Dietary Interventions in Liver Diseases: Focus on MAFLD and Cirrhosis

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Abstract

Purpose of Review Dietary interventions (DI) aimed at improving overweight and metabolic abnormalities in metabolic dysfunction-associated fatty liver disease (MAFLD) and at reducing malnutrition and sarcopenia in cirrhosis should become part of routine care in hepatology. This review focuses on recent advances in this field.

Recent Findings In patients with MAFLD, a gradual reduction, respectively, of 7–10% of body weight if overweight or of 3–5% if lean, obtained by moderately reducing caloric intake, is effective to improve liver disease. Intermittent energy restriction might be an alternative to continuous energy restriction with higher adherence. Qualitative dietary adjustments should include increased intake of unprocessed foods including fruits and vegetables, whole grains, fiber, and unsaturated fatty acids (FAs), for example, through a Mediterranean diet. Refined carbohydrates (CHOs), saturated FA (SFAs), red meat, and processed meat should be limited. DI studies in HIV-infected subjects with MAFLD are very limited, and this is a field for future research. In patients with cirrhosis, DI should aim at correcting malnutrition and improving skeletal muscle mass. Daily diet contents should aim at achieving 30–35 kcal/kg of body weight, including 1.2–1.5 g/kg proteins, and oral or enteral supplementation might be used in patients unable to achieve these targets. In some studies, branched-chain amino acids (BCAAs) proved to be effective in improving muscle mass and were associated with a lower risk of hepatic encephalopathy. Obesity requires adjustment of the above-mentioned targets, and its management is challenging. Studies looking at the efficacy of DI recommended by the existing guidelines on clinical endpoints are a field for future research.

Summary Dietary interventions are able to improve MAFLD and show potential to reduce complications in liver disease. Despite its key importance, there are many barriers limiting the implementation of DI in patients with chronic liver disease. Patients' empowerment is crucial and should be the focus of specific educational programs. In addition, liver clinics would benefit from multidisciplinary teams involving experts in nutrition, physical exercise, primary care physicians, and psychologists when needed.

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Introduction

The liver is a key organ for the metabolism of proteins, fats, and carbohydrates (CHOs). Not surprisingly, liver health is strictly related to metabolic health. Fatty liver disease has become highly prevalent in the general population, mostly driven by excessive food/calorie intake along with sedentary behavior as well as genetic and environmental factors (e.g., exposure to chemicals leading to alterations of the gut microbiome [1]), leading to obesity and metabolic dysfunction. Among the genetic factors modulating the risk of MAFLD and its progression to cirrhosis and hepatocellular carcinoma, confirmed associations include single-nucleotide polymorphisms in patatin-like phospholipase domain-containing 3 (PNPLA3), transmembrane 6 superfamily member 2 (TM6SF2), glucokinase

regulatory protein gene (GCKR), and HSD17B13, encoding for a retinol dehydrogenase [2•].

MAFLD is also more frequent in people living with HIV (PLWH) [3–5], likely due to the inflammation and bacterial translocation related to HIV infection per se, as well as life-long antiretroviral therapy (ART) [6, 7]. Although older drugs most likely to cause lipodystrophy are not used anymore, newer antiretroviral drugs, such as dolutegravir and tenofovir alafenamide (TAF), remain associated with metabolic side effects and weight gain [8–10] as classic metabolic risk factors for MAFLD [11, 12].

On the other hand, protein–calorie malnutrition is frequent in patients with liver disease in the cirrhotic stage due to several mechanisms. Cirrhosis implies impaired hepatic and skeletal muscle glycogen synthesis and storage, increased protein catabolism, and increased lipolysis. In addition, portal hypertension leads to malabsorption through impaired gut motility, dysbiosis and mucosal changes, and decompensated disease. The latter often features systemic inflammation and ascites, conditions requiring increased caloric intake which cannot be easily matched due to loss of appetite, resulting in severe malnutrition and sarcopenia. Genetic and environmental factors in this specific setting have not been investigated so far.

This review will provide an update on the existing dietary interventions to improve the nutritional status of patients with chronic liver disease, focusing on the two most prevalent conditions, namely, metabolic dysfunction-associated liver disease (MAFLD)/metabolic dysfunction-associated steatohepatitis (MASH) (previously termed more generically non-alcoholic fatty liver disease, NAFLD, and non-alcoholic steatohepatitis, NASH) and cirrhosis.

Nutritional Interventions in MAFLD/MASH

While no pharmacological therapy is approved for the treatment of MAFLD, several international guidelines, including HIV guidelines, advocate the use of lifestyle interventions, often including dietary interventions (DI) [13–15], due to the direct link between MAFLD and comorbid metabolic disorders such as obesity and diabetes mellitus type 2, in which such interventions have been proven effective. It should be noted that genetic and environmental factors, which are known to modulate comorbid metabolic conditions, may also mediate the individual response to DI and lifestyle interventions in general. Future studies are needed to further investigate these possible effects.

Interventional studies on nutrition in MAFLD cover a broad spectrum of dietary measures (Table 1). The main categories include energy restriction through changes in dietary composition and certain patterns of food intake such as fasting, as well as changes in the composition of macronutrients and micronutrients, including dietary supplements and

specific foods. Many studies use a combination of these measures, making direct comparison of the results challenging. Fig. 1a summarizes the suggested DI for MAFLD and associated comorbid conditions and areas of uncertainty.

Energy/Calorie Restriction

Several trials have been able to demonstrate the beneficial effects of weight loss on liver enzymes as well as histological outcomes such as steatosis and inflammation, although the evidence regarding fibrosis is less conclusive [34, 35•]. Besides surgical interventions or pharmacotherapy, weight loss can be achieved through dietary measures limiting energy intake, sometimes in combination with increased physical exercise (PE), which may also include increased physical activities of daily living or medications [36, 37]. Generally, DI using caloric restriction can be classified into continuous and intermittent energy restriction, although such a strict distinction is not always possible.

A major concern with diets that include energy restriction or other comprehensive dietary adjustments is the lack of sustainability of weight loss. A brief report of the observational and longitudinal TARGET-NASH cohort study recently demonstrated that while around one third of over 2000 overweight or obese individuals with MAFLD achieved a weight reduction of ≥ 5% in standard clinical care, only 25% of these patients were able to sustain this over a median follow-up of 39 months [38]. Factors that negatively influence the sustainability of DI and other lifestyle interventions include psychological, socioeconomic, physiologic, and genetic factors. A thorough discussion of these factors is beyond the scope of this review, but these have been excellently reviewed elsewhere [39].

Continuous Energy Restriction: Hypocaloric Diet

A hypocaloric diet is a form of continuous energy restriction, usually involving a daily calorie deficit of 500–1000 kcal. In the literature, hypocaloric diets are explored with or without changes in macronutrient composition. In a randomized controlled trial (RCT), an intervention that combined hypocaloric diet and PE in obese patients with type 2 diabetes mellitus showed a reduction of steatosis by nearly 80% in patients who lost ≥ 10% of body weight compared to 14% in those with less body weight loss [40]. In a 48-week lifestyle intervention that included moderate calorie restriction with reduced fat intake as well as coaching on behavior and PE, significant histological improvements in steatosis, parenchymal inflammation, ballooning injury, and overall NAFLD activity score, but not in the fibrosis stage, were observed in patients who achieved the weight loss goal of ≥ 7% of body weight compared to controls [41]. In a more recent trial from Cuba, 81% of patients with fibrosis at baseline who followed a

Table 1 Large ($N > 45$) randomized interventional studies assessing liver outcomes in metabolic patients published between 2018 and 2020

Source, country	Design	Participants (randomization)	Duration, months	Intervention	Results (arm)
Haidari et al. [16], Iran	RCT (double-blind regarding supplement)	MAFLD assessed by US; 40 > BMI ≥ 25 (N = 92; 23:23:23:23)	3	Arm 1: hypocaloric HP-diet (500 kcal/d energy deficit, TEI [%]: 45 CHO, 30 fat, 25 protein of 50% plant and 50% animal source), β-cryptoxanthin 6 mg/d; Arm 2: hypocaloric HP-diet (s. above); Arm 3: hypocaloric NP-diet (500 kcal/d energy deficit, TEI [%]: 55 CHO, 30 fat, 15 protein), β-cryptoxanthin 6 mg/d; Control: hypocaloric NP-diet (s. above), β-cryptoxanthin placebo	Completion rate (%): 91–96; weight loss (% body weight): 6.8 (1), 6.9 (2), 3.9 (3, control); ALT (%): −45.3 (1), −34.6 (2), −28.9 (3), −18.7 (control); AST (%): −19.4 (1), −15.9 (2), −17.9 (3), −13.9 (control)**; GGT (%): −31.2 (1), −22.2 (2), −19.5 (3), −3.3 (control)**; Remission of steatosis (grade 0 by US; % of patients): 82.6 (1), 13.0 (2), 17.4 (3), 0% (control)
Nourian et al. [17], Iran	RCT	MAFLD assessed by US; BMI ≥ 25 (N = 82; 41:41)	2	Arm 1: 8-h nutritional intervention to increase intake of fruits, vegetables, complex CHO, low dairy fat, healthy fat, white meat, and fish; limit the intake of unhealthy fats and refined CHO; Control: usual care	Completion rate (%): 80–87; weight loss not reported; ALT (IU/L): −10.5 (1)*, −5.2 (control)*; AST (IU/L): −18.8 (1)*, −7.7 (control)*; Improvement in steatosis (by US) in arm 1
Campanella et al. [18], Italy	RCT	Metabolic syndrome, 82% MAFLD assessed by US (N = 237; 61:62:57:57)	6	Arm 1: MD (1500 kcal/d, TEI [%]: 45 CHO, 37 fat, 16 protein) with increased intake of fruits/vegetables, white meat, and fish; reduced intake of red meat, dairy, sweets, and refined CHO; Arm 2: LGI diet (1500 kcal/d, TEI [%]: 47 CHO, 33 fat, 18 protein) with increased intake of fruits/vegetables, fish, unrefined CHO; reduced intake of sugars, dairy, alcohol, and processed CHO; Arm 3: LGI–MD (1500 kcal/d, TEI [%]: 40 CHO, 42 fat, 17 protein) with increased intake of fruits/vegetables, fish, olive oil, unrefined CHO; reduced intake of sugars, red meat, and fast food; Control: usual care	Adherence (%): 73; BMI (kg/m²) −2.0 (1, 2 and control), −2.9 (3)***; Remnant cholesterol (mmol/L): −0.10 (1), −0.18 (2), −0.22 (3), −0.12 (control)***; LDL cholesterol (mmol/L): −0.11 (1), −0.20 (2), +0.03 (3), −0.12 (control)***; TGL (mmol/L): −0.23 (1), −0.38 (2), −0.49 (3), −0.26 (control)***; HbA1c (mmol/mol): −0.25 (1), −0.40 (2), −0.45 (3), −0.12 (control)***; Decrease in % of patients with moderate and severe NAFLD in intervention and control groups**
Della Pepa et al. [19], Italy	Parallel randomized trial	Type 2 diabetes, 35 > BMI > 27; 70% MAFLD (N = 49; 26:23)	2	Arm 1: isocaloric MUFA-diet (2000 kcal/d, TEI [%]: 41 CHO, 41 fat [28 MUFA], 18 protein) with decreased intake of fiber and polyphenols; Arm 2: isocaloric multifactorial diet (2000 kcal/d, TEI [%]: 41 CHO, 41 fat [26 MUFA], 18 protein) with increased intake of fiber, MUFA, n-3 and n-6 FA, polyphenols (coffee), and vitamin D	Adherence (%): 91–97; weight loss (kg): −1.2 (1 and 2)*; Hepatic fat content (relative %, by H-MRS): −19 (1), −40 (2); LSM (kPa, by SWE): −0.4 (1), −0.9 (2)**; HbA1c (mmol/mol): −0.23 (1)*, −0.19 (2)*; No significant changes in HOMA-IR, LDL cholesterol, AST, ALT, GGT
Cai et al. [20], China	RCT	MAFLD assessed by LSM > 9.6 kPa; BMI > 24 (N = 271; 95:97:79)	3	Arm 1: alternate-day fasting with a very low-calorie diet (25% of TDEE) on fast days (TEI [%]: 55 CHO, 30 fat, 15 protein), ad libitum diet on non-fast days; Arm 2: time-restricted feeding with ad libitum diet, any energy intake limited to 8 h daily interval; Control: hypocaloric diet (80% of TDEE) without further instructions	Completion rate (%): 95–98; weight loss (% body weight): −5.4 (1), −4.3 (2), −2.5 (control); Total cholesterol (mmol/L): −0.71 (1), nonsignificant in arm 2 and control; TGL (mmol/L): −0.64 (1), −0.58 (2), −0.25 (control); No significant changes in LSM, LDL cholesterol
Marin-Alejandre et al. [21], Spain	Parallel randomized trial	MAFLD assessed by US; 40 > BMI ≥ 27.5 (N = 98; 48:50)	6	Arm 1: hypocaloric diet (70% of TDEE; TEI [%]: 55 CHO, 30 fat, 15 protein) based on AHA recommendations with 3–5 meals/d and healthy FA profile; Arm 2: hypocaloric diet (70% of TDEE; TEI [%]: 40–45 CHO, 30–35 fat, 25 protein) with 7 meals/d, mainly plant-based protein, LGI and increased intake of PUFA	Completion rate (%): 77–78; weight loss (% body weight): −9.7 (1)*, −10.1 (2)*; AST (IU/L): −3.9 (1)*, −2.0 (2)**; ALT (IU/L): −10.2 (1)*, −11.6 (2)*; GGT (IU/L): −12.6 (1)*, −7.2 (2)*; Hepatic fat content (absolute %, by MRI): −3.6 (1)*, −4.2 (2)*; TGL (mmol/L): −0.34 (1)*, −0.44 (2)*; HOMA-IR: −1.9 (1)*, −1.6 (2)*; No significant changes in total cholesterol, LDL cholesterol and LSM. No significant differences between groups
Rosqvist et al. [22], Sweden	Double-blind randomized trial	Obese individuals with 32 > BMI > 25, nondiabetic	3	Arm 1: overfeeding on SFA muffins (energy %: 44 CHO, 51 fat, 5 protein) for 8 weeks	Adherence (%): 97; weight gain (% body weight): +2.6 (1), +2.5 (2); ALT (%): +18 (1), no change [2]

Table 1 (continued)

Source, country	Design	Duration, months	Participants (randomization)	Intervention	Results (arm)
			(N = 60; 30:30)	Arm 2: overfeeding on PUFA muffins (energy %: 44 CHO, 51 fat, 5 protein) for 8 weeks	Hepatic fat content (relative %, by MRI): +53% [1], −2 (2) Significant increase in total cholesterol and LDL cholesterol in SFA group compared to PUFA group
Arab et al. [23]	RCT	2	MAFLD assessed by US; elevated ALT and AST (N = 82; 41:41)	Arm 1: nutritional education with weekly dietary sessions (hypocaloric, balanced diet) Arm 2: usual care	Completion rate (%): 80–88; weight loss (kg): −1.8 (1), −0.6 (2) Total cholesterol (mmol/L): −0.54 (1), +0.1 (2) TGL (mmol/L): −1.38 (1), −0.26 (2) No significant changes in LDL cholesterol
Gepner et al. [24]; Gepner et al. [25], Israel	Parallel randomized trial	18	Abdominal obesity or dyslipidaemia, 53% MAFLD assessed by MRI, 40% metabolic syndrome (N = 278; 76:63:73:66)	Arm 1: low-fat diet (TEI [%]: < 30 fat [10 SFA, ≤ 300 mg cholesterol/d]) with increased intake of fiber, vegetables, and fruits, decreased intake of sweets +/− PE intervention at 6 mo Arm 2: MD with CHO restriction (40 g/d, increase up to 70 g/d), increased intake of plant-based protein, white meat, fish, vegetables and PUFA through walnuts (28 g/d), decreased intake of red meat and SFA +/− PE intervention at 6 mo	Completion rate (%): 86; weight loss (% body weight): −3.2 (similar in groups) Hepatic fat content (absolute %, by MRI): −4.2 (1), −3.8 (2) TGL (mmol/L): −0.12 (1), −0.04 (2) HDL–cholesterol (mmol/L): +0.06 (1), +0.04 (2) Visceral and hepatic fat reduction were associated with improved lipid profile. Different fat depots may respond differently to different interventions.
Shojasaadat et al. [26], Iran	RCT	3	MAFLD assessed by US: 40 > BMI > 25 (N = 114; 38:38:38)	Arm 1: hypocaloric diet (350–700 kcal/d energy deficit; TEI [%]: 52 CHO, 30 fat, 18 protein) Arm 2: supplementation of PUFA (2500 mg/d fish oil with 1500 mg n3-FA) Control: usual care	Completion rate (%): 89–92; adherence (%): 51 (1), 89 (2); weight loss (% body weight): −3.4 (1), −1.4 (2), −1.2 (control) GGT (IU/L): −4.75 (1)*, −4.2 (2)*, −7.8 (control)* Total cholesterol (mmol/L): −0.29 (1)*, −0.33 (2)*, −0.01 (control)** LDL cholesterol (mmol/L): −0.25 (1)*, +0.1 (2)**, −0.05 (control)** HOMA-IR: −1.3 (1)*, −0.3 (2)**, −0.4 (control)*** No significant changes in AST and ALT
Willmann et al. [27], Germany	RCT	6	High metabolic risk, nondiabetic, BMI < 45 (N = 178; 60:58:60)	Arm 1: hypocaloric diet (400 kcal/d energy deficit) without intake of red meat Arm 2: hypocaloric diet (400 kcal/d energy deficit) with increased fiber intake (> 40 g/d) Control: hypocaloric diet (400 kcal/d energy deficit)	Completion rate (%): 67–83 (worst in control group); weight loss (kg): −4.0 (1)*, −2.7 (2)*, −3.2 (control)* Hepatic fat content (relative %, by H-MRS): −29 (1)*, −26 (2)*, −10 (control)** TGL (mmol/l): −0.15 (1)*, −0.10 (2)**, −0.19 (control)* No significant changes in LDL cholesterol and liver iron content
Jang et al. [28], South Korea	Parallel randomized trial	2	MAFLD assessed by US; elevated ALT and AST (N=110; 55:55)	Arm 1: low-CHO diet with intake of 25 kcal/kg of ideal body weight (TEI [%]: 50–60 CHO, 20–25 fat, 20–25 protein) Arm 2: low-fat diet with intake of 25 kcal/kg of ideal body weight (TEI [%]: 60–70 CHO, 15–20 fat, 15–20 protein)	Completion rate (%): 96; weight loss (kg): −2.9 (1)*, −1.1 (2)* AST (IU/L): −12.0 (1)*, −5.2 (2)** ALT (IU/L): −30.5 (1)*, −7.4 (2)** LDL cholesterol (mmol/L): −0.08 (1)*, −0.05 (2)** No significant changes in LDL cholesterol and liver iron content
Wong et al. [29•], Hong Kong	Parallel randomized trial	12	MAFLD assessed by H-MRS; elevated ALT: 50% BMI > 25 (N = 154; 77:77)	Arm 1: hypocaloric diet and increased energy expenditure through PE Arm 2: usual care	By BMI < 25 and BMI > 25; completion rate (%): 96–99; weight loss (kg): −4.2/−7.0 (1), −0.2/−1.0 (2) Resolution of MAFLD (%, by H-MRS): 67/61 (1), 18/21 (2) ALT normalization (%, by H-MRS): 58 (1), 26 (2) ALT (IU/L): −15/−19 (1), −9/−5 (2), not significant in BMI < 25 No significant changes in total cholesterol, LDL cholesterol and TGL. Significant decline in LSM in BMI > 25
Schutte et al. [30], Netherlands	Parallel randomized trial	3	Middle-aged overweight with 35 > BMI > 25 (N = 50; 25:25)	Arm 1: usual diet with whole-grain wheat flour (98g/d) products Arm 2: usual diet with defined wheat flour (98 g/d) products	Completion rate (%): 100; no significant weight loss in both groups Diagnosis of MAFLD (% difference in number of patients, by H-MRS): −10 (1), +11 (2) Hepatic fat content (relative %, by H-MRS): −49.1 (1), −10.6 (2) No significant differences in total cholesterol, TGL, and HOMA-IR between groups
Properzi et al. [30], Australia	Parallel randomized trial	3	MAFLD assessed by MRI-PDFF (N = 51; 25:26)	Arm 1: low-fat diet (TEI [%]: 50 CHO, 30 fat [<10 SFA], 20 protein) Arm 2: MD (TEI [%]: 40 CHO, 35–40 fat [<10 SFA], 20 protein)	Adherence (%): 64–88; weight loss (kg): −1.6 (1)**, −2.1 (2)** Hepatic fat content (relative %, by MRI-PDFF): −25.0 (1)*, −32.4 (2)* Resolution of MAFLD (%, by MRI-PDFF): 37.5 (1), 12.5 (2)

Table 1 (continued)

Source, country	Design	Participants (randomization)	Duration, months	Intervention	Results (arm)
					ALT (IU/L): −12 (1)*, −8 (2)* No significant differences in total cholesterol, LDL cholesterol, TGL, and HOMA-IR between groups
Chan et al. [31], Hong Kong	RCT	Obese adolescents (14–18 years) (N = 52; 26:26)	4 (Follow-up bis 12)	Arm 1: dietitian-led lifestyle modification intervention to improve knowledge about diet and exercise Arm 2: usual care pediatric consultations	Adherence (%): 85–92; weight loss (kg): −5.2 (1), −0.7 (2) Hepatic fat content (absolute %, by H-MRS): −4.0 (1), −1.0 (2)* HOMA-IR: −6.3 (1), −5.3 (2) No significant differences in ALT, AST, total cholesterol, LDL cholesterol, and TGL between groups
Katsagoni et al. [32], Greece	RCT	MAFLD assessed by US; elevated ALT and AST; 40 > BMI > 25 (N = 63; 21:21:21)	6	Arm 1: hypocaloric MD (1500 kcal/d for women, 1800 kcal/d for men; (TEI [%]: 45 CHO, 35 fat, 20 protein) Arm 2: hypocaloric MD (1500 kcal/d for women, 1800 kcal/d for men; (TEI [%]: 45 CHO, 35 fat, 20 protein) and enhanced PE Control: hypocaloric diet (1500 kcal/d for women, 1800 kcal/d for men; (TEI [%]: 45 CHO, 35 fat, 20 protein)	Completion rate (%): 89; weight loss (% body weight): −5.4 (1), −6.3 (2), −2.1 (control) ALT (IU/L): −17 (1), −22 (2), nonsignificant control LSM (kPa): −0.4 (1), −1.0 (2), −0.2 (control) LDL cholesterol (mmol/L): −0.3 (1), −0.1 (2), +0.3 (control) No significant differences in total cholesterol, TGL, GGT, and HOMA-IR
Holmer et al. [33], Sweden	RCT	NAFLD diagnosed radiologically or by obesity and CAP > 280 dB/m or by overweight + increased AST + CAP > 280 dB/m (N = 74; 25:25:24)	3	Arm 1: low-carb high-fat diet (LCHF) Arm 2: intermittent calorie restriction (5:2 diet) Control: standard of care (SoC): general lifestyle advice from a hepatologist	The LCHF and 5:2 diets were superior to SoC treatment in reducing steatosis (absolute reduction: LCHF: −7.2%; 5:2: −6.1%; SoC: −3.6%) and body weight. No difference LCHF and 5:2 diet between 5:2 and LCHF as for steatosis and body weight reduction. Liver stiffness improved in the 5:2 and SoC but not in the LCHF group. The 5:2 diet was associated with reduced low-density lipoproteins (LDL) levels and was tolerated to a higher degree than LCHF.

*Significant vs. baseline

**Nonsignificant

***No p values reported

Otherwise statistically significant difference between groups or vs. control

AHA, American Heart Association; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *BMI*, body mass index; *TDEE*, total daily energy expenditure; *FA*, fatty acids; *GGT*, gamma-glutamyl transferase; *HbA1c*, glycated hemoglobin A1c; *H-MRS*, magnetic resonance spectroscopy; *HOMA-IR*, homeostatic model assessment for insulin resistance; *CHO*, carbohydrates; *HP*, high protein; *IHTG*, intrahepatic triglycerides; *LGI*, low-glycemic index; *MUFA*, monounsaturated fatty acid; *LSM*, liver stiffness measurement; *NP*, normal protein; *PE*, physical exercise; *PDFF*, proton density fat fraction; *PUFA*, polyunsaturated fatty acid; *RCT*, randomized controlled trial; *SWE*, shear wave elastography; *TEI*, total energy intake in % of total kcal; *US*, ultrasound; *VCTE*, vibration-controlled transient elastography

a

Obesity
• Hypocaloric diet combined with increased physical activity, as well as intermittent energy restriction, lead to weight loss
• Weight loss of 7-10% for obese and 3-5% for lean individuals should be attempted

Impaired glucose homeostasis or diabetes
• Medically supervised ketogenic diet may be feasible and appears beneficial with respect to fasting glucose and HbA1c
• The combination of various dietary interventions improves insulin sensitivity

Cardiovascular risk factors
• Improved with the consumption of a well-balanced diet rich in fibers (e.g. Mediterranean diet), with an associated survival benefit

Histological components of MAFLD
• Weight loss leads to reduced steatosis and inflammation, and possibly fibrosis
• Coffee consumption may prevent fibrosis
• Increased intake of poly-unsaturated FAs (including omega-3 and -6) and mono-unsaturated FAs with reduction of saturated FAs may reduce steatosis
• Favoring proteins (especially plant-based) over carbohydrates and limiting intake of free sugars improve steatosis

Areas of uncertainty
• Dietary interventions with definite beneficial effects on fibrosis
• Optimal combinations of dietary interventions (also taking into account comorbidities)
• Lifestyle interventions with maximal adherence in a real life setting
• Influence of genetic and environmental factors on individual response to dietary interventions

b

Ascites
• Reduced with oral supplementation and reduced post-operatively with parenteral supplementation
• Reduced with late evening snack (BCAA-related?)
• Reduced with BCAAs post HCC treatment

Sarcopenia
• Increase in muscle mass with oral supplementation
• Increase in muscle mass and strength with BCAAs

Infections
• Reduced incidence with oral supplementation
• Reduced post-operatively with parenteral supplementation

Hepatic encephalopathy
• Reduced with BCAAs
• Reduced occurence and improved resolution with oral supplementation (BCAA-related?)
• Reduced with late evening snack (BCAA-related?)

Hepatocellular carcinoma
• Reduced post locoregional therapy recurrence with BCAAs
• Improved post treatment liver function with BCAAs

Mortality
• Survival benefit with oral and parenteral supplementation
• No clear survival benefit with BCAAs (except decreased long-term mortality after HCC therapy)

Areas of uncertainty
• Influence of baseline nutritional status and severity of liver disease on response to dietary interventions
• Optimal BCAA dose, ratio and duration

Fig. 1 **a** Suggested dietary interventions for MAFLD and associated comorbid conditions and areas of uncertainties. **b** Reported effects of nutritional interventions on clinical endpoints in cirrhosis and areas of uncertainties. Abbreviations used: MAFLD, metabolic associated fatty liver disease; MD, Mediterranean diet; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; SFAs, saturated fatty acids; BCAAs, branched-chain amino acids; LES, late evening snack; HCC, hepatocellular carcinoma; ONS, oral nutritional supplementation; PNS, parenteral nutritional supplementation

hypocaloric low-fat diet and lost ≥ 10% of body weight had a reduction of at least 1 point in the histological fibrosis score [42]. Two studies suggested that lean patients may also experience MAFLD remission after the loss of 3–5% of body weight through a hypocaloric diet [29•, 43].

Intermittent Energy Restriction: Intermittent Fasting and Time-Restricted Feeding

Previous research has shown a significant increase in hepatic steatosis when a hypercaloric diet was consumed with high meal frequency compared to consumption of the same diet through larger meals [44]. Intermittent energy restriction has been proposed as an alternative to continuous energy restriction. Most interventions can be classified into either intermittent fasting, which implies a > 60% energy restriction on > 2 days per week, or time-restricted feeding, where the daily food intake is limited to 8–10 h [45]. In a Malaysian study, 8 weeks of intermittent fasting with alternate-day calorie restriction resulted in the reduction of body weight and liver enzymes as well as liver steatosis and stiffness compared to a habitual diet [46]. A larger Chinese RCT randomized 271 MAFLD patients to undergo intermittent fasting, time-restricted feeding, or no intervention [20]. Both intermittent fasting and

time-restricted feeding induced significant weight loss of 5.4% and 4.3%, respectively, while LDL, fasting insulin, and liver stiffness did not differ significantly between groups. Finally, satisfactory dietary adherence was reported in both trials, which may indicate a possible advantage with regard to sustainability compared to a hypocaloric diet.

Macronutrient Composition

Several trials have assessed the possible effects of macronutrient composition on MAFLD, but the overlap of different interventions and effects limits the interpretation of results.

Fat Content

Several observational studies have demonstrated an association between MAFLD and higher intake of SFAs as well as decreased intake of polyunsaturated fatty acids (PUFAs), independently of total energy intake, suggesting that favoring PUFAs over SFAs in the diet may improve MAFLD [47]. In an RCT from Finland among 38 obese individuals, intrahepatic triglycerides rose by 55% in those overfed with SFAs, while the increase was 15% and 33% in the unsaturated FA and CHO groups, respectively [48]. In a Swedish double-blind RCT, despite similar weight gain in both groups, overweight subjects showed a 53% relative increase in intrahepatic fat after overeating SFAs from palm oil compared to a 2% decrease with omega-6 PUFAs from sunflower oil [22]. This effect was more pronounced than what had been seen for healthy lean subjects in a previous study [49]. An isocaloric diet containing monounsaturated fatty acids (MUFAs) significantly decreased liver fat fraction by MRI and improved insulin sensitivity compared to a regular or fiber-rich diet over 12 weeks [50].

This has inspired several trials on supplementing unsaturated FAs, such as omega-3 FAs, which showed generally beneficial effects on metabolic factors and liver fat content, although substantial heterogeneity persists among trials [51, 52]. In a recent Australian study in 50 overweight males, supplements containing omega-3 PUFAs from fish oil failed to show a benefit on liver fat content over 12 weeks [53]. With a high dose of 4 g/day for 8 weeks, a decrease of intrahepatic triglycerides by 19% was noted with a supplement containing omega-3 FA (eicosapentaenoic acid and docosahexaenoic acid) [54]. One year supplementation with 3 g/day of fish oil, however, did not improve histological activity in MASH patients [55]. Results from an Italian RCT suggest that an isocaloric diet, encompassing increased intake of MUFAs (from extra virgin olive oil), omega-3 (from salmon), and omega-6 PUFAs (from almonds) as well as fiber and vitamins D, E, and C, might be more efficient in reducing liver fat than an isolated MUFA diet [19]. This concept of synergistic combination of nutrients is the basis of recommended diets such as the Mediterranean diet (MD).

Carbohydrate Content

CHOs, especially the low CHO diet (LCD; < 50% of the total energy intake from CHOs), have been investigated in the context of MAFLD. A meta-analysis of LCD showed no reduction of liver enzymes, but a mean reduction of intrahepatic lipid content by 11.5% in 4 studies, although significant heterogeneity was encountered [56]. Furthermore, the effect may have been confounded by weight loss across intervention groups. In 28 diabetic patients undergoing an isocaloric high-protein LCD, a hepatic fat content reduction by 2.4% compared to 0.2% under conventional diabetes diet was found without significant weight loss [57]. Mardinoglu et al. (2018) performed a multi-omics approach to characterize the metabolic effects of CHO restriction on MAFLD and found an increase in hepatic FA oxidation as well as reduced de novo lipogenesis and hepatic steatosis after 2 weeks of isocaloric high-protein LCD [58].

A subgroup of LCD studies has evaluated the effect of a ketogenic diet, which induces a state of ketosis by significant restriction of CHO intake, on MAFLD. A short-term hypocaloric, ketogenic intervention in 10 overweight individuals over 6 days increased nonesterified FAs, the main substrate for intrahepatic triglycerides, but reduced intrahepatic steatosis by 31%, while increasing insulin sensitivity and metabolizing FAs towards ketogenesis [59]. In 262 diabetic patients who followed for 1 year an intervention based on LCD to induce self-monitored ketosis, noninvasively suspected steatosis and fibrosis resolved in 23% and 17% of patients, respectively, while no changes occurred in the control group [60]. However, evidence on the effects of a ketogenic diet in humans is scarce, and no uniform definition of this diet exists. More studies are needed to prove the safety of this approach in the specific context of patients with liver disease — particularly in those with advanced liver fibrosis.

As for the impact of free sugars, a meta-analysis failed to prove a negative effect of fructose, which is often contained in sweetened beverages and juices, on intrahepatic fat content in an isocaloric diet [61]. Recently, an 8-week open-label RCT of adolescent boys with histologically proven MAFLD, however, showed a mean difference of −6.2% in hepatic steatosis after limiting the intake of free sugars to < 3% of the daily caloric intake [62••].

Fiber Content

A diet rich in fiber is associated with a 15–30% reduction in all-cause and cardiovascular mortality as well as a lower risk for diabetes type 2 [63]. Several observational studies have suggested a lower intake of fiber in MAFLD patients

compared to controls, although the exact impact is difficult to assess as fiber intake is often part of broader dietary patterns [64, 65]. Among 70 obese individuals who underwent 6 months of two hypocaloric dietary regimens with identical energy deficit (RESMENA and AHA diets), the groups did not differ with regard to the improvement of noninvasive markers of liver health, and no association with macronutrient composition was observed [66]. Higher insoluble fiber (≥ 7.5 g/day) and fiber from fruit consumption, however, were associated with improvements of noninvasive scores and liver enzymes, respectively, indicating additional beneficial effects of fiber consumption with energy restriction.

Protein Content

Several studies have examined the impact of high-protein diets, often in combination with a hypocaloric regimen and LCD, on hepatic health. In an Iranian study of 92 patients who underwent a hypocaloric high-protein diet (25% of energy intake) with or without the addition of antioxidant β-cryptoxanthin, the high-protein groups showed a greater reduction in liver enzymes, but weight loss may have mediated this effect [16]. Among 19 bariatric patients, a hypocaloric high-protein diet (30% of energy intake) over 3 weeks prior to surgery led to a decrease of steatosis by 42.6% compared to no effect under identical energy but lower protein intake [67].

Besides the amount of dietary protein, the source of proteins remains an issue for debate. Red and processed meats might contribute to MAFLD and other metabolic conditions, due to the high content of SFAs, nitrites and nitrates, heme iron, and branched-chain amino acids (BCAAs) which excess may be deleterious [68, 69]. It has therefore been hypothesized that a vegetarian diet may aid in reducing MAFLD and other dysmetabolic conditions [70]. In a German study, 37 diabetic MAFLD patients were placed on a 6-week isocaloric diet with high-protein intake either from animal or plant-based sources [71]. While both diets reduced intrahepatic fat by 36–48%, no negative metabolic effects of the omnivorous diet were detected.

Specific Diets

The methods described earlier are often combined into broader and comprehensive dietary patterns such as the MD.

The concept of the MD arose from the so-called Seven Countries Study, where it was first noted that a certain dietary pattern was linked to a decrease in cardiovascular disease and mortality [72, 73]. While the MD generally contains plant-based foods and legumes instead of red meat and saturated FAs, direct comparison of trials is often hampered by the lack of a uniform definition [74]. Two large studies comparing the MD with a low-fat, high CHO diet showed an improvement in hepatic steatosis and insulin sensitivity [25, 75]. A greater

decrease in intrahepatic fat was seen under MD. Reduction in ectopic fat deposits (including hepatic fat) was associated with improved cardiometabolic risk independent of overall weight loss [24]. Currently, the MD is the only specific diet recommended by the European Association for the Study of the Liver (EASL) guidelines [76].

It is unclear whether the recommendations used in the general population can be applied also to PLWH, but given its potential to lower the risk of lipodystrophy, MD may be favorable in PLWH.

Micronutrients, Supplements, and Specific Foods

A large body of research has focused on certain dietary compounds in the treatment of MAFLD, sometimes in the form of dietary supplements, a detailed summary of which is beyond the scope of this review. Hepatoprotective effects have been shown for an array of different foods, including antioxidants such as vitamin E, as well as vitamin D probiotics and synbiotics [77, 78]. Among more readily consumed specific foods, the protective effect of coffee on MAFLD has recently been confirmed by a meta-analysis of observational studies that showed a pooled risk ratio of 0.68 for fibrosis in MAFLD patients who consumed coffee regularly [79].

Nutritional Interventions in Patients with Cirrhosis

Malnutrition is a common complication of cirrhosis. The nutritional evaluation in cirrhosis is however challenging for a variety of reasons: BMI (as well as DEXA) are affected by fluid retention; common biomarkers such as albumin and prealbumin are altered in the presence of impaired hepatic synthetic function [80••, 81••]. The lack of a gold standard to measure nutritional status in cirrhosis makes the study of nutritional interventions in this population particularly difficult.

Energy/Calorie Supplementation

Food intake is overall decreased in patients with cirrhosis, while the metabolic demand is increased. Hence, the main priority in nutritional interventions has been to provide an adequate amount of calories to correct this imbalance. Estimations based on indirect calorimetry and prior studies have led to the current recommendations by the European Society for Clinical Nutrition and Metabolism (ESPEN) and the EASL, i.e., a daily caloric intake of 30–35 kcal/kg of dry weight [80••, 81••]. In obese patients (BMI > 30 kg/m^2) with cirrhosis, a hypocaloric diet (−500–800 kcal/day) is recommended to achieve weight loss and fat mass reduction [81••].

Macronutrient Composition

Protein Content

The overall decreased food intake observed in cirrhosis is almost invariably associated with an inadequate protein intake. The current guidelines recommend a daily intake of 1.2–1.5 g/kg of dry weight in nonobese individuals and >1.5 g/kg of ideal body weight in obese individuals with cirrhosis [81••]. The previous fear of inducing hepatic encephalopathy (HE) with high-protein diets (through hyperammonemia from protein deamination) is no longer a subject of debate, and protein restriction should not be prescribed, as it may worsen sarcopenia, which may in itself increase the risk of HE. Vegetable sources of protein could have additional benefits on HE given their lower content in aromatic amino acids and their higher fiber content compared to animal protein [81••]. A recent epidemiological cohort study comparing Turkish and American patients with cirrhosis suggested that coffee/tea, vegetable, and cereal consumption were associated with a higher intestinal microbial diversity and a lower 90-day hospitalization rate [82].

BCAA Supplementation

BCAAs (leucine, isoleucine, and valine) are essential amino acids involved in the metabolism of proteins, glucose, and fat [83]. Their plasma levels are often low in patients with cirrhosis, especially in the presence of sarcopenia, hyperammonemia, and HE. Two, earlier, well-designed studies (either using isocaloric/isoproteic supplements as control interventions or documenting similar calorie and protein intake in the BCAA and control groups) have demonstrated that BCAA supplementation could prevent the progression of liver failure and liver-related events in patients with cirrhosis [84, 85]. Since then, numerous studies (coming predominantly from Japan; the most recent are summarized in Table 2) have demonstrated a beneficial effect on muscle strength, ascites, edema, and HE (Fig. 1b) [95•, 96]. Additionally, two recent meta-analyses concluded that BCAAs [97] or BCAA-based late evening snacks (LES) [98] could help maintaining liver function after interventions for hepatocellular carcinoma (HCC), preventing ascites, edema, and HE. The beneficial effects of BCAAs may however be overestimated in some studies since part of it could be attributed to an overall increased calorie and protein intake in the BCAA group compared to the control group. Additionally, it is unclear if the severity of the liver disease has an impact on the response to BCAA supplementation [89, 99].

Both the ESPEN and the EASL recommend in their latest guidelines long-term oral BCAA supplementation when adequate intake is not achieved by oral diet (which is almost invariably the case in our personal experience) [80••, 81••]. However, the optimal duration, dose, and amino acid ratio of BCAA supplementation remain unclear. For instance, the dose used in studies ranges between 5.5–30 g/day and 0.104–0.29 g/kg/day (Table 2) [95•]. A recent retrospective Korean study compared multiple doses and concluded that only the highest (12.45 g/day, close to the ESPEN recommendation of 0.25 g/kg/day [80••]) was effective [100], while other studies have observed benefits with doses as low as 6 g/day [86, 88]. Regarding the composition of BCAA supplements, the amino acid ratio varies slightly in studies but approximates 2:1:1 of leucine, isoleucine, and valine, respectively (Table 2) [95•]. The use of leucine or its metabolite beta-hydroxy-beta-methyl-butyrate (HMB) is currently being evaluated in prospective studies.

Beyond their effects on the muscle, BCAAs may have other properties including a potential benefit on carcinogenesis, possibly through an enhanced immune function and improved hyperinsulinemia (reducing IGF-1- and VEGF-mediated cell proliferation) [83]. Some studies have suggested that BCAAs could prevent HCC recurrence after treatment, although a recent meta-analysis concluded a nonstatistically significant effect [97]. More recently, an RCT in patients treated with radiofrequency ablation observed that oral supplementation with a BCAA-enriched supplement was associated with a decrease in HCC recurrence, better event-free survival, and better quality of life over a median follow-up period of 3.9 years (with similar total calorie and protein intake in both groups) [92•]. The effects of BCAAs on insulin resistance in cirrhosis remain unclear. A detailed description of the various potential targets and mechanisms of action of BCAAs is outside the scope of this review and can be found elsewhere [83].

Other Macronutrients Composition and Specific Diets

Although it is recommended in MAFLD, no prospective studies have looked at the impact of the MD in cirrhosis of any etiology, and the optimal proportion of fat and CHOs in the diet is unknown. In patients with ascites, the daily sodium intake should be moderate (~ 80 mmol, corresponding to 5 g of added salt) to keep the diet palatable [81••].

Efficacy of Energy/Calorie and Protein Supplementation

Several studies have shown benefits of calorie and protein supplementation in patients with cirrhosis on various nutrition-related outcomes, mostly reflecting muscle mass (mid-arm muscle circumference, triceps skinfold thickness, CT-derived skeletal muscle index, DEXA, BIA with phase angle) and function (handgrip strength, cardiopulmonary endurance through 6-min walk test [6MWT], short physical performance battery, and Liver Frailty Index) [80••]. Other studies have observed benefits on clinical outcomes including infections, ascites, HE, complications after hepatectomy and liver transplantation, and some even on mortality (Fig. 1b), while others could not reach similar conclusions [101–103].

Table 2 Prospective studies published in the last 5 years looking at the impact of BCAA supplementation in cirrhosis

Author (year)	Study design	N included and etiology/severity	Median follow-up	Intervention(s)** and other dietary recommendations	Duration of intervention(s)	Comparison(s)†	Outcomes in the treatment arm
BCAA supplementation							
Hernandez-Conde [86]*	RCT	34; mixed; most CPT A; all sarcopenia based on CT scan	12 weeks	BCAA daily (5.24 g, ratio 50/19/31, 411 kcal); Personalized diet and PE program (5000–10,000 steps/day)	12 weeks	Placebo (non-isocaloric/isoproteic); Personalized diet and PE program (5000–10,000 steps/day)	- Increased zinc level - Trend in increased albumin - Increased muscle mass compared to baseline - Improved LFI in both groups compared to baseline
Park [87]	Cohort, observational	124; mixed; CPT B and C (8–10)	15.2 months	BCAA granules daily (12.45 g, ratio 48/24/29, caloric content unspecified); Diet following local guidelines recommendations (35–40 kcal/kg and 1.2–1.5 g/kg protein)	Minimum 6 months, median 20.1 months	No BCAAs; Diet following local guidelines recommendations (35–40 kcal/kg and 1.2–1.5 g/kg protein)	- Improved MELD and CPT scores - Improvement in ascites and HE - No improvement in albumin (except in subgroup with < 35 g/L) and bilirubin - Improved event-free survival
Vidot [88]	RCT	49; mixed; all with a history of HE	8 weeks	BCAA daily before bed (6 g, ratio 39/31/30, 180 kcal); Usual diet (no specified targets) and ONS (18 g proteins, 250 kcal)	8 weeks	Isocaloric placebo or synbiotics or BCAA + synbiotics; Usual diet (no specified targets) and ONS (18 g proteins, 250 kcal)	- Improved cognitive performance only in the BCAA + synbiotics group
Kitajima [89]	Prospective, uncontrolled	21; mostly viral; CPT A and B	48 weeks	BCAA granules three times daily (12 g, ratio 48/24/29, caloric content unspecified); Diet containing 25–35 kcal/kg and 1–1.4 g/kg protein (including supplement)	48 weeks	N/A	- Decreased intramuscular adipose tissue content and improved glucose sensitivity in patients with improved hypoalbuminemia
Ruiz-Margáin [90]	RCT	72; mixed; CPT A	6 months	BCAA daily (9.5 g, ratio 39/32/29, 500 kcal); High-protein (1.2 g/kg/day), high fiber (30 g/day) diet	6 months	No BCAAs; High-protein (1.2 g/kg/day), high fiber (30 g/day) diet alone	- Increase in muscle mass and decrease in fat mass
Uojima [91]	Prospective, uncontrolled	82; mixed; mostly CPT A and B	24 weeks	BCAA twice daily (11.1 g, ratio 37/35/29, 420 kcal); Diet containing 25-30 kcal/kg and 1.2–1.3 g/kg protein (including supplement)	24 weeks	N/A	- Increase in handgrip strength compared to baseline - No increase in SMI
Nojiri [92•]	RCT	51; mixed; most CPT A; HCC treated with RFA	3.9 years	BCAA twice daily (11.1 g, ratio 37/35/29, 420 kcal); Diet containing 30–35 kcal/kg, 1–1.3 g/kg protein (including supplement)	Maximum 5 years	No BCAAs; Diet containing 30-35 kcal/kg and 1–1.3 g/kg protein alone (equivalent caloric/protein intake)	- Improved overall survival - Improved event-free survival - Decreased HCC recurrence - Improved QOL (SF-8 questionnaire)
Kikuchi [93]	RCT	77; mixed; CPT A; undergoing hepatectomy for HCC	4 weeks	BCAA granules three times daily (12 g, ratio 48/24/29, caloric content unspecified); Usual diet (no specified targets)	Starting 3 weeks before surgery, for 1 year	Same BCAA dose but starting only after surgery, for 1 year; Usual diet (no specified targets)	- Improved postoperative albumin - Decreased postoperative occurrence of RA and/or pleural effusions
Furuichi [94]	RCT	61; mixed; undergoing EV sclerotherapy	3 months	BCAA daily before bed (5.6 g, ratio 37/35/29, 210 kcal); Diet containing 35 kcal/kg, 1.2 g/kg protein (in addition to supplement)	For 3 months post sclerotherapy	No BCAAs; Diet containing 35 kcal/kg, 1.2 g/kg protein	- Improved platelet count - Maintenance of skeletal muscle volume

BCAA, branched-chain amino acids; *CPT*, Child–Pugh score; *HCC*, hepatocellular carcinoma; *HE*, hepatic encephalopathy; *LFI*, Liver Frailty Index; *N/A*, non-applicable; *ONS*, oral nutritional supplementation; *PE*, physical exercise; *QOL*, quality of life; *RA*, refractory ascites; *RCT*, randomized controlled trial; *RFA*, radiofrequency ablation; *SMI*, skeletal muscle index; *TACE*, transarterial chemoembolization

*Data not fully available (abstract at the Digital International Liver Congress 2020)

**Value in grams corresponds to total amount of BCAAs per day; BCAA ratio corresponds to percentage of leucine/isoleucine/valine

† All listed BCAA studies did not report the mean daily calorie and protein intake in treatment and control groups (or pre/post intervention for uncontrolled studies)

The discrepancy of findings and the inability of meta-analyses to draw firm conclusions on the prevention of complications in cirrhosis with DI can be explained by the significant study heterogeneity in design, included populations, type and duration of the intervention, presence and characteristics of the control group (including total daily calorie and protein intake in comparison to the treatment group, which is inconsistently reported), and follow-up. Nutritional supplementation may not be able to reverse some of the pathophysiological mechanisms of malnutrition (i.e., malabsorption, anabolic resistance) and could be futile in some specific situations, but reliable tools to predict who will or will not respond to nutritional therapy are not currently available. Therefore, it is reasonable to attempt DI in all patients with cirrhosis and malnutrition. Moreover, the intervention should last at least 3–6 months before concluding to any effect. Importantly, the involvement of a dietician in the management of cirrhosis was associated with better survival in a retrospective study [104].

Special Considerations in Cirrhosis

Timing of Supplementation

Since cirrhosis is a state of accelerated starvation (reached in only 10 h vs. 2–3 days in healthy individuals [105]), the timing of oral intake is of utmost importance. Fasting periods should be limited by the use of small and frequent meals of an LES and a breakfast. An earlier RCT showed that LES over a 12-month period improved total body protein, while the same supplement taken during daytime did not and was associated with a trend towards more complications, death, and transplantation [106]. The optimal caloric content of the LES has not been clearly defined, although some authors suggest a high caloric content (200–300 kcal) with a sufficient amount of CHOs (50 g) [107] and a source of protein, including BCAAs.

Route of Supplementation

The patient's oral intake must be evaluated regularly to ensure that the aforementioned targets are reached, otherwise oral nutritional supplementation should be implemented. The latter may however be difficult to tolerate for some patients, especially those with more advanced cirrhosis and dysgeusia, anorexia, or nausea. In this case, enteral nutrition (EN) should be strongly considered, at least temporarily. As for parenteral nutrition, experts agree that it should be reserved for patients with moderate to severe malnutrition who cannot adequately be fed by the oral and/or enteral route or who have contraindications to EN.

The feasibility of EN in the outpatient setting has recently been demonstrated in a retrospective case series looking at 14 patients with refractory ascites who failed to improve with oral nutritional support over a prior mean of 5 months (reasons not specified but likely due to intolerance) [108]. An outpatient-based, continuous, and supplementary EN (with a standard, fiber-enriched polymeric feed) for a median of 7 weeks, in addition to oral intake, was associated with significant benefits: an improvement in the nutritional status and handgrip strength, a significant improvement in ascites control with a decreased need for paracentesis, and a trend towards an improvement in the MELD score. Although all patients required reinsertion of the feeding tube at least once due to dislodgement or blockage, EN was overall well tolerated.

Combining Nutritional Interventions with Physical Exercise

While in MAFLD, PE mainly exerts its positive effects through weight loss, in cirrhosis, however, this effect seems to occur through maintaining/increasing muscle mass. The beneficial effects of PE on aerobic capacity, sarcopenia, and quality of life have repeatedly been shown in this population [109]. However, most of the studies evaluating the effects of exercise in cirrhosis incorporated a DI, and the observed effects could be due to diet alone or to a synergistic effect of diet and PE on muscle mass. Moreover, not all studies systematically report the patients' actual mean calorie and protein intake [110, 111]. Studies looking at the effect of PE alone in cirrhosis are rare, and the isolated effect of physical exercise has not been well defined.

In a recent RCT in 39 patients with Child–Pugh A and B cirrhosis showing a beneficial effect of a 12-week resistance training program on muscle strength and size, both arms received nutritional counseling by a dietician, regular phone calls, and oral supplementation when the daily protein intake was under 1.2 g/kg [112•]. Although the total protein intake was insufficient at the beginning of the study in both groups, it reached the target amount at the second dietician visit, showing the efficacy of the intervention. This was also observed in an earlier Canadian pilot RCT [113]. A study from the UK showing the feasibility of a hospital-based training program offered structured nutritional advice in both arms based on the EASL recommendations [114]. Two studies have also demonstrated a beneficial effect of a combined nutritional and PE intervention on portal pressure [115•, 116].

Since the benefits of PE depend on adequate substrate reserves, some authors have suggested optimizing the nutritional status of patients prior to starting an exercise program [117]. To compensate for the exercise-induced calorie expenditure, the consumption of an additional 250–300 kcal on exercise days [113] or a 20% increase in the caloric intake when following an exercise program [116] has been recommended.

Several recent studies have looked at the potential synergistic effect of PE (especially resistance training exercises) and BCAA supplementation. A pilot RCT showed that

combining BCAA supplementation with a home-based PE program improved 6-min walk test (6MWT) distance and psoas muscle index more than BCAA supplementation alone (both groups also had a daily protein target intake of 1.2–1.5 g/kg) [118]. An uncontrolled study showed that BCAA supplementation and walking (2000 steps/day) increased muscle mass and function compared to baseline [119], while another small uncontrolled trial showed that BCAA supplementation and a home-based exercise program for 12 months improved aerobic capacity and glycemic control [120].

Regarding patients with cirrhosis and obesity, we previously showed that a 16-week intensive lifestyle intervention consisting of a personalized, hypocaloric, normoproteic diet, and 60 min/week of supervised PE led to an improvement in body weight and portal pressure in patients with compensated cirrhosis [115•]. Although the study used a combined intervention, it is likely that the hypocaloric diet was a major contributor to the observed weight loss. More studies are needed in this field, given the obesity pandemic and the high prevalence of sarcopenia in this population [121].

Conclusions

As highlighted in this review, dietary interventions have been proven effective in treating MAFLD/MASH in several large and well-conducted studies. The mainstay in overweight/obese patients remains a daily (continuous or in an intermittent fashion) energy deficit of 500–1000 kcal, with a gradual reduction of 7–10% of body weight, while lean patients might benefit from a reduction by 3–5%. Dietary adjustments should include increased intake of unprocessed foods including fruits and vegetables, whole grains, fiber, and unsaturated FAs, for example, through the MD. Refined CHOs, SFAs, and red and processed meats should be limited.

On the other hand, the amount and quality of data regarding dietary interventions aimed at treating and reverting malnutrition in cirrhosis are more limited. Meta-analyses could not prove the efficacy of DI in cirrhosis, probably in part due to the heterogeneity of studies in this field. DI including BCAAs supplementation (especially as a late snack) in addition to calorie and protein supplementation have demonstrated the potential of improving clinical outcomes in this setting.

There are many challenges to the applicability of these interventions in both MAFLD and cirrhosis populations. Adherence from the healthcare providers to nutritional recommendations remains suboptimal, and guidelines need to include pragmatic and feasible recommendations to improve adherence. In addition, and maybe most importantly, healthcare providers and patients need to be educated on malnutrition and its impact on the evolution of chronic liver diseases [122]. As for patients' awareness and empowerment, simple educational interventions, such as a simple nutrition education class followed by reinforcement phone calls, have been shown to be beneficial [78, 123–125].

The success of DI also strongly depends on proper screening and identification of patients who might benefit from them and from the availability of a structured and well-connected multidisciplinary team. This must include, in addition to the hepatologist and an exercise specialist, a registered nutritionist, who can properly evaluate the patient's nutritional status and provide tailored recommendations (taking also into account the patient's preferences and socioeconomic factors), as well as retroaction and strategy modifications if objectives are not met. The support of a psychologist might be required to improve adherence, particularly in patients with obesity and in patients with anxiety and depression (frequently observed in obese patients with MAFLD and in patients with cirrhosis).

Barriers to the implementation of nutritional interventions need to be identified early and optimized, since these are frequent, particularly in patients with cirrhosis [126]. Finally, further studies should focus on how new technologies can be applied in this field, for instance, to increase adherence to DI (e.g., reinforcement strategies via reminders) or to make expert knowledge more universally available (e.g., web-based programs). Well-designed randomized controlled studies adding targeted DI to standard of care vs. standard of care alone with robust endpoints (e.g., decrease of complications or mortality) in patients with cirrhosis and in particular decompensated cirrhosis are a major unmet need in hepatology.

Declarations

Conflict of Interest The authors have no potential conflicts (financial, professional, or personal) that are relevant to the manuscript to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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• Of importance
•• Of major importance

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