, with effects on metabolic risk factors | • Moderate intensity exercise | | • Resistance exercise may be more feasible than aerobic exercise for patients with poor fitness. |
| | • High rates of inactivity-promoting fatigue and daytime sleepiness reduce compliance with exercise | | | |

Note: Bold-letters indicate the grade of evidence according to the respective guidelines.
Abbreviations: MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NS, not specified.
### TABLE 2  Overview and characterization of individual studies on dietary interventions discussed in this manuscript

| Study                          | Type of study | Duration of intervention | Types of diet (± calorie intake) | Macronutrient composition | Individuals analysed* | Patients | Outcome measure (liver-related) | Outcome (liver-related) |
|-------------------------------|---------------|--------------------------|----------------------------------|---------------------------|-----------------------|----------|---------------------------------|-------------------------|
| Mediterranean diet (MED)      | RCT           | 6w                       | MED vs LFD/HCD (both diets after one another) | MED: 40% C, 20% P, 40% F, LFD/HCD: 50% C, 20% P, 30% F | 6 vs 6               | Biopsy-proven NAFLD | $^{1}$H-MRS | -39% vs -77% reduction in IHLC after MED compared to LFD/HCD |
| Trovato (2015)                | Single-arm    | 6m                       | Increase the adherence to Mediterranean Diet Score and reduce sedentary habits | NS | 90 | Non-diabetic NAFLD | Bright Liver Score (BLS) | Adherence to MED independently explain considerable variance of BLS Negative interaction between time and MED on NAFLD (semi-quantitatively) Decrease in FLI and LSM following both diets |
| Misciagna (2017)              | RCT           | 6m                       | Low Glycemic Index MED vs CD | NS | 44 vs 46 | Moderate or severe NAFLD (US) | US (semi-quantitatively), FLI, LSM (FibroScan) | |
| Abenavoli (2017)              | RCT           | 6m                       | Hypocaloric MED± antioxidant supplementation (1400-1600 kcal/d) vs CD | MED: 50%-60% C, 15%-20% P, <30% F | 20 vs 20 vs 10 | Overweight NAFLD | US (semi-quantitatively), FLI, LSM (FibroScan) | Decrease in LSM following both diets, improvement in ALT only in MED + lifestyle intervention-group |
| Katsagoni (2018)              | RCT           | 6m                       | Hypocaloric diets (1500 kcal/d ♀, 1800 kcal/d ♂) MED vs MED + lifestyle intervention vs CD | 45% C, 20% P, 35% F | 21 vs 21 vs 21 | Overweight/ obese NAFLD | LSM (Aixplorer) | Decrease in IHLC + FLI following both diets |
| Marin-Alejandre (2019)        | RCT           | 6m                       | Personalized hypocaloric diets (~30%): FLiO-diet vs CD (AHA-recommendations) | FLiO: 40%-45% C, 25% P, 30%-35% F, CD: 50%-55% C, 15% P, 30% F | 37 vs 39 | Overweight/ obese NAFLD | MRI, LSM (ARFI) | Reduction in IHLC + FLI following both diets |
| Yaskolka Meir (2020)          | RCT           | 18m                      | Hypocaloric MED +28g/d walnuts ± green tea/Mankai (1500-1800 kcal/d ♀, 1200-1400 kcal/d ♂) vs healthy diet | MED: <35% F | 89 vs 84 vs 91 | Abdominal obesity/ dyslipidemia | $^{1}$H-MRS | IHLC reduced following all diets, greater following green-MED compared to MED |
| **Diet focusing on proteins** |               |                          |                                   |                           |                       |          |                                |                         |
| Markova (2017)                | RCT           | 6w                       | Isocaloric animal-protein vs plant-protein diet | 40% C, 30% P, 30% F | 18 vs 19 | T2DM + NAFLD | $^{1}$H-MRS | -48.0% vs -35.7% reduction in IHLC |
| Xu (2020)                     | RCT           | 3w                       | Hypocaloric LPD vs HPD vs reference-protein diet | LPD: 55%-65% C, 10% P, 25%-35% F, HPD: 35%-45% C, 30% P, 25%-30% F, Ref-prot: 20%-22% P | 10 vs 9 vs 10 | Morbid obesity | $^{1}$H-MRS | -36.7% vs -42.6% reduction in IHLC vs no changes in IHLC |
| **Hypocaloric diet**          |               |                          |                                   |                           |                       |          |                                |                         |
| De Luis (2008)                | Single-arm    | 3m                       | Hypocaloric diet (1520 kcal/d) | 52% C, 23% P, 25% F | 142 | Non-diabetic and obese | Serum biomarkers | Improved ALT/AST |

(Continues)
| Study                | Type of study | Duration of intervention | Types of diet (± calorie intake) | Macronutrient composition | Individuals analysed | Patients | Outcome measure (liver-related) | Outcome (liver-related) |
|---------------------|---------------|--------------------------|---------------------------------|---------------------------|----------------------|----------|--------------------------------|-------------------------|
| Krik (2009)         | RCT           | 48h                      | Hypocaloric LCD vs HCD (-1100 kcal/d) | LCD: ~10% C (<50g), 15% P, 75% F HCD: ~65% C (<180g), 15% P, 20% F | 11 vs 11 | Non-diabetic and obese | 1H-MRS | -29.6% vs -8.9% reduction in IHLC |
| Haufe (2011)        | RCT           | 6m                       | Hypocaloric LCD vs LFD (~30%) | LCD: ≤90g C, 0.8g/kg BW, ≥30% F LFD: 0.8g/kg BW, ≤20% F | 52 vs 50 | Overweight/obese and otherwise healthy (non-diabetic) | 1H-MRS | -42% vs -47% reduction in IHLC |
| Vilarr-Gomez (2015) | Single-arm    | 52w                      | Hypocaloric LFD (~750 kcal/d) + PA | 64% C, 14% P, 22% F | 261 | Histological NASH w/o cirrhosis | Liver biopsy | Correlations between weight loss and histological improvement |

**Low-carbohydrate diet (LCD)/Very-low-carbohydrate diet (VLCD)**

| Study                | Type of study | Duration of intervention | Types of diet (± calorie intake) | Macronutrient composition | Individuals analysed | Patients | Outcome measure | Outcome (liver-related) |
|---------------------|---------------|--------------------------|---------------------------------|---------------------------|----------------------|----------|-----------------|-------------------------|
| Browning (2011)     | Non-randomized controlled trial | 2w                      | VLCD vs hypocaloric (1200 kcal/d, 1500 kcal/d) | LCD: 8% C, 33% P, 59% F Cal-restr.: 50% C, 16% P, 34% F | 9 vs 9 | NAFLD w/o cirrhosis | 1H-MRS | -55% vs -28% reduction in IHLC |
| Mardinoglu (2018)   | Single-arm    | 2w                       | Isocaloric VLCD (~3115 kcal/d) | 4% C (23-30g), 24% P, 72% F | 10 | Obese NAFLD | 1H-MRS | -43.8% reduction in IHLC |
| Gepner (2019)       | RCT           | 18m                      | LFD w/o PA vs LFD with PA vs MED/LCD w/o PA vs MED/LCD with PA (MED +28g walnuts/d); all diets hypocaloric | LFD: <30% F; LCD/MED: <35% F (<40g C in first 2m, then up to 70g/d) | 76 vs 63 vs 73 vs 66 | Abdominal obesity/dyslipidaemia | MRI | -7.3% (MED/LCD) vs -5.8% (LFD) reduction in IHLC after 6 months; -4.2% vs -3.8% after 18 months |
| Luukkonen (2020)    | Single-arm    | 6d                       | Hypocaloric VLCD (~1440 kcal/d) | ~6% C (<25 g), 28% P, 64% F | 10 | Overweight/obese NAFLD | 1H-MRS | -31% reduction in IHLC |
| Goss (2020)         | RCT           | 8w                       | LCD vs LFD                  | LCD: <25% C, 25% P, 50% F LFD: 55% C, 25% P, 20% F | 14 vs 11 | Obese NAFLD (9-17 years) | MRI | LCD: ~6.2% absolute decrease in IHLC, LFD: ~1.0% absolute decrease in IHLC; no significant difference |

**Intermittent calorie restriction (ICR)**

| Study                | Type of study | Duration of intervention | Types of diet (± calorie intake) | Macronutrient composition | Individuals analysed | Patients | Outcome measure | Outcome (liver-related) |
|---------------------|---------------|--------------------------|---------------------------------|---------------------------|----------------------|----------|-----------------|-------------------------|
| Johari (2019)       | RCT           | 8w                       | Modified alternate-day calorie restriction (MACR) vs CD; MACR: 70% calorie-restriction on fasting day, ad libitum on non-fasting day; CD: no changes | NS | 30 vs 9 | NAFLD + elevated ALT/AST | Serum biomarkers, US (semiquantitatively), LSM (Aixplorer) | ALT reduced; reduction in steatosis and LSM scores |
| Study                        | Type of study | Duration of intervention | Types of diet (± calorie intake)                                                                 | Macronutrient composition | Individuals analysed | Patients                  | Outcome measure (liver-related)                  | Outcome (liver-related) |
|------------------------------|--------------|--------------------------|------------------------------------------------------------------------------------------------|---------------------------|----------------------|--------------------------|-----------------------------------------------|------------------------|
| Cai (2019)                   | RCT          | 12w                      | ADF vs TRF vs. CD  
ADF: −75% calorie-restriction on fasting day, ad libitum on non-fasting day  
TRF: 8h ad libitum eating CD: −20% calorie-restriction  | ADF: 55 C, 15% P, 30% F; TRF: NS | 90 vs 95 vs 79 | Overweight/obese NAFLD  
(BMI >24kg/m²), ≥9.6kPa, 18-65y | LSM (Liver Stiffness Measurement) | LSM not different |
| Holmer (2021)                | RCT          | 12w                      | LCD vs 5:2 diet vs CD;  
LCD: 1600 kcal/d ♂, 1900 kcal/d ♀;  
5:2 diet: 500 kcal/d ♂ and 600 kcal/d ♀ on 2 non-consecutive days;  
2000 kcal/d ♂ and 2400 kcal/d ♀ on other days  
CD: healthy diet  | LCD: 5%-10% C, 15%-40% P, 50%-80% F;  
5:2 diet: 45%-60% C, 10%-20% P, 25% F | 20 vs 24 vs 20 | NAFLD  
1H-MRS; LSM (Liver Stiffness Measurement) with CAP | −53.1% vs −50.9% vs −16.8% reduction in IHLC; −61.9% vs −63.8% vs −20.2% reduction in CAP; change in IHLC 3.9% greater in LCD compared to CD and 2.6% in 5:2 diet compared to CD; reduction in LSM in 5:2 diet and CD compared to LCD |
| Fructose-restriction         |              |                          | SSB with 80g/day of fructose vs sucrose vs glucose vs no SSB  | 45%-56% C, 15%-19% P, 30%-37% F | 32 vs 31 vs 32 vs 31 | Healthy men  | Fatty acid-synthesis  | 2-fold increase in basal hepatic fractional fatty acid-secretion rates compared to controls in fructose/sucrose group; no diff in glucose group IHLC reduction greater by −0.7% absolute difference in the intervention group; IHLC reduction in both groups |
| Geidl-Flück (2021)           | RCT          | 7w                       | Dietary fructose-restriction; control-group; supplemented with fructose powder; intervention group; supplemented with glucose powder | 35%-40% C, 15%-20% P, 35%-40% F | 21 vs 16 | Overweight + FLI ≥ 60 | 1H-MRS  |  |
| Simons (2021)                | RCT          | 6w                       | SSB with 80g/day of fructose vs sucrose vs glucose vs no SSB  | 45%-56% C, 15%-19% P, 30%-37% F | 32 vs 31 vs 32 vs 31 | Healthy men  | Fatty acid-synthesis  | 2-fold increase in basal hepatic fractional fatty acid-secretion rates compared to controls in fructose/sucrose group; no diff in glucose group IHLC reduction greater by −0.7% absolute difference in the intervention group; IHLC reduction in both groups |

*per protocol; ADF, alternate date fasting; BLS, bright liver score; BW, body weight; C, carbohydrates; CAP, controlled attenuiation parameter; CD, control diet; F, fat; FLI, fatty liver index; 1H-MRS, proton magnetic resonance spectroscopy; HFF, hepatic fat fraction; HPD, high-protein diet; ICR, intermittent calorie restriction; IHLC, intrahepatic lipid content; LCD, low-carbohydrate diet; LFD, low-fat diet; LPD, low-protein diet; LSM, liver stiffness measurement; m, months; MED, Mediterranean diet; MRI, magnetic resonance imaging (Dixon techniques); NS, not specified; P, protein; PA, physical activity; RCT, randomized controlled trial; SSB, sugar-sweetened beverages; TRF, time-restricted feeding; US, ultrasonography; w, weeks; w/o, without; WL, weight loss.
promoting WL-interventions including calorie restriction over specific dietary compositions in NAFLD/NASH. Nevertheless, further adherence to a MED might enhance the decrease in BW, total fat mass and hepatic fat.

### 3.4 | High-carbohydrate/low-fat diet

For years, high dietary fat has been considered the cause of obesity and the metabolic syndrome because of its high energy density leading to an increase in total energy intake. Thus, scientists called for a low-fat diet (LFD) with compensatory increase in dietary carbohydrates. Although early studies suggested that dietary fat might inhibit hepatic glucose disposal and increase storage of glucose, increasing concerns regarding the harmful effect of HCD are arising and the number of studies promoting HCD over LCD are a minority. However, if a caloric deficit is achieved, HCD/LFD may still improve liver histology in the mid-term. With this regard, the type of fat consumed in these studies needs to be taken into account, with saturated fatty acids (FA) and trans-FA increasing and poly-unsaturated FA decreasing BW despite their high energy content.

### 3.5 | Low-carbohydrate/high-fat diets

According to the “Carbohydrate-Insulin-Model” of obesity, an increase in the consumption of processed carbohydrates produces hormonal changes (especially inducing insulin secretion) that promote “energy storage” in adipose tissue, exacerbate hunger and lower energy expenditure. By stimulating glucose uptake, suppressing release of FAs from adipose tissue, and promoting fat and glycogen production, hyperinsulinemia following carbohydrate intake again induces hunger and predisposes to weight gain. Animal models have previously confirmed several advantages of LCD (especially those with a low glycemic-index) over HCDs. In these studies, energy restriction while on a high glycemic-index diet did not prevent weight gain nor increases in blood lipids and glucose, while a LCD indeed increased energy expenditure and decreased BW.

Thus, several types of LCD or “very-low carbohydrate diet” (VLCD) have been studied for their effect on NAFLD. Important differences exist for their respective carbohydrate-content and associated ketogenic potential, with ketogenesis occurring if <20-50 g/d carbohydrate are consumed corresponding to carbohydrate constituting 5%-10% of daily energy intake (ie VLCD, see chapter 7.1). Early studies comparing hypocaloric diets low or high in carbohydrates (LCD vs HCD) showed a significant stronger short-term reduction of IHLC after VLCD, similar levels in the long-term (ie after 7% WL) while insulin sensitivity was durably improved also in the long-term. An important study by Gepner et al demonstrated that a hypocaloric LCD in combination with a MED (≤PA) achieved the greatest reduction in visceral adipose tissue and IHLC compared to an hypocaloric LFD. Interestingly, this effect was achieved despite only moderate WL, which might inadequately reflect the beneficial effects of a LCD. Also, the reduction in IHLC was similar between patients performing different amounts of PA, highlighting the essential role of diet for this outcome parameter.

Similarly, Mardinoglu et al observed significant short-term changes in IHLC following an isocaloric VLCD, linking it to increased ketogenesis and changes in gut microbiota (see chapters 7.1 and 7.2). Ebbeling et al used heavy water to assess energy expenditure following HCD, moderate or LCDs. Interestingly, energy expenditure followed a linear trend of -52 kcal/d for every 10% decrease in the contribution of carbohydrates to total energy intake. Also, ghrelin and leptin levels were significantly lower contributing to decreased hunger, fat deposition and increased leptin sensitivity. Again, these effects were independent of BMI and were greatest in patients with high post-prandial insulin levels suggesting pronounced benefits in patients with pre-existing hyperinsulinemia. These data go in line with a previous meta-analysis showing reduced appetite and increased satiety following VLCD.

Finally, a recent study by Luukkonen et al assessed IHLC using proton magnetic resonance spectroscopy ($^1$H-MRS) in 10 overweight individuals with NAFLD on VLCD/ketogenic diet and showed a marked decrease in IHLC by 31% accompanied by a decrease in insulin resistance (IR, -57%). Also in adolescents, LCD seems to outperform HCD regarding WL and reduction in IHLC and IR.

Despite these data on LCDs seem promising, meta-analyses directly comparing several dietary interventions in NAFLD are still lacking. Also, improvements of BMI, HDL-cholesterol and triglyceride profiles must be balanced with potential consequences of raised LDL- and total-cholesterol levels in the long-term. On a long-term perspective, carbohydrate intake and overall mortality might still follow a U-shaped curve.

Last but not least, a recent Mendelian randomization analysis aimed at validating the aforementioned Carbohydrate-Insulin-Model. In this study, 30 genetic polymorphisms being linked with glucose-stimulated insulin secretion were tested in ~500.000 subjects and found to be significantly associated with BMI. In contrast, SNPs linked with BMI were not associated with glucose-stimulated insulin secretion. The authors thus hypothesize that post-prandial hyperinsulinemia centrally influences BMI and associated comorbidities while vice-versa, BMI itself might be less important for hyperinsulinemia.

### 3.6 | Intermittent calorie restriction

Intermittent calorie restriction (ICR) is another way to reduce calorie intake. Following this approach, individuals consume significantly reduced calories or no calories over a certain period (“fast days”) followed by intervals with ad-libitum food consumption (“feast days”). A common variant is the intermittent fasting (or alternate day fasting, ADF) which consists of fasting periods over 36-hours and periods of ad-libitum food consumption over 12 hours, among other
forms (reviewed in Ref. [63]). This periodic calorie restriction seems to provoke several physiological changes contributing to health benefits (reviewed in Refs. [64–66])—among others, it might counteract the disruption of circadian rhythm being associated with development of NAFLD and metabolic syndrome. 67

Among the first, Stekovic et al 68 investigated the effects of ADF for 4 weeks and >6 months on BW and markers of ageing. Compared with the control group continuing their usual diet, ADF led to a significant reduction in BMI, central fat, Framingham Risk Score, LDL, total cholesterol, triglyceride and triiodothyronine levels after 4 weeks and 6 months. Also, serum β-hydroxybutyrate (β-OHB) levels significantly increased after 4 weeks indicating an induction of ketogenesis (see chapter 7.1). The authors conclude that the periodic stimulus to the organism seems to exert several beneficial effects on human health that cannot be solely attributed to calorie restriction. 68

So far, three studies have been performed focusing on NAFLD patients. Johari et al 69 applied a modified alternate-day calorie restriction (ie 70% calorie-restriction on fasting day, ad-libitum eating on non-fasting day) to demonstrate an improvement in ALT levels as well as LSM and sonographically assessed steatosis. 69 Another study showed a decrease in BMI and triglyceride levels following 12 weeks of ADF or time-restricted feeding (energy intake only during an 8h-window each day) despite no changes in LSM. 70 Finally, Holmer et al 71 compared ICR on two non-consecutive days/week (ie 5:2 diet, <500/600 kcal/d) vs a LCD/HFD in patients with NAFLD. This diet was associated with a significant reduction of IHLC on MRI and was assessed via controlled attenuation parameter, as well as improvement of BMI and IR was compared to a "healthy diet", among others. Interestingly, ICR was similarly effective as LCD/HFD. In general, previous studies have largely demonstrated effective WL following ICR in overweight/obese individuals without serious adverse events. 72 However, it remains to be answered whether ICR is equally or more effective than continuous calorie restriction, 73,74 and whether it is effective if no calorie-restriction/dietary counselling is applied. 75 Also, although ICR has also been shown to be effective and safe in overweight/obese patients with type-2 diabetes mellitus, 76 close monitoring of diabetes medication and blood glucose is needed because of concerns about hypoglycemia. 77

4 | DIETARY COMPOSITION AND SELECTED FOOD GROUPS

4.1 | Red and processed meat

An increasing number of recent studies showed a striking inverse association between red and processed meat and NAFLD. 21,78–80 Importantly, this association seems to be driven by animal protein since vegetable protein did not show a similar association. 78,80 A compelling explanation for this phenomenon was reported by Alferink et al 81 proposing that the diet-dependent acid-load is the driving component of this association. Specifically, animal protein might cause low-grade metabolic acidosis by supplementation of acid precursors, 82 which lead to a disturbance in acid-base balance. 83 Other studies reporting on the U-shaped association between carbohydrate-consumption and mortality hypothesized that the substitution with animal-protein might cause the rise in mortality following a LCD, which was not evident when plant-based protein was substituted. 61

4.2 | Sugar-sweetened beverages and high-fructose consumption

By searching for explanations between the parallel increase of fructose-consumption through high-fructose corn syrup (HFCS) and the increase in NAFLD/metabolic syndrome, 84 fructose has been associated with IR, intrahepatic lipid accumulation and hypertriglycerideremia, which contribute to the development of type 2 diabetes and cardiovascular diseases. 84 This is because the first-pass hepatic extraction of fructose is nearly 100% after ingestion, and metabolization occurs solely in the liver. 85,86 In contrast to glucose, it might provide a more direct substrate for de-novo lipogenesis (DNL) and increase IHLC on a larger scale. 86 Unlike glucose metabolism, gluconeogenesis from fructose occurs independent of insulin and the energy status of the cell, 85,86 leading to a depletion in ATP and subsequent generation of uric acid, in terms promoting oxidative stress and IR. 87,88

Thus, fructose- but not glucose-sweetened beverages have been associated with increased DNL, dyslipidemia, visceral adiposity and impaired insulin sensitivity. 59 This was recently confirmed by a RCT showing an increased basal secretion rate of FA in both fructose and sucrose (ie glucose and fructose) groups raising the hypothesis of an adaptive response to regular fructose exposure by SSB consumption. 90 Also, restricting fructose-intake led to a reduction in IHLC  91

In line, SSB have been associated with higher NAFLD prevalence, 92–95 NASH presence 96 and even a higher degree of fibrosis. 97 However, the differences in study design need to be considered since less significant alterations seem to occur in otherwise healthy subjects. 89 Interestingly, this might provide an explanation why young and metabolically healthy subjects could compensate for increased fructose intake while these mechanisms tilt in the presence of metabolic dysregulation.

Aiming at investigating physiological differences in mice fed with either glucose- or fructose-supplemented water, Softic et al 99 found that fructose supplementation was associated with an increased expression of Srebp1c and Chrebp-β, increased FA synthesis and hepatic IR, while glucose supplementation was associated with increased total Chrebp and Chrebp-β and liver triglyceride accumulation, but not with IR. 99 The increased expression of Chrebp-β further upregulating FGF-21 could be one mechanism of action by which fructose contributes to fibrogenesis and hepatic stellate cell activation 100
4.3 | Alcohol

In the context of NAFLD, the controversy on the potential beneficial effects of moderate alcohol consumption (<20 g/d for females and <30 g/d for males) on the prevalence and severity of NAFLD is still ongoing. Although data on the protective effect of moderate alcohol consumption on the prevalence of NAFLD and NASH exist, several concerns have been raised questioning the rationale behind this phenomenon and adequate addressing of confounders. Within the last two years, evidence is accumulating that supports a rather harmful effect, and recent guidelines recommend complete abstinence. Ajmera et al (2018) showed that modest alcohol use was associated with less improvement in steatosis and liver-related death as well as lower odds of non-alcoholic steatohepatitis resolution compared to non-drinkers. Another study reported faster worsening of non-invasive fibrosis scores in patients with moderate alcohol consumption compared to abstainers. Recent analyses also support a linear positive association with NAFLD and advanced liver disease.

4.4 | Coffee

Any coffee consumption was associated with a 29% lower risk of NAFLD, a 30%-39% lower risk of liver fibrosis and a 39% lower risk of cirrhosis in two meta-analyses. Also, a dose-dependent inverse relationship was evident in two different meta-analyses for cirrhosis and liver-related death as well as chronic liver disease and HCC. However, another meta-analysis describes a non-linear relationship with a reduced risk of NAFLD only starting at >3 cups/d. In line, the proportion of patients with LSM ≥8.0 kPa decreases among higher coffee consumption. On a mechanistic basis, these beneficial effects might be explained by a reduction in hepatic fat accumulation by increased β-oxidation, and a reduction of systemic and liver inflammation and oxidative stress. Specifically, coffee enhances the expression of chaperones and antioxidant proteins such as glutathione ensuring correct protein folding and degradation in the liver. Also, chlorogenic acid, caffeine and kahweol exhibit antifibrotic properties by inhibition of hepatic stellate cell activation via down-regulation of the transforming-growth-factor-β (TGF-β) pathway and inhibiting connective tissue growth factor. Possible influences on the gut microbiome could contribute to these observed associations including an increase in Bifidobacterium spp. and a decrease in Escherichia coli and Clostridium spp. With this regard, coffee consumption seems to be associated with microbial richness even in patients with cirrhosis.

4.5 | Nuts and seeds

Nuts and seeds contain several bioactive compounds that have been regarded beneficial for human’s health including monounsaturated FAs and polyunsaturated FAs (PUFA), vegetable protein, fiber, minerals, vitamins, tocopherols, phytosterols and polyphenols. Recently, several studies investigated their influence on NAFLD: a Chinese study reported a significantly lower prevalence of NAFLD in patients consuming nuts ≥4 times/wk while another Chinese study confirmed this inverse association of NAFLD and nut consumption only in men when consuming ≥8.86 g/d. These findings have been validated in a Caucasian cohort being again more pronounced in males, and another cross-sectional study. Interestingly, daily nut consumption might even be negatively associated with advanced fibrosis in NAFLD patients with further research needed to confirm these associations. Despite their high energy content, nut consumption has not been associated with weight gain. In contrast, anti-inflammatory components might contribute to their beneficial effects on NAFLD, and they have recently been added to a MED showing a significant WL and decrease in IHLC in NAFLD patients.

5 | Micronutrient Composition

Although the pathogenic role of specific food-types and macronutrients is well-established in NAFLD, the impact of micronutrients (including minerals, fat and water-soluble vitamins, and carotenoids) on disease pathogenesis has garnered less attention (reviewed in Ref. [137]). While the relevance of dysmetabolic iron overload in NAFLD has been largely studied, both zinc and copper deficiencies have also been observed in NAFLD. Interestingly, zinc supplementation has shown favorable effects on glycemic parameters and plasma lipids. The link between high fructose-consumption and copper deficiency potentially contributing to NAFLD pathogenesis also deserves further research. Building upon the negative influence of red meat consumption on NAFLD (see chapter 4.1), an increased amount of iron intake— independent of red meat as a source— may also contribute to NAFLD pathogenesis.

Apart from minerals, deficiencies in vitamins A, B3, B12, C, D and E— although mostly of mild severity— have been reported in NAFLD. While systematic supplementation of these vitamins has not been studied, vitamin E supplementation has been addressed several beneficial properties in NAFLD. Just recently, vitamin E supplementation has been reported to improve transplant-free survival and hepatic decompensation in patients with NASH and advanced fibrosis, and published guidelines recommend vitamin E supplementation to non-diabetic patients with NASH. Finally, the beneficial effects of nuts and seeds in NAFLD might partially be explained by their high content of micronutrients and antioxidative compounds.

6 | Physical Activity and Exercise

While the EASL and AASLD both recommend ≥150 min of moderate-intensity PA per week, novel ESPEN and APASL guidelines only recommend an increase of PA tailored based on patient preferences.
This might be the case since meta-analyses proved that PA reduces IHLC and markers of hepatocellular injury (especially in patients with increased BMI), but fail to clearly recommend one type of exercise over another. Also, there does not seem to be a significant difference between dose or intensity of aerobic exercise.

Despite aerobic exercise cannot be recommended over resistance training, overall energy consumption seems to be lower during resistance training compared to aerobic exercise while leading to a similar improvement of steatosis. Thus, resistance exercise might be better tolerated by NAFLD patients with poor cardiorespiratory fitness and musculoskeletal issues because of overweight.

Several aspects need to be highlighted which go beyond WL and explain benefits from PA and exercise: Exercise improves peripheral insulin sensitivity with only little effect on hepatic insulin sensitivity, leading to a net improvement in insulin metabolism. Also, exercise increases very-low-density-lipoprotein clearance enabling the liver to export triglycerides, improves appetite-control and counteracts sarcopenia, which has been identified as independent risk factor for NAFLD and fibrosis. Thus, exercise is also recommended and is safe in patients with NASH cirrhosis and portal hypertension improving physical function, sarcopenia and even portal hypertension.

6.1 | Sedentary behaviour

Sedentary behaviour is not only associated with obesity, but also >30 health outcomes and NAFLD. Specifically, television-viewing-time was independently associated with higher fatty-liver-index in Finnish adults and computer/mobile-devices-usage-time with Odds of NAFLD in Chinese adults. Nevertheless, PA in between sitting time/sedentary time still attenuates post-prandial glucose and insulin, with greater glycaemic attenuation in people with higher BMI.

Interesting data about a protective effect on carcinogenesis can be derived from mice-models comparing mice with access to a running wheel to those without. All studies showed a striking reduction of HCC cases in the exercise groups compared to the sedentary groups, which might even be independent of weight gain and diet. Similar results were obtained from epidemiological studies reporting a lower incidence of liver cancer and especially HCC between the groups with the least and most-frequent PA.

6.2 | Combination of physical activity and dietary interventions

Noteworthy, evidence exists that the combination of exercise and dietary interventions lead to a greater improvement of metabolic parameters and IHLC. The combination of a low-glycemic-index-MED with either aerobic exercise or both aerobic exercise and resistance training led to the greatest reduction in controlled attenuation parameter as a measure of hepatic steatosis in NAFLD patients after three months. However, further research is needed regarding potentially counteracting effects of antioxidants (vitamin C and E) and exercise-induced mitohormesis.

7 | NOVEL MOLECULAR AND TRANSLATIONAL ASPECTS

7.1 | PPARα-signalling and ketogenesis

An important aspect contributing to the success of (V)LCD is ketogenesis, leading to the alternative term "ketogenic diet" (KD). Ketogenesis is the production of ketone bodies acetoacetate (AcAc), β-hydroxybutyrate (β-OHB) or acetone from FAs which serve as an alternative energy supply from the liver to peripheral tissues when the supply of glucose is too low for the body’s energetic needs. From a historical perspective, mild ketosis was the normal metabolic state in most cultures before the agricultural revolution leading to a shift from hunter-gathered diets to rather monotonous carbohydrate-based diets. However, when carbohydrate stores are available, the main source of energy is glycogenolysis and gluconeogenesis in case of a catabolic state while ketogenesis is suppressed by the presence of insulin.

The nuclear receptor peroxisome proliferator-activated receptor α (PPARα) is a central transcriptional factor regulating FA metabolism (ie FA oxidation, FA transport and ketogenesis), which is upregulated during fasting or ketogenic states. One mechanism of action is the induction of fibroblast growth factor 21 (FGF-21) while PPARα-independent activation of FGF-21 also exists. Fasting significantly induces hepatic expression and circulating levels of FGF-21, which is then rapidly suppressed by refeeding.

As a proof-of-concept, PPARα-deficient mice or FGF-21 knockout mice developed severe metabolic abnormalities including fatty liver during feeding-period and hypoglycemia/hypoketonemia during starvation, highlighting the regulatory role of the PPARα-FGF-21-pathway for ketogenesis in response to fasting or (V)LCD/KD. Fasting-induced ketogenesis might therefore not be the target-substrate to consider in the therapy of NAFLD.

Another regulator of PPARα function is the mechanistic target of rapamycin complex 1 (mTORC1) kinase, the inhibition of which is necessary for ketogenesis.

Based on knowledge of the impaired PPAR-signalling in NAFLD and NASH, the induction of this pathway may serve as an additional explanation of the beneficial effects of KD or ICR. Specifically, PPARα exerts several anti-inflammatory activities and protection from intrahepatic lipid accumulation, inflammation and fibrosis. For example, while PPARα gene expression in the liver negatively correlates with NASH severity, histological improvement is associated with an increase in expression of PPARα. Thus, while waiting for selective or pan-PPAR-agonists to be proven effective for NAFLD/NASH therapy, KD or ICR might be the alternatives to induce the PPARα-pathway. However, in human studies it has been shown that FGF-21 serum levels largely vary as dietary response, and might therefore not be the target-substrate to
measure. Nevertheless, regarding other PPARα targets in the liver, an upregulation has been shown in a mice model only following KD without any carbohydrate intake, but not following a non-ketogenic LCD/HFD, highlighting the importance of carbohydrate restriction for ketogenesis.

Moreover, ketone bodies β-OHB and AcAc have several direct and indirect signalling-properties that contribute to the success of KD or ICR. Apart from their function as an energy substrate, β-OHB and AcAc themselves have several anti-inflammatory functions (reviewed in Refs. 194,195). For example, both protect against oxidative stress by decreasing the production of mitochondrial reactive oxygen species, by increasing expression or protein content of antioxidant enzymes through inhibition of histone deacetylases, and by directly scavenging hydroxyl radicals (•OH). The inhibition of the NLRP3 inflammasome—which controls the activation of caspase-1 and the release of the pro-inflammatory cytokines IL-1β and IL-18 in macrophages—and activation of the hydroxycarboxylic acid receptor 2 (HCA2) seem to be other mechanisms.

Following a 6-day KD (~6% carbohydrate, ~64% fat, ~28% protein), Luukonen et al (2020) demonstrated a 10-fold and six-fold increase in β-OHB and AcAc serum concentrations while endogenous β-OHB assessed by stable isotope infusions of [13C]β-OHB increased three-fold. However, this increase seems to depend on the presence and severity of NAFLD as shown by Fletcher et al (2019). They measured non-esterified FAs (NEFAs) from peripheral lipolysis and AcAc+β-OHB serum concentrations in NAFLD patients after 24h of fasting, and showed ~30% lower levels compared to controls. Interestingly, patients with higher IHLC had lower β-OHB serum levels after 24h indicating an inverse relationship between the severity of HS and ketogenesis after fasting. Contrarily, oxidation of acetyl-CoA in the tricarboxylic-acid-cycle (TCA, ie the alternative pathway for acetyl-CoA metabolism) increased ~60% in NAFLD patients compared to controls. Most interestingly, these differences were independent of BMI indicating that NAFLD itself seems to influence ketogenesis. Another recent study confirmed ~15% lower β-OHB serum concentration correlating weakly with liver fat.

These studies go in line with previous ones showing that keto genesis is significantly impaired in NAFLD (‘ketogenic insufficiency’) independent of fasting. Simultaneously, the high ‘energy-processing burden’ is mismatched to the mitochondrial capability of the liver leading to an increase in anaerobic and oxidative TCA flux and consecutive oxidative stress and inflammation. Most interestingly, a study in obese NAFLD/NASH patients showed that this compensatory upregulation of mitochondrial activity (ie ‘hepatic metabolic flexibility’) seems to fail following excessive hepatic oxidative stress, leading to a decrease in mitochondrial functionality and progression to NASH and IR. Evidence that impaired ketogenesis contributes to this phenomenon comes from mice models. After blocking the ketogenic pathway by knocking-out the 3-hydroxy-3-methylglutaryl-CoA synthase 2 (ie a key enzyme during ketogenesis), LFD induced hyperglycaemia, increased hepatic gluconeogenesis and increased DNL because of excess acetyl-CoA and increased TCA flux.

### 7.2 Gut microbiota and exercise

An emerging research topic is the relationship between exercise and the gut microbiota (reviewed in). Despite methodological difficulties and inhomogeneities in the studied cohorts, cardiorespiratory fitness and active individuals are usually associated with higher microbial diversity. Two prominent studies on professional rugby players earlier reported this higher diversity, which translates into differences in faecal metabolites (eg short-chain FA) and lower BW while supplementation reversed metabolic dysfunction in mice.

Regarding the effects of PA on gut microbiota, PA could lead to a assimilation of microbiota to healthy individuals already after 12 weeks of training. However, these changes might be small, and it is unclear whether these changes are only transient returning to a baseline profile after termination of the PA-intervention. Also, the effect of one PA on the efficacy of PA is similarly interesting. Liu et al (2020) identified the intestinal microbiota as a potential driver of exercise-induced alterations in fasting glucose and insulin. If these microbiota were transplanted to obese mice, it induced similar changes as in the respective humans. Again, abundance of Akkermansia muciniphila was significantly higher in subjects with metabolic changes following exercise intervention, and a machine-learning algorithm could successfully predict glycemic response to exercise based on gut microbiota. Similarly, another study reported different exercise gains following cardiorespiratory exercise or resistance training. Finally, an increase in Veillonella abundance in marathon runners metabolizing lactate led to the hypothesis that this genus might increase athletic performance.

### 7.3 Gut microbiota and nutrition

In recent years, promising data have evolved characterizing the interactions between diet and intestinal microbiota (reviewed in Refs. [221,222]). Specifically, differences in gut microbiota have been reported in the short-term following a LCD as well as a KD. Specifically, significant differences among Actinobacteria, Bacteroidetes, Firmicutes and Bifidobacterium were observed between KD vs LFD vs HFD with Bifidobacterium showing the greatest decline following KD. Interestingly, Bifidobacterium negatively correlated with β-OHB concentration in the intestinal lumen indicating that β-OHB inhibits Bifidobacterium growth, which was also confirmed in vitro. What is more, the KD-associated microbiota-signature reduced the level of intestinal pro-inflammatory Th17 cells.

Also, different formulations of high-fructose diets induce distinct alterations of gut microbiota: HFCS reduced butyrate-producing bacteria and the Firmicutes/Bacteroidetes ratio, while a high-fructose-diet from fruits created an opposite shift. This is relevant...
since a higher Firmicutes/Bacteroidetes ratio has been linked to the pathogenesis of the metabolic syndrome.\(^{225,226}\)

Finally, individuals with higher abundance of Akkermansia muciniphila displayed greater improvement in insulin sensitivity markers and other clinical parameters after calorie restriction.\(^{214}\) Also, a LCD/KD increased Akkermansia muciniphila abundance.\(^{227}\) Oral supplementation of Akkermansia muciniphila even improved insulin sensitivity and cholesterol levels in overweight/obese insulin-resistant volunteers.\(^{228}\)

### 7.4 | Personalized approaches

Future nutritional and lifestyle interventions will largely benefit from personalized treatment strategies tailored to individual subjects (ie "precision nutrition"). A landmark study from Zeevi et al (2015)\(^{229}\) demonstrated that large interindividual variability exists in the postprandial glycemic response to identical meals. Most surprisingly, a machine-learning algorithm including blood-derived metabolic parameters, dietary habits, PA and data on microbiota could predict the individual postprandial glycemic response. Similarly, the PREDICT1 study assessed postprandial glucose, insulin and triglycerides in 1002 twins and unrelated healthy adults.\(^{230}\) Notably, microbiota had a greater influence than macronutrients on postprandial triglycerides, and the influence on postprandial glucose was considerable. Also, machine-learning algorithm considering genetic variants allowed for prediction of triglyceride and glucose responses to food intake.\(^{230}\)

As the first of its kind, the PNPLA3 polymorphism has been studied as a modifier for dietary response. Specifically, the improvement in IHLC and insulin sensitivity following a LCD was influenced by PNPLA3-genotype with (homozygous) carriers of the G-allele achieving a higher reduction in IHLC than individuals harbouring only PNPLA3 C/C alleles.\(^{231,232}\) The DNA methylation profile may also provide prognostic information on successful WL during dietary/lifestyle interventions.\(^{233}\) Recently, Vilar-Gomez et al\(^{234}\) confirmed a modulatory effect of PNPLA3 on the relationship between reported carbohydrate-/PUFA-/flavonoid-intake and significant fibrosis. From these data, one might hypothesize that the genetic predisposition centrally influences one response to a specific diet, and implications on liver disease severity.

Finally, web-based applications might increase adherence to lifestyle interventions.\(^{235}\) As they have been discussed as alternatives to group-based interventions for maintaining individuals’ adherence to lifestyle interventions\(^{235}\) or exercise programs\(^{236}\) despite concerns about lower attrition rates.\(^{235}\)

### 8 | STRENGTHS AND LIMITATIONS OF LIFESTYLE INTERVENTIONS

From a holistic point of view, lifestyle interventions have certain unique advantages, but also limitations that need to be considered. Given promising data on NASH regression when WL is achieved,\(^{239,245}\) the cost-effectiveness of lifestyle interventions is favorable. Noteworthy, the annual healthcare expenditure for unhealthy diets are estimated to range from 3 to 148€ per capita and from 3-181€ per capita for low PA,\(^ {238}\) and unhealthy lifestyle can be attributed to ~6 years of life-expectancy lost.\(^ {239,240}\) Targeting both aspects by lifestyle interventions does therefore indeed make sense although specific data on the cost-effectiveness in NAFLD are missing. Moreover, diet and lifestyle interventions improve metabolism and health in a versatile way as outlined above, triggering beneficial health effects presumably more efficient than NASH drugs targeting only a certain mechanism of NASH-development.

Nevertheless, several caveats need to be kept in mind that limit these promising aspects. As a result of the heterogeneity of dietary interventions and study cohorts (see also Table 2), results of individual studies can hardly be directly compared, making strong guideline-recommendations significantly more difficult. Next, outcome measures differ across studies, and it remains to be answered whether changes in IHLC/ transaminase levels are a valid endpoint for dietary interventions with questionable influence on long-term prognosis. Also, the adherence to lifestyle interventions declines in parallel with the duration of the intervention, resulting in a rebound-phenomenon that has largely been shown for BW.\(^ {241}\) In terms of adherence, underestimated factors such as gender, intrinsic and extrinsic motivation (including monitoring of the intervention), socioeconomic status, among others, are also known to influence adherence to lifestyle interventions, and thus complicate interpretation of the outcome.\(^ {242}\)

### 9 | CONCLUSION

In conclusion, diet and exercise will likely remain the key therapeutical elements to fight the burden of fatty liver disease. Recent studies have highlighted the importance of calorie restriction regardless of dietary composition and while low-carbohydrate diets were most promising for reducing metabolic dysregulation and severity of NAFLD. Promotion of ketogenesis—potentially achieved via intermittent calorie restriction—seems to be the central mechanistic aspect of beneficial diets in NAFLD/NASH. Interactions of diet and exercise with the gut microbiota and the individual genetic background will need to be comprehensively understood to develop personalized life-style intervention strategies for patients with NAFLD/NASH.

### CONFLICTS OF INTEREST

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