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EASL Clinical Practice Guidelines on nutrition in chronic liver disease

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Introduction

Malnutrition is frequently a burden in patients with liver cirrhosis, occurring in 20–50% of patients. The progression of malnutrition is associated with that of liver failure. While malnutrition may be less evident in patients with compensated cirrhosis it is easily recognisable in those with decompensated cirrhosis. Malnutrition has been reported in 20% of patients with compensated cirrhosis and in more than 50% of patients with decompensated liver disease(1). Both adipose tissue and muscle tissue can be depleted; female patients more frequently develop a depletion in fat deposits while males more rapidly lose muscle tissue(2)(1).

As detailed in these clinical practice guidelines (CPGs), malnutrition and muscle mass loss (sarcopenia), which has often been used as an equivalent of severe malnutrition (3), are associated with a higher rate of complications (4) such as susceptibility to infections (5), hepatic encephalopathy (HE) (6) and ascites (4), as well as being independent predictors of lower survival in cirrhosis (7, 8) and in patients undergoing liver transplantation (9). Given these observations, malnutrition and sarcopenia should be recognised as a complication of cirrhosis, which in turn worsens the prognosis of cirrhotic patients.

Whether malnutrition can be reversed in cirrhotic patients is controversial. Although there is general agreement about the need to improve the dietary intake of these patients, avoiding those limitations and restrictions that are not evidence based, amelioration of the nutritional status and muscle mass is not always achievable (10–12).

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Supplementary Table 1. Nutritional guidelines for patients with chronic liver disease proposed by different medical societies in different settings.

Although the term “malnutrition” refers both to deficiencies and to excesses in nutritional status, in the present CPGs “malnutrition” refers to “undernutrition”. More recently, in addition to undernutrition, overweight or obesity are increasingly observed in cirrhotic patients because of the increasing number of cirrhosis cases related to non-alcoholic steatohepatitis (NASH). Muscle mass depletion may also occur in these patients, but due to the coexistence of obesity, sarcopenia might be overlooked. Obesity and sarcopenic obesity may worsen the prognosis of patients with liver cirrhosis (13–15)(3).

No previous guidelines released by the European Association for the Study of Liver Disease (EASL) have dealt with nutrition in advanced liver disease and/or have evaluated the relationship between nutritional status and the clinical outcome of patients. Therefore, the EASL Governing Board has asked a panel of experts in the field of nutrition and hepatology to produce the present CPGs.

Methodology

The panel initially established the most relevant questions to answer, considering relevance, urgency and completeness of the topics to be covered. The main questions addressed were: How can nutritional problems be recognised? In which conditions are nutritional assessments recommended? What are the available methods of evaluation? What are the consequences of malnutrition and its correction? Different clinical scenarios have been considered with special attention paid to nutrition in HE and before and after liver transplantation. A section devoted to bone metabolism in chronic liver disease has also been included. Each expert took responsibility and made proposals for statements for a specific section of the guideline.

The literature search was performed in different databases (PubMed, Embase, Google Scholar, Scopus) and reference from papers identified. The initial key words were: “Nutrition” OR “Nutritional status” OR “Malnutrition” OR “Sarcopenia” AND “Liver cirrhosis” OR “Chronic liver Disease”. Further, more specific key words were also utilised: “nutritional assessment”, “nutrition risk”, “hepatic encephalopathy”, “osteoporosis”, “liver transplantation”) for each specific topic of the guideline. The selection of references was based on appropriateness of study design, number of patients, and publication in peer-reviewed journals. Original data were prioritised. The resulting literature database was made available to all members of the panel.

All recommendations were discussed and approved by all participants. The Committee met on two occasions during international meetings with experts who were available to participate, two *ad hoc* teleconferences also took place for discussion and voting.

The evidence and recommendations in these guidelines have been graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (16). The classifications and recommendations are therefore based on three categories: the source of evidence in levels I through III; the quality of evidence designated by high (A), moderate (B), or low quality (C); and the strength of recommendations classified as strong (1) or weak (2) (Table 1). All recommendations based on expert opinion because of the lack

of available data were graded as C. The recommendations were peer-reviewed by external expert reviewers and approved by the EASL Governing Board.

These guidelines are directed at consultant hepatologists, specialists in training, and general practitioners and refer specifically to adult patients with cirrhosis. Their purpose is to provide guidance on the best available evidence to deal with nutritional problems in patients with chronic liver disease. A few schemes were produced by the panel and are included in these guidelines to help with the management of nutritional problems in patients with liver cirrhosis.

For clarity, the terms and definitions used in the present CPGs are summarised (Box 1).

Screening and assessment for malnutrition and obesity in liver cirrhosis: Who, when and how

Given the worse prognosis associated with malnutrition, all patients with advanced chronic liver disease, and in particular patients with decompensated cirrhosis are advised to undergo a rapid nutritional screen. Those at risk of malnutrition should complete a more detailed nutritional assessment to confirm the presence and severity of malnutrition (17–19), in order to actively manage this complication.

Nutrition screening tools

Two simple criteria stratify patients at high risk of malnutrition: being underweight, defined as a body mass index (BMI) (kg.body weight [BW]/[height in metre]^2) <18.5 kg/m^2 (20), in which the vast majority of cirrhotic patients have sarcopenia, and having advanced decompensated cirrhosis (Child-Pugh C patients) (17, 21).

There are several possible scoring tools to classify patients who are at risk of malnutrition. Most have not been validated in cirrhotic patients, and are prone to bias in cases of fluid retention, which should be accounted for. There are two liver disease-specific tools: however, both need further validation. The Royal Free Hospital-nutritional prioritizing tool (RFH-NPT) score was reported to correlate with clinical deterioration, severity of disease (Child-Pugh score, model for end-stage liver disease [MELD] score), and clinical complications such as ascites, hepatorenal syndrome, and episodes of HE (22). Furthermore, improvement in RFH-NPT score was associated with improved survival (22). This scheme takes less than 3 mins to be completed and can be used by non-specialist staff. The liver disease undernutrition screening tool is based on six patient-directed questions regarding: nutrient intake, weight loss, subcutaneous fat loss, muscle mass loss, fluid accumulation and decline in functional status. However, it relies almost completely on the patient's subjective judgment and has low negative predictive value (23). If the initial screening using these tools is negative, it is recommended that the evaluation be repeated over time.

Detailed nutritional assessment

It is advisable that patients who are at risk of malnutrition during screening undergo a detailed nutritional assessment for the diagnosis of malnutrition, preferably by a registered

dietitian or nutrition expert. In patients with cirrhosis whose screening results indicate a high risk of malnutrition, it is suggested that each component be assessed and documented every 1–6 months in the outpatient setting and for inpatients, at admission and periodically throughout the hospital stay (17). The components of a detailed nutritional assessment include evaluation of: muscle mass, global assessment tools and a detailed nutritional intake, as described below.

Sarcopenia: How to assess

Sarcopenia is a major component of malnutrition. Direct quantification of skeletal muscle mass requires cross-sectional imaging (24). Computed tomographic (CT) image analysis at the L3 vertebra is almost universally recognised as a specific method to quantify muscle loss. Psoas muscle and possibly para spinal and abdominal wall muscles are considered core skeletal muscles that are relatively independent of activity and water retention, but are consistently altered by the metabolic and molecular perturbations of cirrhosis. Any of the several possible image analysis software packages can be used to analyse the total cross-sectional area (cm^2) of abdominal skeletal muscles at L3. This area is then normalised to height to calculate the skeletal muscle index (cm^2/m^2). Even though magnetic resonance imaging has also been suggested, data in patients with liver cirrhosis are scarce and normal values are still required.

The routine use of CT imaging for nutritional assessment, especially for repeated assessments, is obviously limited in clinical practice, due to cost and exposure to radiation. However, since CT scanning is frequently available in cirrhotic patients (second line imaging for screening hepatocellular carcinoma, evaluation for liver transplant, evaluation of vascular shunts or portal thrombosis), it can be utilised at least once for assessment of sarcopenia.

All measures require normal values that are based on age, gender and ethnicity. In addition, there are gender differences in the interpretation of muscle mass and function, indicating lower predictive validity in women (21, 25). Normal CT measures and cut-off values to define sarcopenia were initially derived from an oncologic population (26). Cut-off values derived from cirrhotic patients on the liver transplant list and based on clinical outcomes have only recently been suggested (50 cm^2/m^2 for men and 39 cm^2/m^2 for women) (27), and still need to be further validated. The predictive role of CT-assessed skeletal muscle mass in liver transplant candidates was demonstrated in a meta-analysis, showing an independent association between low muscle mass and post-transplantation mortality (pooled hazard ratios of sarcopenia 1.84, 95% CI 1.11–3.05), independent of the MELD score (28).

Body mass assessment can also be performed by simple bedside anthropometric methods (29) including mid-arm muscle circumference (MAMC, defined as mid-arm circumference minus [triceps skinfold (TSF) x 0.314])(30), mid-arm muscular area (MAMA = MAMC/ 4×0.314) and TSF, which are simple to perform, rapid, low cost, and not affected by the presence of fluid retention. Both MAMC and TSF have a demonstrated prognostic value for mortality among cirrhotic patients, with MAMC having a higher prognostic power than TSF(31). If performed by trained personnel, these measurement have good intra and inter-

observer agreement (intra-class correlation of 0.8 and 0.9 for TSF and MAMC, respectively) (32). Compared to the diagnosis of sarcopenia by cross-sectional imaging (by CT or magnetic resonance), the predictive value of MAMC was shown to be good, with an area under the receiver operating characteristic curve (AUROC) of 0.75 for men and 0.84 for women(30). In a small sample study, a significant but moderate correlation was observed between CT measurement and MAMC in cirrhotic men (r = 0.48, p <0.001), but not in women (31). In addition, low MAMC was found to be an independent predictor of mortality after liver transplant (33), and in a large sample of the general population, but only among men(34).

Whole body dual-energy X-ray absorptiometry (DEXA) allows measurement of bone mineral density, fat mass and fat-free mass. However, fat-free mass is not necessarily only skeletal muscle mass. Radiation exposure, cost and logistics are additional limitations, while water retention may limit the validity of the formula applied to assess body composition. The ability to quantify limb muscle mass, which could be more reliable and has corresponding cut-offs in the healthy population, is an advantage and may overcome the confounding effect of overhydration.

Tetrapolar bioelectrical impedance analysis (BIA) uses the two-compartment model, and segmental BIA measurements allow limb non-fat mass quantification. Low cost, portable equipment and ease of use are advantages of BIA. However, the validity of these methods also depends on stable hydration status, which may be altered in patients with cirrhosis (35).

Skeletal muscle contractile function is not a direct measure of muscle mass but has been used as a measure of sarcopenia. Handgrip strength is a simple, inexpensive, and effective method to detect malnutrition in cirrhotic patients; predicting incidence of major complications and mortality (36–38).

Measures of frailty, defined as patient's vulnerability to stress, decreased physiologic reserve and functional status deficits (39, 40) can also be used in the assessment of cirrhotic patients. There are several measures of frailty that are used in geriatrics and were also demonstrated to have predictive value in cirrhotic patients. The Fried frailty phenotype is characterised by five domains: unintentional weight loss, self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity(39). An increase in the Fried frailty score was demonstrated to be associated with increased risk of waiting list mortality, even when adjusting for MELD (40). The short physical performance battery (SPPB) consists of timed repeated chair stands, balance testing, and a timed 13-ft walk and takes 2–3 mins to complete. Although the SPPB does not correlate with CT-based muscle mass in men or women (38), it predicts transplant waiting list mortality (38, 40). At present, there are no standardised or universally accepted criteria to diagnose frailty in cirrhosis.

Global assessment tools in cirrhosis

The technique of subjective global assessment (SGA) uses data collected during clinical evaluation to determine nutritional status without recourse to objective measurements (32). Overall, SGA has fair to good inter-observer reproducibility (41) and is associated with

various clinical and prognostic variables of liver transplantation(42). However, agreement of SGA with other methods of assessment of nutritional status (total lymphocyte count, MAMC, MAMA, TSF, subscapular skinfold thickness, BMI and handgrip measurement) is low (K <0.26) (43). Furthermore, SGA underestimates the prevalence of muscle loss in liver disease patients, compared with other objective measures (36, 44–47).

The Royal Free Hospital-global assessment (RFH-GA) (32), for determining nutritional status in patients with cirrhosis is reproducible, correlates with other measures of body composition and predicts survival and post-transplant complications (32, 48, 49). Patients are stratified into one of three categories based on their dry weight-based BMI and their MAMC: adequately nourished, moderately malnourished (or suspected to be), or severely malnourished. The limitations of this tool include the time required, and the need for trained personnel for consistent results.

Reported dietary intake

Dietary interviews provide practical information for nutritional interventions by identifying what and how much the patient is willing and capable of eating and determining specific nutrient deficiencies that need to be corrected. A detailed assessment of dietary intake is suggested to include: food, fluids, supplements, number of meals and their timing throughout the day (*e.g.* interval between meals, breakfast and late-night meals as recommended), as well as calories and quality and quantity of protein intake. It should also include barriers to eating: nausea, vomiting, aversion to certain foods, taste, low-sodium diet, early satiety, gastrointestinal pain and diarrhoea or constipation. The symptoms section of the abridged scored patient-generated subjective global assessment (abPG-SGA) can be used to construct the questions (50).

Evaluation of dietary intake is time consuming, requires skilled personnel and relies on patient recall and cooperation. The best method that relies the least on patient recall is a three-day food diary. However, it requires patients to cooperate and follow detailed instructions, which may make it difficult to implement in those with advanced disease. Therefore, repeated 24 h dietary recalls are also optional (51). The 24 h recall technique requires short-term recall, is less burdensome, less likely to alter eating behaviour than food records, and can be used across diverse populations because it does not require a high level of literacy (52).

At a minimum, patients should be asked if their relative food intake has changed and, if so, by how much (by half *etc.*) and over what period of time (for example, as indicated in the SGA – nutritional assessment tool) (53).

Obesity in cirrhosis: Assessment and interpretation

With the increasing prevalence of obesity and NASH-related cirrhosis, attention needs to be paid to obesity in patients with cirrhosis. Obesity does not rule out malnutrition. The combination of loss of skeletal muscle and gain of adipose tissue is termed sarcopenic obesity and is observed in a significant number of patients with cirrhosis (14, 54, 55). Moreover, post-transplant obesity and metabolic syndrome are common and weight gain

after transplantation is considered to be primarily due to an increase in the adipose tissue, with concomitant loss in skeletal muscle (55, 56). Therefore, malnutrition needs to be estimated routinely and treated in the obese cirrhotic patient. In clinical practice, BMI is adequate to recognise obesity (defined as BMI equal or greater than 30 kg/m^2) in cirrhotic patients, in the absence of fluid retention. In the case of fluid retention, BW needs to be corrected by evaluating the patient's dry weight, commonly estimated by post-paracentesis BW or weight recorded before fluid retention if available, or by subtracting a percentage of weight based upon the severity of ascites (mild 5%; moderate 10%; severe 15%), with an additional 5% subtracted if bilateral pedal oedema is present, as performed in several studies (21, 30). This is still not validated but excellent inter-observer agreement has been demonstrated. The dry-weight BMI is then calculated dividing by the patient's estimated dry weight (kg) by the square of the patient's height (m).

The proposed process for nutritional screening and assessment in patients with chronic liver disease is summarised (Fig. 1)

Recommendations

- Perform a rapid nutritional screen in all patients with cirrhosis and complete a detailed assessment in those at risk of malnutrition, to confirm the presence and severity of malnutrition. (**Grade II-2, B1**)
- Assume risk for malnutrition to be high if BMI <18.5 kg/m^2 or Child-Pugh C. Utilise nutritional screening tools to assess the risk of malnutrition in all other instances. (**Grade II-2, B1**)
- When diagnosing obesity (BMI >30 kg/m^2) consider the confounding effect of fluid retention. Estimate dry BW, even though the accuracy is low. (**Grade II-2, B2**)
- Always include an assessment of sarcopenia within the nutritional assessment. (**Grade II-2, B1**)
- Whenever CT scan has been performed, assess muscle mass on images by this method. Anthropometry, DEXA or BIA are possible alternatives, which also enable serial measurements. (**Grade II-2, B1**)
- Assess muscle function, in the clinical setting, with the most appropriate tool, such as handgrip strength and/or the short physical performance battery. (**Grade II-2, B1**)
- Assess dietary intake by trained personnel (ideally a dietician with knowledge of managing patients with liver disease) working as part of a team with the hepatologist. Assessment should include: quality and quantity of food and supplements, fluids, sodium in diet, number and timing of meals during the day and barriers to eating. (**Grade II-2, B1**)

Nutritional management principles in patients with liver cirrhosis

Since malnutrition and sarcopenia are independent predictors of adverse clinical outcomes including survival (57),(58, 59), (17) (60) any nutritional approach in cirrhotic patients needs to follow some general principles of nutritional management.

Energy and protein requirements in cirrhosis

Cirrhosis is a state of accelerated starvation demonstrated by a rapid post absorptive physiology which is characterised by a reduction in the respiratory quotient(61, 62). The reduction in the respiratory quotient is the manifestation of a metabolic switch in the primary fuel from glucose to fatty acids. During this state of accelerated starvation, protein synthesis is decreased and gluconeogenesis from amino acids is increased, necessitating proteolysis, which contributes to sarcopenia. Gluconeogenesis is an energy-expensive procedure which may further increase resting energy expenditure (REE) in these patients. Accelerated starvation is aggravated by reduced dietary intake due to a variety of factors including dysgeusia, anorexia of chronic disease, salt restricted food that is not tasty, portal hypertension that contributes to impaired gut motility, decreased nutrient absorption and protein losing enteropathy (63–66). Additional factors that result in decreased dietary intake include inappropriate dietary protein restriction, hospitalisation with periods of fasting for diagnostic and therapeutic procedures, encephalopathy and gastrointestinal bleeding.

Energy supply needs to balance total energy expenditure (TEE), which includes REE, food-related thermogenesis and energy expenditure related to physical activity. TEE is measured ideally with doubly labelled water or in a respiratory chamber, but these methods are not feasible in the clinical setting. Physical activity is reduced in patients with decompensated cirrhosis and negligible when patients are hospitalised. In cirrhotic patients, TEE varies between 28 to 37.5 kcal/kg.BW/d. (63, 67–70). Some studies evaluated whether decompensated liver cirrhosis affected REE. One small longitudinal study suggested that ascites increases REE (71). However, a cross-sectional study found no difference in REE between patients with varying levels of liver disease severity and fluid retention (72–74). Measured REE may be higher than predicted, a situation termed hypermetabolism. However, hypermetabolism cannot be identified by clinical or laboratory parameters (75), the severity and the aetiology of liver cirrhosis and the presence of ascites (25). REE may be estimated by predictive formulae but these are inaccurate in advanced cirrhotic patients, and thus measurement by indirect calorimetry is advisable whenever possible (61, 62). The availability of the hand held calorimeter at the bedside is a possible alternative to determine a patient’s daily caloric needs (76).

The approach of most nutritional intervention studies in liver cirrhosis is to supply at least 35 kcal/kg.BW/d. The use of actual BW, corrected for ascites (see previous section), is considered safe. This can be achieved primarily by tailoring the oral dietary intake, even though this goal is frequently difficult to accomplish. The role of a nutrition support team has recently been underlined by a retrospective study showing that nutritional intervention, led by a multidisciplinary team, and in which cirrhotic patients participated in teaching sessions about the relevance of appropriate nutrition in chronic liver disease, was able to improve survival rates and quality of life(77).

Whether frequent feeding can help prevent accelerated starvation and the related proteolysis has also been extensively evaluated. Since the longest inter-meal duration is at night, strategies to shorten nocturnal fasting with a late evening snack have been explored, achieving an improvement in metabolic profile and quality of life, although muscle mass did not show consistent improvement(78). The adoption of a breakfast containing some proteins (79) and a late evening snack (80) to shorten the period of fasting are therefore recommended in cirrhotic patients.

Protein needs are based on the minimum protein intake required to maintain nitrogen balance. In alcoholic cirrhosis, nitrogen balance was achieved with intakes of 0.8 g/kg.BW/d (81). This cut-off was confirmed in studies wherein cirrhotic patients received diets with increasing protein content (70, 82). These studies also showed that cirrhotic patients are able to utilise up to 1.8 g/kg.BW/d of protein (70). In the past, there has been controversy about whether patients suffering from HE should undergo a transient restriction in protein intake, in order to limit the synthesis of ammonium and the deamination of protein to aromatic amino acids. However, normal to high protein intake does not precipitate HE (83),(84) and may even improve mental status (85), (86) (see paragraph on hepatic encephalopathy).

The recommended protein intake in patients with a diagnosis of liver cirrhosis is 1.2–1.5 g/kg.BW/d to prevent loss of muscle mass and reverse muscle loss in those who are sarcopenic. Indeed, sarcopenia, as previously stated, contributes to worse clinical outcomes, independent of the severity of liver disease (27, 63). Options for the treatment of sarcopenia will be discussed in the next section.

Short dietary advice for use when treating a cirrhotic patient at bedside or during an outpatient visit is provided (Table 2).

Approach to sarcopenia in patients with liver cirrhosis

Factors related with sarcopenia in patients with cirrhosis

Skeletal muscle mass is the largest protein store in the body. A balance between skeletal muscle protein synthesis and breakdown is responsible for protein homeostasis (or proteostasis) that maintains skeletal muscle mass(66, 87, 88). In the past, whole body protein turnover studies have yielded conflicting results with unaltered, increased or decreased protein synthesis and breakdown in cirrhosis (3, 89). Skeletal muscle mass depends on a number of factors including age, gender and ethnicity in physiological states. The severity and aetiology of liver disease also affects muscle mass, with cholestatic and alcoholic liver disease leading to the most severe muscle loss independently of the severity of the underlying liver disease, although data on alcoholic liver disease are not consistent (66, 90). Hepatocellular dysfunction and portosystemic shunting also result in biochemical and hormonal perturbations in cirrhosis that contribute to sarcopenia.

Increased skeletal muscle ammonia, reduction in testosterone and growth hormone, endotoxemia, as well as decreased dietary nutrient intake contribute to sarcopenia(89, 91–93). In addition, amino acid perturbations, specifically reduction in the branched chain amino acid, L-leucine, and consequent impaired global protein synthesis has also been

reported to contribute to sarcopenia in cirrhosis(3, 94–97). To better understand the progressive depletion of muscle mass in cirrhotic patients, molecular mechanisms of muscle wasting have recently been investigated (Fig. 2). Molecular pathways that regulate skeletal muscle mass include myostatin, a TGFβ superfamily member that inhibits protein synthesis and potentially increases proteolysis (88). Data in animal models, humans and cellular systems have consistently shown that myostatin expression is increased in cirrhosis (95, 98, 99). In addition to impaired protein synthesis, proteolysis is also required for loss of muscle mass (63, 66). The ubiquitin proteasome pathway and autophagy are currently believed to be the dominant mechanisms of skeletal muscle proteolysis (63, 100). Human skeletal muscle from patients with cirrhosis and preclinical models of hyperammonaemia show increased autophagy with impaired or unaltered proteasome-mediated proteolysis (95, 100, 101). A more extensive view of molecular mechanisms of muscle wasting in patients with liver cirrhosis is reviewed in reference 19 (18).

Strategies to improve muscle mass in cirrhosis

A number of potential therapeutic strategies to improve muscle mass in patients with cirrhosis have been evaluated. These include dietary manipulations, increased physical activity and exercise (3, 102–104), hormone replacement therapies, (105) ammonia-lowering strategies and targeting the underlying liver disease. (106–109)

Nutritional supplementation

It is advised that any nutritional interventions follow the general recommendations reported as “energy and protein requirements in cirrhotic patients” (previous paragraph). However, an adequate calorie and protein intake is difficult to achieve in malnourished sarcopenic patients with advanced liver disease. Oral nutritional supplement and branched chain amino acid (BCAA) supplements have been utilised in clinical trials to overcome this issue(110, 111) showing some benefits. In patients with malnutrition and cirrhosis, who are unable to achieve adequate dietary intake with the oral diet (even with oral supplements), short-term enteral or parenteral nutrition should be to overcome the phase of underfeeding. Nutritional guidelines proposed by international medical societies for enteral and parenteral nutrition in patients with chronic liver disease are reported (Table S1).

Enteral feeding has been utilised in malnourished cirrhotic patients admitted to hospital, but despite promising individual studies, systematic meta-analyses have not shown significant benefits in terms of survival(11, 12, 112). There are also conflicting data on the benefits of parenteral nutritional supplementation in patients with cirrhosis, but this is likely to have a beneficial role during prolonged periods of poor oral intake including encephalopathy, gastrointestinal bleeding and impaired gut motility or ileus (113). The use of enteral and parenteral nutrition in the perioperative setting is dealt with in a dedicated section.

There is limited but consistent data that supplemental nutrition improves quality of life if it results in an increase in lean body mass, even though direct studies on sarcopenia are currently unavailable (114).

Exercise and physical activity

In addition to nutritional supplementation, increased physical activity and exercise are also anabolic stimuli that can improve muscle mass and function. However, consistent long-term data in cirrhosis are lacking (87, 115). Endurance or aerobic exercise improves skeletal muscle functional capacity but not necessarily muscle mass (116). Resistance exercise promotes an increase in skeletal muscle mass(116). However, exercise also increases muscle ammonia generation and portal pressure (117, 118), both of which can have adverse effects in cirrhotic patients. Despite these potential adverse responses, beneficial effects have been reported (103, 104). Since both muscle loss and impaired contractile function are components of sarcopenia in cirrhosis, a combination of resistance and endurance exercise would probably be appropriate and beneficial, as confirmed by emerging data indicating the benefit of a moderate intensity exercise regimen in cirrhosis (104).

Nutrient supplementation following physical activity is beneficial in physiological states, but whether such an intervention is beneficial in cirrhosis is currently unknown (119, 120). Continued impaired functional capacity and reduced peak oxygen consumption are associated with decreased survival and poor post-transplant outcomes(121, 122). Hence measures to increase functional capacity are likely to improve long-term clinical outcomes in cirrhosis(102).

Other strategies

Hormone replacement therapy utilising growth hormone or testosterone has been proposed but has not been consistently effective(91, 92, 123, 124). Furthermore caution is needed when using testosterone because of the possibility of increasing the risk of hepatocellular carcinoma(105).

A number of reports in preclinical models have shown that hyperammonaemia results in impaired protein synthesis and increased autophagy, both of which result in loss of muscle mass(99, 100).

Long-term ammonia-lowering strategies may result in increased muscle mass and contractile strength but the data are derived from preclinical studies and require validation in human studies (109).

Nutritional approach and management of obesity in patients with liver cirrhosis

Two studies have shown that obesity is at least as frequent in compensated cirrhosis as it is in the general population, ranging from 20 to 35% (13, 125), regardless of the origin of liver disease. In NASH-related cirrhosis obesity is present in most cases. Moreover, a sedentary lifestyle is highly prevalent in patients with cirrhosis and might be seen as a cofactor, leading to an increase in BW in this population. In the HALT-C trial (125) the risk of histological progression or decompensation increased by 14% for each increase in BMI quartile, and the risk of progression increased by 35% in patients whose BW increased by >5% at one year.

In a randomised controlled trial comparing the use of timolol or placebo to prevent the onset of gastroesophageal varices, BMI was associated with clinical decompensation, independently of portal hypertension and albumin, in patients with no varices and an hepatic venous pressure gradient ≥6 mmHg (13).

Data from different studies suggest that a reduction in BW improves outcomes in obese patients with compensated cirrhosis (102, 125, 126). This was achieved by a programme of lifestyle intervention including nutritional therapy and supervised moderate intensity physical exercise. A weight decrease ≥5–10% is considered an adequate goal, associated with a reduced rate of disease progression in patients included in the HALT-C trial (125). Dietary intake is aimed to guarantee both moderate caloric restriction and adequate protein intake. Indeed, although good quality data are lacking, particular attention must be paid to the protein intake needed to maintain muscle mass, because of the potential risk of exacerbating sarcopenia during weight loss interventions.

No clear-cut data is available regarding the best type of physical exercise (aerobic *vs.* anaerobic; endurance *vs.* resistance/strength training) and its duration in this population. In patients with portal hypertension, avoidance of abdominal pressure seems reasonable even though there is some data suggesting that resistance exercise is probably safe (126). Exercise needs to be tailored to the patient's ability, beginning with moderate intensity and maintained for the long-term.

Recommendations

- Nutritional counselling by a multidisciplinary team should be provided to cirrhotic patients with malnutrition, helping patients to achieve adequate caloric and protein intake. (**Grade II-2, C2**)
- Optimal daily energy intake should not be lower than the recommended 35 kcal/kg.BW/d (in non-obese individuals). (**Grade II-2, B1**)
- Optimal daily protein intake should not be lower than the recommended 1.2–1.5 g/kg.BW/d. (**Grade II-2, B1**)
- Include late evening oral nutritional supplementation and breakfast in dietary regime of malnourished decompensated cirrhotic patients. (**Grade II-1, B1**)
- BCAA supplements and leucine enriched amino acid supplements should be used in decompensated cirrhotic patients to achieve adequate nitrogen intake. (**Grade II-1, C1**)
- In patients with malnutrition and cirrhosis who are unable to achieve adequate dietary intake with the oral diet (even with oral supplements), a period of enteral nutrition is recommended. (**Grade II-1, B1**)
- Patients with cirrhosis, whenever possible, should be encouraged to avoid hypomobility and to progressively increase physical activity. (**Grade II-1, C2**)

- Implement a nutritional and lifestyle programme to achieve progressive weight loss (>5–10%) in obese cirrhotic patients (BMI >30 kg/m^2 corrected for water retention). (**Grade II-2, C1**)
- A tailored, moderately hypocaloric (−500–800 kcal/d) diet, including adequate protein intake (>1.5 g proteins/kg.BW/d) can be adopted to achieve weight loss without compromising protein stores in obese cirrhotic patients. (**Grade II-1, C2**)

New research should answer the following topics

1. Does the improvement in muscle mass and/or muscle function improve clinical outcomes (lower the risk of first decompensation, ascites, infection and encephalopathy, reduce hospital readmissions, decrease length of hospital stay, reduce risk of falls, improve survival)?
2. Do ammonia-lowering strategies in decompensated cirrhosis reverse muscle loss and improve clinical outcomes?
3. Does a gradual increase in physical activity delay or reverse muscle loss and contractile dysfunction? What type and duration of exercise are beneficial in cirrhotic patients need to be determined
4. Is the addition of supplements (leucine, isoleucine or other nutrient supplements) needed to lower ammonia and increase mitochondrial intermediates during training?
5. How can therapies targeting the muscle protein synthesis pathway or dysregulated muscle autophagy be implemented?
6. How can anabolic resistance be overcome, or the underlying causes of anabolic resistance in cirrhotic patients be reversed?

Micronutrients

In general, vitamin deficiencies in liver disease are related to hepatic dysfunction, diminished reserves and, with increasing disease severity, inadequate dietary intake and malabsorption.

Fat-soluble vitamin deficiencies are common. A retrospective study reported that the majority of liver disease patients being considered for transplantation presented with vitamin A and D deficiencies (127).

The prevalence of vitamin D deficiency in the general population ranges from 20 to 100% when referring to serum 25(OH)D concentrations <20 ng/ml, and affects all age groups (128). In patients with chronic liver disease vitamin D (25-hydroxyvitamin D) levels below 20 ng/ml have been reported in between 64 and 92% of patients, predominantly in chronic cholestatic conditions, and usually inversely correlated with more advanced disease and Child-Pugh score(129, 130). Although low vitamin D levels might, in part, be due to decreased plasma binding proteins in the presence of liver insufficiency, some evidence in

pre-cirrhotic stages provide support for a true nutritional deficit. Recent data suggest a close correlation between vitamin D levels and response to treatment in patients with hepatitis C virus infection, non-alcoholic fatty liver disease and those who develop hepatocellular carcinoma (130–132).

Based on these data, it is advisable to assess plasma vitamin 25 hydroxy-D (25OHD) levels in all patients with chronic liver disease, particularly in those with advanced disease (128, 130), non-alcoholic fatty liver and cholestatic disorders (133). Although there are no specific recommendations in patients with chronic liver disease except for those with chronic cholestasis, it seems reasonable to supplement all chronic liver disease patients with vitamin D levels below 20 ng/ml with oral vitamin D until reaching a serum vitamin D level above 30 ng/ml. Higher doses may be necessary in patients with non-alcoholic fatty liver disease (134). Vitamin K deficiency should always be considered in patients who are jaundiced or whose liver disease is cholestatic in origin, and parenteral supplementation might be needed.

Patients with both alcohol and non-alcohol related cirrhosis are prone to deficiencies in water-soluble vitamins, particularly thiamine (B1). They often exhibit evidence at autopsy of Wernicke's encephalopathy, even in the absence of a history/clinical signs during life (135). If Wernicke's encephalopathy is suspected, generous parenteral thiamine supplementation is mandatory. Deficiencies in pyridoxine (B6), folate (B9) and cobalamin (B12) may also develop rapidly in chronic liver disease resulting from diminished hepatic storage (136). However, good quality data on their prevalence and/or need for supplementation are scarce. As vitamin status is not easily assessed and multivitamin supplementation is cheap and substantially side effect free, a course of oral multivitamin supplementation could be justified in decompensated patients.

Hyponatraemia is common in patients with cirrhosis and is more likely to occur when the intake of sodium is low, and that of water unchanged or increased (137). Thus, careful monitoring of both sodium and water intake is required. If severe hyponatraemia is corrected, this needs to be done slowly, to avoid the risk of central pontine myelinolysis (138). A reduction in dietary sodium intake is recommended in patients with ascites (139), although evidence in this respect is limited and conflicting (140). Sodium intake should certainly not be reduced below 60 mmol/d, as this makes the diet unpalatable, potentially compromising energy and protein intake (141). Reductions in circulating levels of calcium, magnesium, and iron need to be considered and corrected (142). Tissue zinc concentrations are reduced in patients with cirrhosis and zinc has been implicated in the pathogenesis of HE. However, data on the effects of zinc supplementation on mental performance have been conflicting (143–145). Selenium deficiency has been related to the severity of hepatic fibrosis in patients with hepatitis C and identified as one of the factors contributing to insulin resistance in these patients (146). Patients with cirrhosis have elevated total body manganese levels, which may result in selective manganese accumulation in the basal ganglia (147). While there is no clear relationship between such a phenomenon and HE, it is probably reasonable to avoid nutritional supplements containing manganese.

Specific evidence about the beneficial effect of micronutrients and vitamin supplementation in cirrhotic patients is not available. However, confirmed or clinically suspected deficiency should be treated based on accepted general recommendations and common practice.

Recommendations

- In cirrhotic patients, administer micronutrients and vitamins to treat confirmed or clinically suspected deficiency. (**Grade II-1, C1**)
- Assess Vitamin D levels in cirrhotic patients, as deficiency is highly prevalent and may adversely affect clinical outcomes. (**Grade II-3, B1**)
- Supplement vitamin D orally in cirrhotic patients with vitamin D levels <20 ng/ml, to reach serum vitamin D (25(OH)D) >30 ng/ml. (**Grade II-1, B1**)
- In cirrhotic patients with ascites under sodium restriction (recommended intake of sodium ~80 mmol day = 2 g of sodium corresponding to 5 g of salt added daily to the diet according to EASL guidelines) take care to improve diet palatability as this regime may cause a reduction in caloric intake. (**Grade II-2, B1**)

Nutritional treatment options for hepatic encephalopathy

The relationship between malnutrition and HE has been known since the seminal observation that decreased energy intake determines weight loss and coma in Eck's fistula dogs (148). Human studies also support this association. HE occurs more frequently in malnourished patients with cirrhosis, and there is an inverse relationship between muscle mass and blood ammonia levels (149, 150). Sarcopenia, as assessed by the skeletal muscle index, is an independent risk factor for the development of HE after transjugular intrahepatic portosystemic shunt placement (151). Muscle plays an important role in ammonia removal (152) by increasing glutamine synthesis, a reaction that is catalysed by the enzyme glutamine synthetase (153). This has generally been thought of as a straightforward, benign process of ammonia disposal but evidence is accumulating that hyperammonaemia may impair muscle function and contribute to muscle loss (154), thus establishing a vicious circle. There is also evidence that ammonia lowering can reverse sarcopenia in animal models (155). Recently a randomised clinical trial showed that nutritional intervention (30–35 kcal/kg.BW/d, 1.0–1.5 g vegetable protein/kg.BW/d for 6 months) *vs.* no nutritional intervention was able to improve neuropsychiatric performance in patients with minimal HE, and decrease their risk of developing overt HE (114).

Energy requirements in patients with cirrhosis and HE are thought to be the same as those of patients with cirrhosis *per se* (156). Patients with HE need to avoid long periods of fasting, and should be encouraged to split their caloric and protein intake into small, frequent meals. It is advisable that breakfast (79) and a late evening snack (80) also include some proteins (see also paragraph: *Energy and Protein requirements in patients with liver cirrhosis*).

Dysregulated nitrogen metabolism plays a major role in the development of HE and its modulation is key to HE management. Up to the middle of the 20th century, meat protein

loads were administered to patients with cirrhosis to avoid catabolism (157). Then, a few uncontrolled studies showed that decreased protein intake was associated with better mental status in patients with HE and portosystemic shunts (158), leading to a widespread practice of chronic protein restriction (159). Protein restriction is now considered detrimental, except perhaps, for very short periods of time, in patients with severe overt HE and gastrointestinal bleeding. There is sufficient evidence that, in general, patients with HE tolerate diets with a normal protein content (86), and their nitrogen requirements are the same as those of patients with cirrhosis *per se* (160).

The type of protein ingested may be important. The original demonstration that Eck's fistula dogs fed with fish/milk protein rather than meat developed fewer/no behavioural abnormalities (161) lead to the idea that patients with HE may benefit from the replacement of meat with dairy/vegetable protein. Subsequent uncontrolled, human studies showed that dairy protein is better tolerated than protein from mixed sources and that vegetable protein is better tolerated than meat protein (162–164). While there is a good pathophysiological basis for the use of dairy/vegetable diets in patients with HE, the results of the clinical studies undertaken to date remain unconvincing (165). In addition, concerns have been raised in relation to tolerability/palatability, and thus potential negative effects on overall caloric intake (156). This is likely to depend on the features of the staple diet. Interestingly, a 14-day casein-vegetable, high-protein, high-calorie diet was shown to improve mental performance and to decrease ammonia levels in 150 patients with overt HE (166). One of the advantages of vegetable diets may be due to their fibre rather than protein content, as fibre has both prebiotic and laxative property. While increased dietary fibre may be of value in patients with HE, the available literature is limited (167), and increase in fibre consumption is difficult even in the healthy population. Of interest, support from a multidisciplinary nutrition team has been shown to be useful in patients with cirrhosis (77) and should be considered in patients with HE.

A decreased serum ratio of BCAA to aromatic amino acids has been associated with a poor prognosis (168), but there is limited evidence that the original assumptions behind BCAA supplementation in HE, namely that their use could prevent and treat HE, liver injury and sarcopenia are correct.(169) However, BCAA supplements, in daily divided doses, may facilitate the provision of an adequate nitrogen intake in patients who are intolerant to meat protein (170). The replacement of meat with dairy/vegetable protein plus BCAA supplements is likely to be preferable to a reduction in total protein intake. Long-term, oral BCAA supplementation may also have nutritional value (110, 171). Palatability has proven to be a significant issue. In addition, costs plus the possibility to prescribe BCAA as drugs (*vs.* food supplements) vary considerably between countries.

In addition, it has been shown that L-leucine alone can reverse the decrease in disturbed muscle protein homeostasis (proteostasis) due to hyperammonaemia (172). A Cochrane meta-analysis included 16 randomised clinical trials, comparing oral or intravenous BCAA supplementation *vs.* a control intervention in 827 patients with HE (173). Oral BCAA had a positive impact on HE. Oral or intravenous BCAA however did not influence mortality, quality of life or nutritional status. No firm conclusions could be reached on their nutritional

effects and on how they compare with non-absorbable disaccharides/antibiotics (174). Their use intravenously for episodic overt HE is not supported by the available evidence.

In patients with HE grade III-IV, as oral dietary intake is unfeasible or impossible, in keeping with common practice in patients with neurologic coma, nutrition should be provided by nasogastric tube or parenterally.

Recommendations

- Nutritional status should be evaluated and sarcopenia sought for in patients with hepatic encephalopathy (HE). (**Grade II-3, B1**)
- Avoid protein restriction in patients with HE. (**Grade II-1, A1**)
- Optimal daily protein and energy intake should not be lower than the general recommendations for cirrhotic patients (recommendations 14 and 15). (**Grade II-1, A1**)
- Encourage the consumption of vegetables and dairy protein. (**Grade II-3, B1**)
- BCAA supplementation can be considered to improve neuropsychiatric performance and to reach the recommended nitrogen intake. (**Grade I-1, A1**)
- In patients who can tolerate oral intake prefer dietary intake by mouth. In patients with grade III-IV encephalopathy, who are unable to eat, provide nutrition by nasogastric tube (in patients with protected airways) or parenterally. (**Grade II-1, B1**)

Nutritional treatment options in cirrhotic patients with bone diseases

‘Hepatic osteodystrophy’, including osteoporosis and osteomalacia, has been used for years to describe the bone disease of patients with liver damage. Osteoporosis, characterized by loss of bone mass and quality that leads to fragility fractures, is common in patients with chronic liver disease (175). Osteomalacia resulting from poor bone mineralization is uncommon and only present when associated with persistent vitamin D deficiency in subjects with severe and long-lasting cholestasis and intestinal malabsorption (176). Nutritional, hormonal, metabolic, genetic, and inflammatory factors play a significant role in the pathogenesis of osteoporosis in patients with chronic liver disease, mainly as a result of a decreased bone formation.

The diagnosis of osteoporosis is based on bone mineral density (BMD) that is generally measured by DEXA. According to World Health Organization, osteoporosis is considered when BMD is 2.5 standard deviations below the young average value (T-score < 2.5) and to have osteopenia when the T-score is between −1 and −2.5, and severe or ‘established’ osteoporosis refers to individuals who meet densitometric criteria and have one or more fragility fractures (177). Osteopenia is considered when the T-score is between −1 and −2.5.

Prevalence of osteoporosis in patients with chronic liver disease depends mostly on patient selection and diagnostic criteria. In summary, about 30 % of patients have osteoporosis, with higher prevalence in patients with cholestasis including primary biliary cholangitis (PBC)

and primary sclerosing cholangitis (PSC) (178–190). In patients eligible for liver transplantation the prevalence of osteoporosis is 30% (190–193). Fracture prevalence ranges between 7% and 35% (178–190, 194–200), being more frequent in postmenopausal than in young women and males (184), and in patients under corticosteroid therapy (201). Vertebral fractures are associated with osteoporosis and osteopenia with a T-score lower than −1.5 in patients with PBC and primary sclerosing cholangitis (182). Patients with a T-score below −1.5 have a high risk for hip and vertebral fractures, thus supporting that this T-score may be a practical guide for starting specific therapy.

Osteoporosis is frequently observed in transplanted patients (202), and associated with a high incidence of fractures (25 to 35%) within the first year of liver transplantation (203, 204). Improvement of bone health in the management of transplanted patients have reduced the incidence (205).

According to the WHO, bone densitometry of the lumbar spine and hip is the gold standard procedure for the diagnosis of osteoporosis and osteopenia. Lateral X-rays of dorsal and lumbar spine should also be performed to disclose vertebral fractures (206). Laboratory measurements to identify abnormal calcium and vitamin D metabolism are also appropriate. The biochemical markers of bone turnover can be determined, but they are mainly helpful for monitoring the response to therapy. Undecalcified transiliac bone biopsy is recommended only in the exceptional cases with presumed osteomalacia.

The diagnosis and management of bone disease in patients with chronic liver disease is summarised in fig. 3. Bone densitometry should be evaluated in patients with previous fragility fractures and those treated with corticosteroids and before liver transplantation (182, 206); and needs to be assessed in patients with cholestatic diseases or if any of the described risk factors are found, and in cirrhotics. In patients within normal BMD, it is advisable to repeat DEXA after two-three years, as is suggested in the non-cirrhotic population. In conditions associated with a rapid bone loss such as in cholestatic patients with more than one risk factor for osteoporosis, and in those with recently initiated high-dose of corticosteroid therapy DEXA can be repeated in a shorter interval of approximately one year This schedule is also recommended for patients with advanced cirrhosis, particularly in those eligible for transplantation. Inaccuracies in BMD and bone marker measurements in patients with cirrhosis or chronic cholestasis need to be taken into consideration (207, 208). Recognition of the risk factors for bone loss including those for osteoporosis and fractures in patients with chronic liver disease is recommended as in general population and in postmenopausal women (Table 3) (206). The proposed management of bone disease in patients with chronic liver disease is summarised (Fig. 3).

A balanced diet is recommended because chronic liver disease patients often are malnourished. Supplements of calcium (1,000–1,500 mg/d) and 25-hydroxy-vitamin D (400–800 IU/d or 260 μg every 2 weeks) or the dose required to preserve normal levels should be provided.- There is however no definite data confirming the efficacy of these supplements in preventing bone loss in patients with liver disease (134). Physical activity is recommended, in particular with exercises designed to improve the mechanics of the spine. Factors contributing to bone loss need to be reduced to a minimum, including

discontinuation of alcohol and tobacco use. Corticosteroids ought to be minimized whenever possible.

Different pharmacological therapies have been proposed for improving bone mass in patients with chronic liver disease, but most studies have included small numbers of patients, and therefore it is difficult to reach any definite conclusions. Furthermore, no clear anti-fracture effect has been demonstrated, and except for osteoporosis in PBC and after liver transplantation, no systematic studies have been reported.

There is no general agreement concerning the appropriate time to start treatment but patients with established osteoporosis, and therefore with fragility fractures, should be treated to reduce the risk of further fractures. Since patients with PBC with a lumbar or a proximal femur T-score lower than <−1.5 have a high risk for vertebral fracture, it seems reasonable to consider specific therapy in these patients (182), and in all patients with osteoporosis before transplantation.

Bisphosphonates are anti-catabolic drugs which increase bone mass and reduce the incidence of fractures in postmenopausal osteoporosis. Their effects in chronic liver disease are not entirely defined, mostly because of the very limited number of studies and small numbers of patients (209–214). Nonetheless, etidronate, alendronate and ibandronate increase bone mass in patients with PBC, and results in these patients are similar to that in patients with osteoporosis associated with other causes (210, 213). Serious adverse events have not been observed and potential harmful effects of bisphosphonates have not been reported in liver patients. Moreover, bisphosphonates appear to be well tolerated, although it would be reasonable to exercise caution in using the drug in cirrhotics with recent oesophageal banding/sclerotherapy to avoid oesophageal injury. Bisphosphonates may also have a role in transplanted patients (215–217). Favourable effects have been reported using zoledronic acid (218), and weekly alendronate (219). Moreover, zoledronic acid reduces bone turnover and results in lower fracture rate (218).

In patients with liver disease, hormonal replacement therapy was limited as for many years was considered harmful. Transdermal oestrogens prevent bone loss or even increase BMD in patients with PBC or autoimmune cirrhosis and in postmenopausal women after liver transplantation, with no liver adverse effects (220–223). In males with hemochromatosis and hypogonadism, treatment with testosterone and venesection is also effective (224). One concern about restoring testosterone levels in cirrhotic patients is the increased risk of hepatocellular carcinoma (105).

There are no studies assessing the effects of anabolic drugs in liver patients with osteoporosis, but PTH 1–34 can be a potential therapy for osteoporosis in these patients (225) as well as denosumab, a human monoclonal IgG antibody that binds to RANKL and inhibits bone resorption.

Recommendations

- Evaluate BMD in cirrhotic patients and in patients with cholestatic liver diseases, long-term corticosteroid treatment, and before liver transplantation. (**Grade II-2, A1**)
- Utilise lumbar and femoral densitometry (DEXA) for diagnosing osteoporosis and osteopenia. Lateral X-rays of dorsal and lumbar spine for diagnosing vertebral fractures. (**Grade II-3, A1**)
- Repeat DEXA after 2–3 years in patients within normal BMD, and within 1 year when rapid bone loss is expected. (**Grade II-1, B1**)
- Include supplements of calcium (1,000–1,500 mg/d) and 25-hydroxy-vitamin D (400–800 IU/d or 260 μg every 2 weeks), in patients with chronic liver disease and a T-score below −1.5. (**Grade II-3, A1**)
- Utilise bisphosphonates in cirrhotic patients with osteoporosis and in those waiting for liver transplantation. (**Grade I, A1**)
- Consider testosterone supplementation and venesection in males with hemochromatosis and hypogonadism. (**Grade II-2, B1**)

New research should answer the following topics

1. The use and safety of anabolic drugs, such as PTH 1–34 and denosumab as potential new therapies for osteoporosis in patients with cirrhosis.

Clinical scenarios requiring special considerations

Malnutrition in patients undergoing liver surgery and liver transplantation

Preoperative nutrition

Both severe under nutrition (BMI < 18.5 kg· m^{-2}) and severe obesity (BMI > 40 kg· m^{-2}) prior to liver transplantation are associated with increased mortality and morbidity (226–229). Severe obesity prior to liver transplantation is associated with a higher prevalence of comorbidities (diabetes, hypertension), cryptogenic cirrhosis and increased mortality from infectious complications, cardiovascular disease and cancer (228, 229). Some investigators found that severe obesity was associated with increased morbidity and mortality even when patients were classified according to “dry BMI” (229) while others have reported that the amount of ascites and not BMI contributes to the increase mortality risk (230).

Numerous descriptive studies have shown higher morbidity and mortality in cirrhotic patients with protein malnutrition when such patients undergo liver transplantation (57, 231–233). Recently, sarcopenia and frailty have been shown to carry an increased risk of morbidity and mortality on the waiting list and after transplantation (58, 234–243). Patients on the wait are at risk due to an inadequate food or caloric intake (244) and those consuming a low protein diet (<0.8 g/kg.BW/d) have an increased waiting list mortality (245). Nevertheless, there are no formal trials showing that preoperative nutritional intervention improves clinical outcome.

In less advanced and predominantly cholestatic liver cirrhosis, nutritional counselling plus oral nutritional supplement (ONS) improved MAMC and grip strength compared to nutritional counselling alone while there was no difference in mortality (246). In one pilot study, ONS enriched with ω−3 fatty acids, arginine and nucleotides appeared to reduce infectious complications (247). In a subsequent randomised trial, perioperative immunonutrition did not provide significant benefits in terms of preoperative total body protein status or postoperative outcome compared to standard ONS (248).

A combined meta-analysis of different interventions like glutamine or ω−3 fatty acids by parenteral or enteral route reported overall beneficial effects regarding morbidity and liver function but no significant difference in survival (249). Kaido and colleagues observed less postoperative infections in their transplanted patients who received preoperative immune-modulating ONS (250). Interestingly, BCAA supplementation conferred better survival only to sarcopenic patients on the waiting list but not to non-sarcopenic individuals (251).

In malnourished cirrhotic patients, the risk of postoperative morbidity and mortality is increased after abdominal surgery (252, 253). Liver glycogen is depleted in cirrhotic patients and therefore it is advisable to take great care to shorten periods without nutrient intake in order to avoid gluconeogenesis from muscle protein in an already protein depleted individual (254, 255). Also in liver surgery, adoption of enhanced recovery after surgery (ERAS) protocols improves morbidity and length of stay when among other measures, patients are given carbohydrate containing clear liquids until two hours preoperatively, early feeding and mobilization (256–258).

Recommendations

- Screen for malnutrition and sarcopenia cirrhotic patients listed for transplantation or scheduled for elective surgery. Treat sarcopenia prior to elective surgery, as this will allow improvement in body protein status and clinical outcomes. (**Grade III, B2**)
- Screen for sarcopenic obesity, with body composition analysis, obese cirrhotic patients considered for surgery in order to identify those at higher risk for morbidity and mortality. (**Grade III, C1**)
- Preoperatively, if the treatment goal is maintenance of nutritional status, plan a total energy intake of 30 kcal/kg.BW/d and a protein intake of 1.2 g/kg.BW/d. If improvement of nutritional status is the goal, plan a total energy intake of 35 kcal/kg.BW/d and a protein intake of 1.5 g/kg.BW/d. (**Grade II-3, B1**)
- For preoperative nutrition, utilise standard nutrition regimens since specialised regimens (*e.g.* BCAA-enriched, immune-enhancing diets) have not been shown to improve morbidity or mortality in intervention trials. (**Grade II-1, B1**)

Postoperative nutrition

After transplantation, postoperative PN or EN is superior to just infusing fluids and electrolytes to decrease time on the ventilator and length of stay in ICU or reduce risk of bacterial infections and bile duct complications (260). Early EN (12 hours after the

operation) is associated with fewer viral infections and better nitrogen retention than parenteral nutrition (260). In a direct comparison between PN and early EN, both strategies proved to be equally effective with regard to the maintenance of nutritional state but EN reduced complication rates and costs (261). For early EN in adult liver transplant recipients, whole protein formulae with (262) or without pre- and probiotics (260, 261) or peptide-based formulae via catheter jejunostomy (263, 264) have been used. Formulae were administered via nasogastric or nasoduodenal tubes after endoscopic placement(261) or via catheter jejunostomy (263, 264) (265) placed during laparotomy. According to an European survey (258) the combination of EN and PN was used in 10/16 centres, while 3/16 stated to use PN or EN alone.

After liver transplantation there is a considerable nitrogen loss and patients remain in negative nitrogen balance for a prolonged period (247, 266) necessitating an increase in the provision of protein or amino acids. Protein or amino acid provision of 1.0–1.5 g/kg.BW/d has been reported (259) which is slightly lower than recommended for hospitalized or critically ill patients (267–269). No difference was observed between a standard and a BCAA-enriched amino acid PN solution after liver transplantation (259).

In the early postoperative phase there is often a disturbance of glucose metabolism associated with insulin resistance. In this situation blood glucose levels should be managed like in other surgical patients (258). In the first 48 h postoperatively, a lower provision of energy (<18 kcal/kg.BW/d)(270) may be advisable in the light of the growing recognition of autophagy as a source of endogenous substrate supply (271). Less postoperative morbidity and shortened length of stay was reported, seemingly in duplicate, when ω−3 fatty acids were used for PN (272, 273). Hepatic RES function was reported to show better recovery with a medium chain triglyceride (MCT)/long chain triglyceride (LCT) compared to an LCT emulsion given as PN after liver transplantation (274).

For the growing subgroup of obese surgical patients, recent guidelines recommend energy (25 kcal/kg ideal BW/d) and protein (2.0 g/kg ideal BW/d) intakes based on ideal BW calculated based on height and gender (275).

Chronic dilutional hyponatraemia is not infrequent in LC patients and should be corrected carefully after transplantation in order to avoid pontine myelinolysis (276). Magnesium levels need to be monitored in order to detect and treat cyclosporine or tacrolimus induced hypomagnesaemia (277). The simultaneous administration of enteral feeding with tacrolimus did not interfere with tacrolimus absorption (278).

Long-term survivors after liver transplantation are at considerable risk of becoming overweight or even obese and develop relevant morbidity due to metabolic syndrome (279–281). Attention should be paid to avoid the sarcopenic obesity (282) by stringent postoperative physiotherapy and dietary counselling to overcome the deconditioning of pre-transplant chronic liver disease (283–285).

Sarcopenic cirrhotic patients undergoing non-transplant surgery like resection for HCC have an increased mortality risk (286, 287). In LC patients undergoing non-transplant visceral surgery, complication rate and nitrogen economy can be improved when nutrition support

instead of just fluid and electrolytes is provided (288) (265). It may safely be assumed that EN in the early postoperative period would yield at least equally beneficial results. There are, however, no studies comparing the two regimens in cirrhotic patients. There are data to suggest a beneficial effect on gut permeability of sequential PN/EN (via jejunostomy) as compared to PN alone or no postoperative nutrition at all (265).

In cirrhotic patients undergoing liver resection, oesophageal transection and splenectomy or splenorenal shunt, the rate of HE was not increased when a conventional amino acid solution (50 $g \cdot d^{-1}$) was used for postoperative PN instead of a BCAA-enriched amino acid solution (40 $g \cdot d^{-1}$) (288). Tang and colleagues reported improved immune function and preserved gut mucosal integrity when PN supplemented with glutamine and human growth hormone was used in LC patients (289).

Recommendations

- After liver transplantation initiate normal food and/or enteral tube feeding preferably within 12–24 hours postoperatively, or as soon as possible, to reduce infection rates. (**Grade II-2, B1**)
- When oral or enteral nutrition are not possible or impracticable, prefer parenteral nutrition to no feeding in order to reduce complication rates and time on mechanical ventilation and ICU stay. (**Grade II-2, B1**)
- After the acute postoperative phase, provide an energy intake of 35 kcal/kg.BW/d and a protein intake of 1.5 g/kg.BW/d. (**Grade II-2, C1**)
- After other surgical procedures, manage patients with chronic liver disease according to the ERAS protocol. (**Grade III, C2**)
- Consider PN in patients with unprotected airways and hepatic encephalopathy (HE) when cough and swallow reflexes are compromised or enteral nutrition is contraindicated or impractical. (**Grade II-2, C1**)
- Utilise enteral tube feeding and/or PN with a reduced target energy intake (25 kcal/kg.BW/d) and an increased target protein intake (2.0 g/kg.BW/d) in obese patients. (**Grade III, C2**)

Nutrition in the critically ill cirrhotic patient

In critically ill cirrhotic patients (patients hospitalized for severe complications of the disease, acute on chronic liver failure, patients in an intensive care unit, those with acute alcoholic hepatitis), maintenance of an adequate nutritional support is a relevant target. Direct measurement of REE by indirect calorimetry is advisable in these patients whenever possible. Of note, like in all critically ill patients, a tight glucose control is indicated to prevent hyper- and hypoglycemia (29, 113). Critically ill cirrhotic patients more frequently require to be supplied by enteral or parenteral nutrition. Nutritional guidelines exist, proposed by different medical societies, for patients with chronic liver disease in different settings (Supplementary Table 1).

Alcoholic liver disease and severe/acute alcoholic hepatitis

Nielsen *et al.* focused on patients with alcoholic cirrhosis and found a mean TEE of 32±7 kcal/kg.BW/d (70) and, in another study, a median TEE of 28 kcal/kg.BW/d (81), similar to that in patients with cirrhosis of different aetiologies. However patients with active alcohol abuse may have a higher REE than healthy controls (290) (291). An early study in alcoholic hepatitis showed that the intravenous addition of 70 to 85 g of amino acids to a diet containing 3000 kcal and 100 g of protein over 4 weeks, was safe and associated with a lower mortality rate (292). A low protein intake was also shown to worsen HE in 136 patients with alcoholic hepatitis and HE (293).

Two meta-analyses evaluated the impact of nutritional supplementation in patients with alcoholic liver disease (12, 112). The first included seven randomised controlled studies testing a nutritional oral or intravenous supplementation *vs.* a hospital diet in 262 patients, for 21 to 28 days. Nutritional support improved the resolution of clinical encephalopathy but did not influence mortality, ascites or laboratory parameters (112). The second included studies comparing PN, EN and ONS with no nutritional support (12). No benefits of nutritional support were observed but a trend towards a better nitrogen balance with PN was noted.

It was hypothesized that EN improves survival to the same extent as corticosteroids. One study found no difference in mortality in 71 patients with severe alcoholic hepatitis (71% with cirrhosis) randomised to prednisone or EN for 28 days (294). In another study, 136 patients with alcoholic hepatitis were randomised to methylprednisolone and EN or methylprednisolone with conventional nutrition. No difference in the 6-months mortality was observed but caloric intake lower than 21.5 kcal/kg.BW/d was associated with a higher mortality (295).

Immunonutrition

Immunonutrition, *i.e.* nutritional solutions enriched with ω−3 fatty acids, arginine and nucleotides, has been also proposed. One retrospective study examined patients undergoing elective liver resection, who received preoperative oral immunonutrition for seven days (n = 84; 14 patients with cirrhosis) *vs.* no oral supplementation (n = 63, 5 patients with cirrhosis). The authors found no impact on postoperative complications (296). When considering the components of immunonutrition separately, oral ω−3 fatty acids administered to cirrhotic patients with ascites and renal failure did not improve renal function but increased bleeding time and arterial blood pressure, leading the authors to argue against their use in cirrhotic patients (297).

Nutritional support in gastrointestinal bleeding

In a randomised study, 22 patients with liver cirrhosis were administered EN by a nasogastric tube or no oral intake during the first 4 days after acute bleeding from esophageal varices (298). No difference in re-bleeding, nutritional status, liver function, duration of hospital stay and mortality was observed between the groups after a follow-up of 35 days. Nevertheless, expert recommend to withhold enteral nutrition for 48–72 hours after

acute bleeding (299) (300) because EN increases the splanchnic blood flow, which in turn may increase portal pressure and risk of variceal re-bleeding.

Recommendations

- Consider nutritional status and presence of sarcopenia in all critically ill cirrhotic patients and provide nutritional support while treating other manifestations of severe decompensation. (**Grade II-3, C1**)
- Supplement dietary intake by enteral nutrition in critically ill cirrhotic patients who are unable to achieve adequate diet by mouth. If oral diet or enteral nutrition are not tolerated or contraindicated, consider parenteral nutrition. (**Grade III, A1**)
- Naso-gastroenteric tubes are not contraindicated in patients with non-bleeding esophageal varices. (**Grade II-2, A1**)
- Avoid PEG insertion in cirrhotic patients due to risk of bleeding. (**Grade III, B2**)
- Take care that daily energy intake in critically ill cirrhotic patients is not lower than the recommended 35–40 kcal/kg.BW/d or 1.3 times measured resting energy expenditure. (**Grade II-2, B1**)
- Take care that daily protein intake in critically ill cirrhotic patients is not lower than the recommended 1.2–1.3 g/kg.BW/d. (**Grade II-2, B1**)
- Utilise standard nutrition regimens since no advantage has been shown for specialised regimens (*e.g.* BCAA-enriched, immune-enhancing diets) in terms of morbidity or mortality. (**Grade II-1, B2**)
- In patients with HE, consider BCAA-enriched solutions to improve its resolution. (**Grade I, A1**)
- In cirrhosis and severe/acute alcoholic hepatitis, consider nutritional support as it may accelerate resolution of HE, and, improve survival in patients with low calorie intake. (**Grade II-1, A1**)

New research should answer the following topics

1. In the absence of indirect calorimetry, what is the best way to calculate energy needs in critically ill patients with liver diseases?
2. Does increased energy and protein intake improve outcome in critically ill patients with liver diseases?
3. Should the nutritional recommendations differ according to the nutritional status at baseline?

Conclusion

These practice guidelines have been produced with the aim of summarising the current knowledge in a field of clinical research which is the object of growing interest and is evolving rapidly. Nutritional impairment and sarcopenia have been recognized as a crucial

complication of chronic liver disease, which severely impinges on prognosis. Undernutrition and sarcopenia are also interconnected with other complications of cirrhosis such as HE, ascites and the susceptibility to infection. The molecular mechanisms underlying sarcopenia have been investigated in depth and clarified to some extent. At the same time, a novel condition has emerged, *i.e.* the occurrence of overweight and obesity in cirrhotic patients. This deserves both clinical attention and further study. Recent research has provided preliminary data on the potential benefit of physical activity in patients with cirrhosis. However, both the target population and the exact features of the activity (*i.e.* isometric *vs.* aerobic) need to be better defined.

While working on these guidelines the authors had to recognize that high quality studies in the field of nutrition in liver disease are often lacking. This is due to many reasons, including uncertainties in definitions, lack of standardized outcomes and scarcity of interventional studies. These require large, homogeneous groups of patients and long-term observation. In consequence, the available studies are often underpowered, and even meta-analyses have failed to reach definite conclusions. Thus in several instances the working panel produced recommendations, and sometimes even strong recommendations, despite the lack of high quality, specific evidence. These were based on the literature from parallel research and clinical fields, recommendations directed to the general population, standard practice, feasibility, costs and, ultimately, common sense. While lack of strong evidencerepresents a limitation, the present document reflects the actual situation of this clinical and research field, and it will hopefully serve as a basis for future studies providing better data to reinforce or modify current practices.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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BOX:

TERMINOLOGY UTILIZED

Malnutrition	A nutrition-related disorder resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass leading to diminish physical and mental function and impaired clinical outcome from disease. In the present CPGs, we have used “malnutrition” as a synonymous of “undernutrition”.
Undernutrition	Synonym of malnutrition (see above)
Muscle wasting	The active, progressive loss of muscle mass due to an underlying disease, ultimately leading to muscle atrophy. Most inflammatory diseases, malnutrition and increased catabolism induce muscle wasting.
Sarcopenia	A generalized reduction in muscle mass and function due to aging (primary sarcopenia), acute or chronic illness (secondary sarcopenia), including chronic liver disease.
Frailty	Loss of functional, cognitive, and physiologic reserve leading to a vulnerable state. Frailty may be considered a form of nutrition-related disorder
Immunonutrition	Use of specific nutrients in an attempt to modulate the immune system (not necessarily in the presence of malnutrition) and function to improve health state. Examples include enteral nutritional formulas enriched with ω−3 fatty acids, arginine, glutamine and nucleotides
Deconditioning	Deterioration of muscle functional capacity related to immobility and chronic debilitating disease

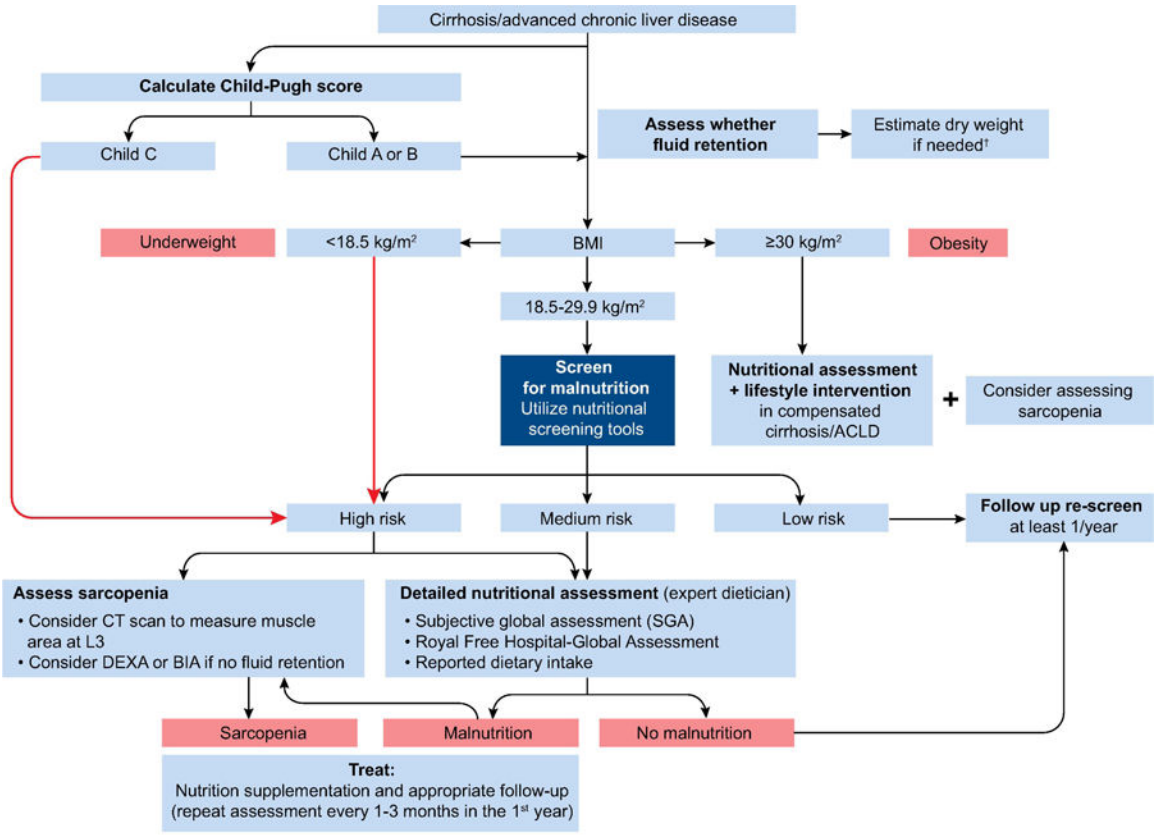

Figure 1. Nutritional screening and assessment in patients with cirrhosis.

All patients should undergo a rapid screening of malnutrition using validated, accepted tools. A liver specific screening tool which takes into consideration fluid retention may be advisable (Royal Free Hospital Nutritional Prioritizing Tool (RFH-NPT). Patients found to be at high risk of malnutrition should undergo a detailed nutritional assessment, and based on the findings they should receive either supplementation or regular follow-up. †In a case of fluid retention, body weight should be corrected by evaluating the patient's dry weight by post-paracentesis body weight or weight recorded before fluid retention if available, or by subtracting a percentage of weight based upon severity of ascites (mild, 5%; moderate, 10%; severe, 15%), with an additional 5% subtracted if bilateral pedal edema is present.

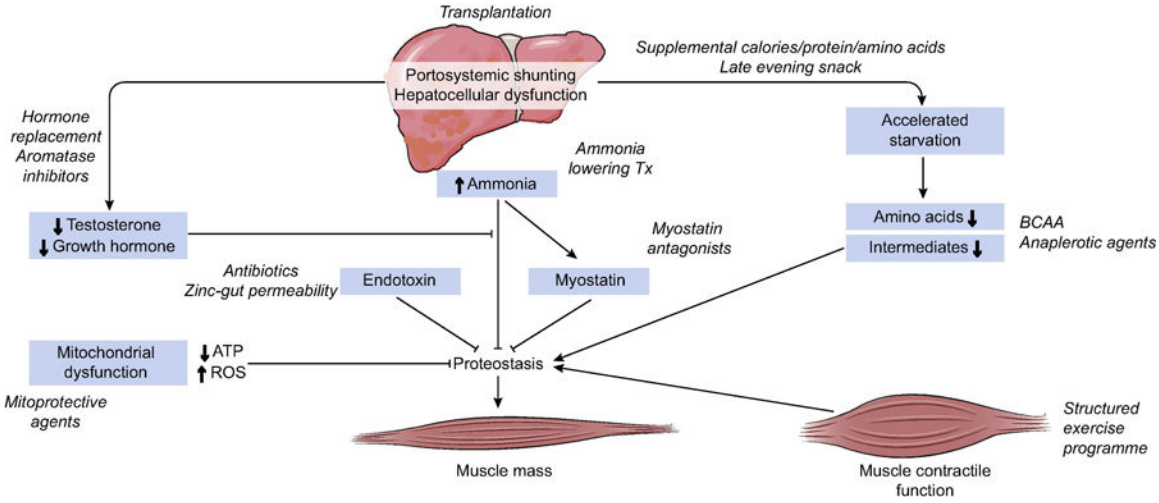

Figure 2. Mechanisms and potential targets for anabolic resistance and dysregulated proteostasis resulting in sarcopenia and/or failure to respond to standard supplementation.

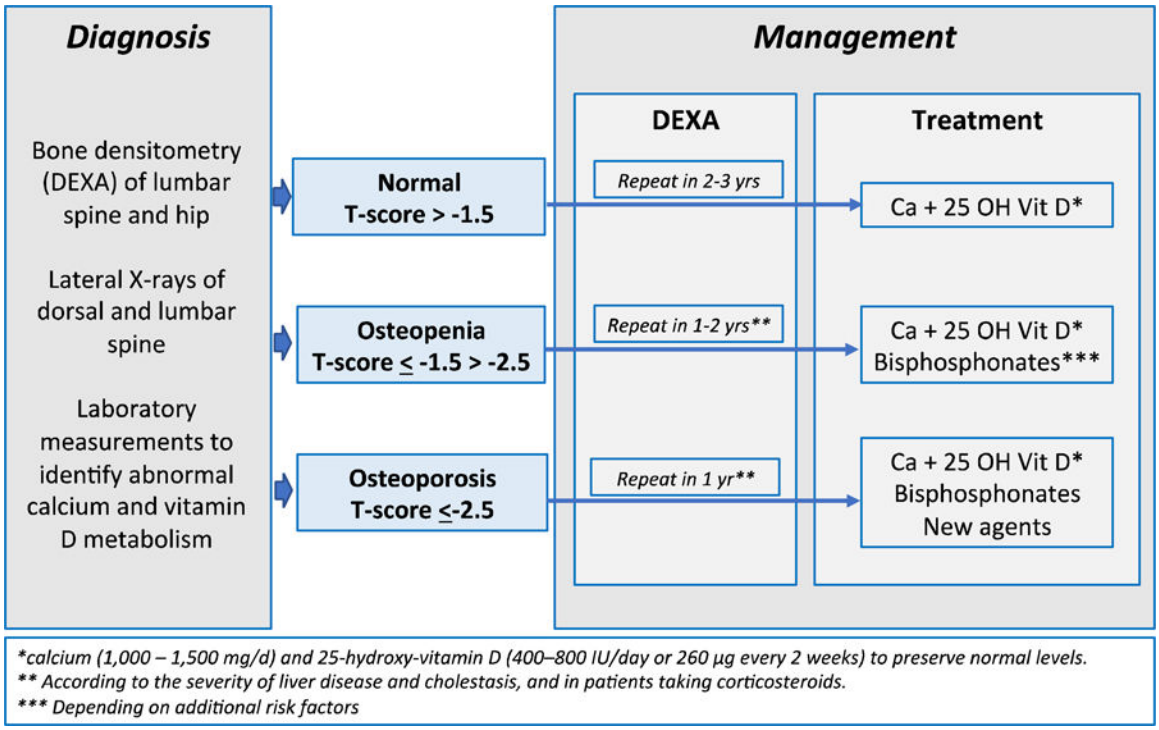

Figure 3. Diagnosis and management of bone disease in patients with chronic liver disease.

Table 1.

Evidence quality according to the GRADE scoring system.

Grade	Evidence	
I	Randomized, controlled trials	
II-1	Controlled trials without randomization	
II-2	Cohort or case-control analytic studies	
II-3	Multiple time series, dramatic uncontrolled experiments	
III	Opinions of respected authorities, descriptive epidemiology	
Evidence (quality)	**Description**	
High	Further research is very unlikely to change our confidence in the estimated effect	**A**
Moderate	Further research is likely to have an important impact on our confidence in the estimate effect and may change the estimate	**B**
Low	Further research is likely to have an important impact on our confidence in the estimate effect and is likely to change the estimate. Any change of estimate is uncertain	**C**
Recommendation		
Strong	Factors influencing the strength of recommendation included the quality of evidence, presumed patient-important outcomes, and costs	**1**
Weak	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher costs, or resource consumption	**2**

Table 2

Short, practical dietary advice for bedside or outpatient clinic use.

● Most of what you have heard/read on the relationship between food and the liver has limited scientific evidence to support it. Generally, healthy eating of a variety of foods is advisable to all patients.
● Virtually no food other than alcohol does actually damage the liver and/or is genuinely contraindicated in patients with chronic liver disease.
● In most patients with chronic liver disease, eating an adequate amount of calories and protein is much more important than avoiding specific types of food, so it is important that you have a good, varied diet that you enjoy.
● You should try to split your food intake into 3 main meals (breakfast, lunch and dinner) and 3 snacks (mid-morning, mid-afternoon, late evening). The late-evening snack is the most important, as it covers the long interval between dinner and breakfast.
● You should try to eat as much vegetables and fruit as you can. If you feel that this makes you feel bloated, and that it makes you eat less, please report to your doctor or dietician.
● You should try not to add too much salt to your food. It may take some time to adjust, but it usually gets easier with time. However, if you keep feeling that this makes your food unpleasant to eat, and that it makes you eat less, please report to your doctor or dietician.
● A limited proportion of patents with liver disease have a complication called hepatic encephalopathy, which may make them tolerate animal protein (meat) less well than vegetable protein (beans, peas etc) and dairy proteins. Before you make any changes to your protein intake, you should always ask your doctor or dietician. Please do not reduce your total protein intake as it is not advisable in cirrhosis.
● Some patients with liver disease have other diseases, for example diabetes or overweight/obesity, which require dietary adjustments. Please remember to tell your doctor about all your illnesses and about any dietary advice you have already received from other doctors, nurses or dieticians.

Table 3.

Risk factors for the development of osteoporosis in chronic liver disease.

● alcohol abuse
● smoking
● body mass index lower than 19 Kg/m^2
● male hypogonadism
● early menopause
● secondary amenorrhea of more than 6 months
● family history of osteoporotic fracture
● treatment with corticosteroids (5 mg/d or more of prednisone for 3 months or longer)
● advanced age