Nutritional support in liver disease

Module 13.2

Nutritional support in chronic liver disease

Learning Objectives:

To know:
- the pathophysiology and consequences of malnutrition in cirrhosis of the liver;
- how to diagnose malnutrition in cirrhosis;
- how to treat malnutrition in cirrhosis;

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Key Messages:

- Expect severe malnutrition requiring immediate treatment;
- Protein malnutrition and hypermetabolism are associated with a poor prognosis;
- Ensure adequate energy intake (total energy 30-35 kcal kgBW\(^{-1}\) d\(^{-1}\); non-protein energy 25 kcal kgBW\(^{-1}\) d\(^{-1}\));
- Use indirect calorimetry if available;
- Provide enough protein (1.2 - 1.5 g kgBW\(^{-1}\) d\(^{-1}\));
- Use BCAA after gastrointestinal bleeding and in hepatic encephalopathy grades III\(^{o}\)/IV\(^{o}\);
- Use fat as fuel (recommended fatty acid ratio n6:n3 = 2:1);
- Use enteral tube or sip feeding;
- Use parenteral nutrition if enteral feeding alone is not sufficient;
- Avoid refeeding syndrome and vitamin/trace element deficiencies.

1. Introduction

Nutrition has long been recognized as a prognostic and therapeutic determinant in patients with chronic liver disease [1] and was therefore included as one of the variables in the original prognostic score introduced by Child & Turcotte [2]. Yet, not all hepatologists consider nutrition issues in the management of their patients. In this module the scientific and evidence base for nutritional management of patients with liver disease is reviewed to give recommendations for nutrition therapy.

2. Nutritional risk in liver disease patients

Understanding adequate nutrition requires its recognition as a complex action which in healthy organisms is regulated in a condition adapted way. Accordingly, the assessment of the nutritional risk of patients must include variables indicative of the physiologic capabilities – the nutritional status – and the burden inflicted by the ongoing or impending disease and/or medical interventions. Thus, a meaningful assessment of nutritional status should encompass not only body weight and height, but information on energy and nutrient balance as well as body composition and tissue function, reflecting the metabolic and physical fitness of the patient facing a vital contest. Furthermore, such information can best be interpreted only when available with a dynamic view (e.g. weight loss per time).

Numerous descriptive studies have shown higher rates of mortality and complications, such as refractory ascites, variceal bleeding, infection, and hepatic encephalopathy (HE) in cirrhotic patients with protein malnutrition, as well as reduced survival when such patients undergo liver transplantation [3-11]. In malnourished cirrhotic patients, the risk of postoperative morbidity and mortality is increased after abdominal surgery (12,13). The identification of patients with liver disease who are at risk of malnutrition is therefore important, and the NRS-2002 is a validated and ESPEN-recommended screening tool that is very suitable for this purpose (14).

In cirrhosis or alcoholic steatohepatitis (ASH), poor oral food intake is a predictor of increased mortality. In nutrition intervention trials, patients with the lowest spontaneous energy intake showed the highest mortality (15-21). In clinical practice, the plate protocol of Nutrition Day (22) is an easy to use and reliable tool to assess food intake in hospitalized patients. For more detailed analyses, dietary intake should be assessed by a skilled dietitian, and a three day dietary recall can be used in outpatients. Appropriate tables for food composition should be used for the calculation of proportions of different nutrients. As a gold standard, food analysis by bomb calorimetry may be utilized (19,23).
Simple bedside methods like the “Subjective Global Assessment” (SGA) or anthropometry have been shown to identify malnutrition adequately (4,6,11). Composite scoring systems have been developed based on variables such as actual/ideal weight, anthropometry, creatinine index, visceral proteins, absolute lymphocyte count, delayed type skin reaction, absolute CD8+ count, and hand grip strength (15-17). Such systems, however, include unreliable variables such as plasma concentrations of visceral proteins or 24-h urine creatinine excretion and do not confer an advantage over SGA.

Accurate measurement of nutritional status is difficult in the presence of fluid overload or impaired hepatic protein synthesis (e.g. albumin) and necessitates sophisticated methods such as total body potassium counting, dual energy X-ray absorptiometry (DEXA), in vivo neutron activation analysis (IVNAA) (24,25) and isotope dilution. Among bedside methods the measurement of phase angle alpha or determination of body cell mass (BCM) using bioimpedance analysis is considered superior to methods such as anthropometry and 24-h creatinine excretion (26-28), despite some limitations in patients with ascites (29,30).

Muscle function is reduced in malnourished chronic liver disease patients (25,31,32) and, as monitored by handgrip strength, is an independent predictor of outcome (17,33). Plasma levels of visceral proteins (albumin, prealbumin, retinol-binding protein) are however highly influenced by liver synthesis, alcohol intake or acute inflammatory conditions (34,35).

Immune status, which is often considered a functional test of malnutrition, may be affected by hypersplenism, abnormal immunologic reactivity and alcohol abuse (35).

3. Effect of nutritional state on liver disease

**Undernutrition.** Severe malnutrition in children can cause fatty liver (36-38) which in general is fully reversible upon refeeding (38). In children with kwashiorkor, there seems to be a maladaptation associated with less efficient breakdown of fat and oxidation of fatty acids (39,40) than is seen in children with marasmus. Impairment of fatty acid removal from the liver could not however be observed (41). Malnutrition impairs specific hepatic functions like phase-I xenobiotic metabolism (42,43), galactose elimination capacity (44) and the plasma levels of C-reactive protein in infected children (45,46). In nutritional intervention trials in cirrhotic patients, quantitative liver function tests improved more, or more rapidly in treatment groups. These included antipyrine (20), aminopyrine (47), and ICG clearance (48), as well as galactose elimination capacity (49,50). It is unknown whether the fatty liver of malnutrition can progress to chronic liver disease.

Quantitative liver function tests seem to be useful for monitoring the effects of nutritional intervention on liver function. They are not useful, however, for identification of patients who will benefit from nutritional intervention, since none of the tests can distinguish between reduced liver function due to reduced hepatocellular mass and liver function which is diminished due to a lack of essential nutrients. A simple test is needed that can distinguish between these two alternatives, (in analogy to the i.v. vitamin K test), in order to estimate the potential benefit of nutritional support in individual patients.

**Overnutrition.** In obese humans subjected to total starvation, weight reducing diets or small-bowel bypass, the development of transient degenerative changes with focal necrosis was described nearly four decades ago (51). Non-alcoholic steatohepatitis (NASH) was initially described in weight losing individuals (52) and, to date, insulin resistance and obesity are the most common causes (53). It is estimated that in Europe 20% of the population with moderate or no alcohol consumption have non-alcoholic fatty liver (NAFL), of whom 20% progress from NAFL to NASH (54). Analyses of dietary habits in NASH patients do not show a uniform pattern. Increased consumption of fat and n-6 fatty acids (55,56) and increased consumption of carbohydrate and energy (57) have been observed. Body mass index and total body fat are predictors for the presence of NASH in the obese (55,58); in patients undergoing bariatric surgery the prevalence of NASH is 37% (24% - 98%) (59).
Furthermore, the key role of obesity is illustrated by the observation that weight reduction regardless of whether it is achieved by dietary counselling, bariatric surgery or drug treatment has the potential to ameliorate or even cure NASH (60-64).

4. Effect of chronic liver disease on nutritional state

**Cirrhosis.** Mixed type protein energy malnutrition with coexisting features of kwashiorkor-like malnutrition and marasmus is commonly observed in patients with cirrhosis (65,66). The prevalence and severity of malnutrition are related to the clinical stage of chronic liver disease, increasing from 20% of patients with well-compensated disease up to more than 60% of patients with severe liver insufficiency (67). Patients with cirrhosis frequently suffer from substantial protein depletion and the resulting sarcopenia is associated with impaired muscle function (25) and survival (6). Recovery from this loss in body cell mass can be achieved by the control of complications (such as portal hypertension) and adequate nutrition (68,69). The aetiology of liver disease per se does not seem to influence the prevalence and degree of malnutrition and protein depletion (25,66,67) and the higher prevalence and more profound degree of malnutrition in alcoholics result from an unhealthy life style and poor socio-economic conditions.

In hospitalized cirrhotics, fatigue, somnolence, or psychomotor dysfunction often lead to insufficient oral nutrition even in the absence of overt HE (70,71). The liver plays a role in normal appetite regulation and liver disease may impair food intake e.g. by reduced clearance of satiation mediators such as cholecystokinin or by splanchnic production of cytokines which impair hypothalamic appetite stimulation (71). Moreover, taste acuity and thresholds for salty, sweet and sour taste are impaired (72), and these disturbances can be aggravated further by hypomagnesaemia. In addition, the mechanical effect of ascites and intestinal oedema may cause a sensation of abdominal fullness and early satiety.

Fat malabsorption and steatorrhoea occur in cholestatic liver disease, such as primary biliary cirrhosis and cystic fibrosis, leading to severe malabsorption of dietary fat as well as of fat-soluble vitamins. Other than in cholestatic liver disease neither fat nor protein are malabsorbed (73,74) and faecal energy excretion is found to be normal (23). Upon administration of lactulose, however, faecal mass and nitrogen increase, most likely due to increased bacterial protein synthesis (74). Likewise, use of a high-fibre vegetable diet for the treatment of hepatic encephalopathy is associated with an increased faecal nitrogen loss (75).

**Surgery & Transplantation.** A large number of patients, in whom normal liver function has been restored by liver transplantation show an enormous weight gain in the first year after surgery (76,77) and, unfortunately, a considerable number put their regained health in jeopardy by the development of full blown metabolic syndrome (78). In the first year after transplantation patients expand their body fat mass while there is no gain in lean body mass (76,79) and there is persisting impairment of non-oxidative glucose disposal in skeletal muscle (80,81). There is growing evidence that in solid organ-transplanted patients skeletal muscle deconditioning persists from the time of decreased physical performance prior to transplantation (32,82-84). This should be addressed by appropriate comprehensive rehabilitation programmes including physiotherapy. Taken together, these observations indicate that upon restoration of hepatic function and cessation of portal hypertension full nutritional rehabilitation is possible.
5. Pathophysiology and nutrient requirements in chronic liver disease

5.1. Energy

5.1.1. Cirrhosis

On average the measured REE is of the same magnitude as energy expenditure predicted by use of formulae (Harris & Benedict, Schofield, etc.) (85-87). Likewise, in alcoholic steatohepatitis (ASH) patients one study showed the same relationship between measured REE and predicted REE as in healthy individuals (88). However, whenever available, indirect calorimetry should be used to measure REE, since in the individual patient the measured REE may differ considerably from estimated values (89). The question of hypermetabolism has been addressed in cirrhosis and ASH patients. ASH patients may be considered hypermetabolic when their measured REE is disproportionate to their reduced muscle mass (88). Measured REE is higher than predicted in up to 35% of cirrhotic patients (hypermetabolism), and below the predicted value in 18% of the patients (85-87). In cirrhosis, hypermetabolism has been shown to be associated with reduced event-free survival and unfavourable outcome after transplantation (10,87); it seems to regress with improvement of body composition (68) and after liver transplantation (90). For the formal diagnosis of hypermetabolism, however, indirect calorimetry is required: in daily practice most clinicians cannot use this approach.

Measurements of total energy expenditure indicate that the 24 h energy requirement of cirrhotic patients amounts to about 130% of their basal metabolic rate (23,91). Diet-induced thermogenesis (92-94) and the energy cost of defined physical activity in stable cirrhosis (95-97) also show no deviation from values obtained in the healthy. However, the spontaneous physical activity level is considerably lower in patients with cirrhosis. Obviously, the increased energy requirement in advanced illness is balanced by diminished physical activity reflecting the poor physical condition (21,97).

In cirrhotics without ascites the actual body weight should be used for the calculation of the basal metabolic rate when using formulae such as that proposed by Harris & Benedict. In patients with ascites the ideal weight according to body height should be used, despite the suggestion from a series of 10 patients with liver cirrhosis of whom only 4 were completely evaluated (98), that ascites mass should not be omitted when calculating energy expenditure by use of body weight.

5.1.2. Surgery & Transplantation

On average liver transplant patients have the same energy requirements as other patients undergoing major abdominal surgery. In general, non-protein energy provision of 1.3 x REE is sufficient (99,100). In a longitudinal study, postoperative hypermetabolism peaked on day 10 after the transplantation at 124% of the predicted REE (79). By 6 to 12 months after transplant there was no longer a difference between the measured and predicted REE (79,101).

5.2. Carbohydrate metabolism

5.2.1. Cirrhosis

The utilisation of oxidative fuels is characterized by an increased rate of lipid oxidation in the fasting state and the frequent occurrence of insulin resistance (even in Child-Pugh class A patients) (85,102-104). In the post-absorptive state, glucose oxidation rate is reduced and
hepatic glucose production rate is low despite increased gluconeogenesis due to a depletion of hepatic glycogen (105). Insulin resistance affects skeletal muscle metabolism: glucose uptake and non-oxidative glucose disposal such as glycogen synthesis are reduced, while glucose oxidation and lactate production are normal after glucose provision (80,93,105). It is not known to what extent glucose deposition as glycogen is impaired just in skeletal muscle or in both muscle and liver (106,107). Some 15–37% of patients develop overt diabetes, indicating an unfavourable prognosis (108,109).

5.2.2. Surgery & Transplantation

In the early postoperative phase there is often a disturbance of glucose metabolism associated with insulin resistance. In this situation hyperglycaemia should be managed by reducing glucose intake because higher insulin doses are unable to increase glucose oxidation (110).

5.3. Fat Metabolism

5.3.1. Cirrhosis

In the fasting state, the plasma levels of free fatty acids, glycerol, and ketone bodies are increased and free fatty acid and glycerol concentrations do not fully respond to low insulin infusion rates as they would in healthy subjects (111). Lipids are oxidized as the preferential substrate and lipolysis is increased with active mobilisation of lipid deposits (102,104). There is insulin resistance with regard to the antilipolytic activity. After a meal, the suppression of lipid oxidation is not uniformly impaired (94,112). Plasma clearance and lipid oxidation rates are not reduced, and thus the net capacity to utilize exogenous fat does not seem to be impaired (113,114). Essential and polyunsaturated fatty acids are decreased in cirrhosis and this decrement correlates with nutritional status and severity of liver disease (115,116).

5.4. Protein and amino acid metabolism

5.4.1. Cirrhosis

Protein turnover in cirrhotic patients has been found to be normal or increased. Some authors focused mainly on the presence of increased protein breakdown, while others suggest that reduced protein synthesis plays the main role (117). Albumin but not fibrinogen synthesis rates correlate with quantitative liver function tests and clinical stages of cirrhosis (118,119). Nevertheless, stable cirrhotics are apparently capable of efficient nitrogen retention and significant formation of lean body mass from increased protein intake during oral refeeding (23). Protein catabolism influences the amino acid imbalance of cirrhosis and indirectly causes nitrogen overload to the liver leading to hyperammonaemia (120-122). In cirrhotics, after an overnight fast glycogen stores are depleted and metabolic conditions are similar to prolonged starvation in healthy individuals. It has been shown that a late evening carbohydrate snack was associated with improved protein metabolism in cirrhotic patients (123-125). Insulin resistance apparently is without effect on amino acid disposal (126). An explicit and systematic determination of the protein requirement of patients with liver cirrhosis has been carried out in only a few studies. Patients with stable cirrhosis were found to have an increased protein requirement leading to the recommendation of 1.2 g·kgBW⁻¹·d⁻¹ contrasting with the recommended minimal intake of 0.8 g·kgBW⁻¹·d⁻¹ in healthy humans (21,23,44,127). Cirrhotic patients exhibit an altered pattern of plasma amino acids characterized by the elevation of aromatic (phenylalanine, tyrosine) and sulphur-containing
amino acids (methionine) and tryptophan on the one hand, and the decrease in BCAA (leucine, isoleucine, valine) on the other (128,129). Decreased metabolic clearance (130) by the failing liver of aromatic and sulphurous amino acids and increased breakdown in skeletal muscle of BCAA due to portal systemic shunting (131) and hyperammonaemia (120,132-134) are discussed as causal. Recently, it has been pointed out that, due to the absence of isoleucine from haemoglobin, blood is a protein source of low biologic value leading to BCAA antagonism after upper gastrointestinal haemorrhage (135). This BCAA antagonism readily explains the long known clinical observation that blood and vegetable protein represent the two extremes in the hierarchy of food proteins regarding their potential to induce coma. Moreover, this antagonism leading to hyperammonaemia could be overcome by the infusion of isoleucine alone (136).

5.4.2. Surgery & Transplantation

After transplantation there is a considerable nitrogen loss and patients remain in negative nitrogen balance for up to 28 days (79,99,137) necessitating an increase in the provision of protein or amino acids.

5.5. Vitamins and minerals

No recommendation on the requirement of micronutrients can be made on the basis of controlled studies. As in other diseases, the administration of micronutrients has no proven therapeutic effect apart from the prevention or correction of deficiency states.

The altered body composition of cirrhosis with protein depletion and overhydration (24,25) goes hand-in-hand with salt retention, which therefore does not usually lead to hypernatraemia. On the contrary, depletion of potassium, magnesium, phosphate and other intracellular minerals is frequent.

Zinc and selenium deficiencies have been observed in alcoholic and non-alcoholic liver disease (138-141). An impressive association between HE and zinc deficiency has been described in case reports (142,143). A deficiency in water-soluble vitamins, mainly group B vitamins, is common in cirrhosis, especially that of alcoholic origin (144,145). Deficiency in fat-soluble vitamins has been observed in cholestasis-related steatorrhoea, bile salt deficiency, and in alcoholics (146,147).

Patients with hypophosphataemia after acetaminophen-induced liver damage have a better prognosis. Severe hypophosphataemia, however, results in respiratory insufficiency and dysfunction of the nervous system and erythrocytes (148), and thus, serum phosphate levels should be monitored and corrected in order to support liver regeneration.

6. Disease Specific Nutrition Therapy

6.1. Alcoholic Steatohepatitis (ASH)

Supplementary enteral nutrition is indicated when ASH patients cannot meet their caloric requirements through normal food and when there are no contraindications such as ileus. Clinical trials (15-18,149,150) in ASH patients show, that supplementary enteral nutrition either by oral nutritional supplement or by tube feeding ensures adequate energy and protein intake without the risk of complications such as HE. Enteral nutrition appears preferable to parenteral nutrition but there has been no large randomised trial comparing the feeding regimens in ASH patients.

Enteral nutrition was as effective as prednisolone in patients with severe alcoholic hepatitis. Survivors of the 28-day treatment period who had been treated with enteral nutrition
showed a lower mortality rate in the following year (150). Severely malnourished ASH patients who achieve an adequate intake of oral nutrition supplements have an improved survival, regardless of whether additional anabolic steroids are used or not (16). Malnourished ASH patients are at great risk of developing refeeding syndrome and additional phosphate, potassium and magnesium will be required, together with water-soluble vitamins.

In general, oral nutrition supplements are recommended, but if patients are not able to maintain adequate oral intake, tube feeding should be used. There is no evidence that the use of fine bore nasogastric tubes poses an undue risk in patients with oesophageal varices (19,20,151). Placement of a PEG is associated with a higher risk of complications (due to ascites or varices) and is not recommended (152).

As a standard approach standard whole protein formulae should be used aiming for a total energy intake of 30-35 kcal·kgBW\(^{-1}\)·d\(^{-1}\) and a protein intake of 1.2-1.5 g·kgBW\(^{-1}\)·d\(^{-1}\) (152-154). Formulae with high energy density (1.5–2.4 kcal·ml\(^{-1}\)) are preferable in patients with ascites to avoid positive fluid balance. When patients develop HE during enteral nutrition BCAA-enriched formulae should be used (152). A direct comparison between standard formula and BCAA-enriched formula has not yet been made in ASH patients. It should be kept in mind that in ASH patients as in cirrhotics, a low protein intake can worsen HE (20,155).

Parenteral nutrition should be commenced immediately in ASH patients with moderate or severe malnutrition who cannot be fed sufficiently either orally or enterally. Parenteral nutrition supplemental to oral nutrition ad libitum did not improve survival but did not negatively affect mental state (48-50,149,156-159). Parenteral nutrition should be formulated and administered as in cirrhotic patients (cf 6.3). All water-soluble vitamins, in particular thiamine (vitamin B\(_1\)), pyridoxine (vitamin B\(_6\)), nicotinamide (vitamin PP) and folic acid, and the fat-soluble vitamins should be administered daily in a standard PN dosage. Due to the high risk of Wernicke's encephalopathy, vitamin B\(_1\) must be administered prior to starting i.v. glucose in alcoholic patients. Recently, high doses for both prophylaxis (250 mg i.m. daily for three to five days) and treatment (500 mg i.v. t.i.d. for two to three days) of Wernicke's encephalopathy have been advocated (160). In jaundiced patients vitamin K deficiency due to cholestasis-induced fat malabsorption may require i.v. vitamin K for correction.

6.2. Non-alcoholic steatohepatitis (NASH)

In overweight individuals with NASH, weight reduction is the key to the successful treatment of the NASH. The histopathological changes of NASH can be ameliorated or even fully reversed by weight reduction regardless of whether it is achieved by dietary counselling (60), bariatric surgery (61-63), or inhibition of intestinal fat absorption by orlistat (64). Likewise, insulin resistance (60,64) and lipid metabolism (60,63) can be improved. When targeting insulin resistance by use of insulin-sensitizing drugs like pioglitazone or rosiglitazone, the beneficial effects on liver histology (161,162) seem to be offset by a considerable gain in body weight and body fat mass (161,163).

Taken altogether, overweight NASH patients benefit from effective long-term weight reduction regardless of the therapeutic strategy implemented.

6.3. Cirrhosis

In patients with cirrhosis the primary goal is to ensure a quantitatively adequate nutrient intake (17-20,164-166). Increasing protein intake by nutrition therapy can decrease mortality (20), and adequate nutrition after successful treatment of portal hypertension by transjugular intrahepatic portosystemic stent-shunt (TIPS) has the potential to improve body composition (68,69).

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Regarding the method of nutritional intervention, nutritional counselling alone (164) or in combination with oral nutrition supplements (17,18,166) will often prove successful. Supplemental enteral nutrition should be given when patients with cirrhosis cannot meet their nutritional requirements from normal food despite adequate individualized nutritional counselling. Very often, the spontaneous food intake of these patients is overestimated and the opportunity for therapeutic gain (19,20,70,71) by the timely use of tube feeding is missed. Due to somnolence and psychomotor dysfunction oral nutrition is often insufficient even when there is no or mild HE (I°-II°) (70,71). Therefore, tube feeding may be required to ensure adequate nutrient provision. The risk of aspiration in uncooperative patients and those with advanced HE should be considered when deciding on whether to feed by the enteral or the parenteral route. As already discussed for ASH patients (cf 6.2.), tube feeding is not contraindicated in the presence of oesophageal varices but the use of PEGs in cirrhotics is discouraged. Ascites, impairment of the coagulation system, and the presence of a porto-systemic collateral circulation due to portal hypertension have been reported as contraindications to PEG placement (167).

Cirrhotic patients should achieve a total energy intake of 30-35 kcal·kgBW⁻¹·d⁻¹ and a protein intake of 1.2-1.5 g·kgBW⁻¹·d⁻¹ (152-154) using a standard whole protein formula. The appropriateness of this recommendation has been tested recently. Diets containing 1.2 g·kgBW⁻¹·d⁻¹ protein could safely be administered to patients with cirrhosis suffering from episodic HE and – even transient – protein restriction did not confer any benefit to patients during an episode of encephalopathy (168). Patients with cirrhosis suffer from a depletion of hepatic glycogen stores and thus are less prepared to master periods of even short-term food deprivation adequately. A late evening carbohydrate snack can improve protein metabolism in cirrhotics (123-125) Recently, it has been shown that nocturnal oral supplements, (i.e. ones given after 21:00h), are more efficient in improving the total body protein status of cirrhotic patients than isonitrogenous and isocaloric amounts given during daytime (169).

In stable cirrhotics formulae enriched in BCAA are not necessary. Such formulae are helpful in the very select subgroup of protein intolerant patients with HE (170). In stable patients with cirrhosis long-term (12 and 24 months) nutritional supplementation with oral BCAA granulate given as an oral nutrition supplement has the potential to slow the progression of hepatic failure and prolong event-free survival (171-173), but this treatment is not reimbursed in many countries. When patients develop HE during enteral nutrition BCAA-enriched formulae should be used (152).

Regarding trace elements and vitamins, in a pragmatic approach, liberal supplementation is recommended in the first two weeks of nutritional support, because the laboratory diagnosis of a specific deficiency may be more costly, and would delay provision. Oral zinc supplementation as a treatment of HE has been disappointing in controlled trials (174-176), despite encouraging case reports (142,143). Urea production capacity increased after oral zinc application when previously subnormal plasma levels were normalised (177). Supplementing zinc and vitamin A may indirectly improve food intake and nutritional state by improving dysgeusia (178,179). Supplementation with calcium and vitamin D is recommended for patients with osteopenia, although this did not result in any improvement in bone density in patients with primary biliary cirrhosis; oestrogen substitution proved to be much more effective in female patients (146,147,180). Vitamin B₁ must be provided to all patients with alcoholic liver disease before providing glucose as outlined in section 6.2. Parenteral nutrition is a valuable second line option and must be implemented immediately when moderately or severely malnourished cirrhotics cannot be nourished sufficiently by either oral or enteral route. Parenteral nutrition should be considered in patients with unprotected airways and advanced HE when swallow and cough reflexes are compromised. In analogy to the observations regarding the benefit of nocturnal oral supplements every patient with cirrhosis who needs to be managed nil by mouth for more than 12 hours (including nocturnal fasting!) should be given i.v. glucose at 2 - 3 g·kgBW⁻¹·d⁻¹ as the
minimum metabolic intervention. When this fasting period lasts longer than 72 h TPN should be implemented and, as an intermediary measure, hypocaloric peripheral parenteral nutrition may be used when fasting periods are expected to last for less than 72 h (154).

If parenteral nutrition is used as the exclusive form of nutrition, then the i.v. provision of all macro- and micronutrients must be ensured from the beginning of TPN. Carbohydrate should be given as glucose to cover 50-60% of non-protein energy requirements (30 kcal·kgBW⁻¹·d⁻¹). Ensuring euglycaemia has been shown to confer a survival and morbidity benefit to critically ill patients regardless of aetiology. Great care, however, must be taken to avoid hypoglycaemia. In case of hyperglycaemia glucose infusion should be reduced to 2-3 g·kgBW⁻¹·d⁻¹ and i.v. insulin infusion should be used.

The simultaneous infusion of lipid and glucose provides a better metabolic profile than glucose alone (181). Plasma clearance and oxidation of infused lipids are normal in cirrhosis patients (113,114). Regarding the optimal composition of i.v. oxidative fuels, only limited information is available (182,183). The ESPEN guidelines recommend fat provision to cover 40-50% of non-protein energy requirements using emulsions with a content of n-6 unsaturated fatty acids lower than in traditional pure soy bean oil emulsions (154). Compared to the traditional soy bean based long-chain triglyceride (LCT) emulsions (n-6:n-3 = 8:1), newer fat emulsions have a lower content of n-6 unsaturated fatty acids due to the admixture of medium-chain triglycerides (MCT) and/or olive oil and/or fish oil rendering them less suppressive to leukocyte and immune function and less stimulant of pro-inflammatory modulators (184-188).

The infusion of amino acids should provide an amount of 1.2 g·kgBW⁻¹·d⁻¹ in compensated cirrhosis without malnutrition and 1.5 g·kgBW⁻¹·d⁻¹ in decompensated cirrhosis with severe malnutrition. In clinical trials, studying patients with liver cirrhosis and severe HE the provision of protein or amino acids ranged from 0.6 to 1.2 g·kgBW⁻¹·d⁻¹ (189). In patients with alcoholic hepatitis or alcoholic cirrhosis with or without low-grade HE the provision ranged from 0.5 to 1.6 g·kgBW⁻¹·d⁻¹ (18-20,49,50,156-159,190). For parenteral nutrition in compensated cirrhosis amino acid solutions with a special "hepatic formula" composition are not required.

For parenteral nutrition of cirrhotics with overt HE amino acid solutions with a special "hepatic formula" high in BCAA (35–45%) but low in tryptophan, aromatic and sulphur-containing amino acids were developed (191-193). Such solutions help to correct the amino acid imbalance in liver cirrhosis. The efficacy of BCAAs in the treatment of hepatic encephalopathy has been studied (182,183,194-198) and a meta-analysis showed an improvement in mental state by the BCAA-enriched solutions, but no definite benefit in survival (189). Hepatic encephalopathy of cirrhotic patients, however, is precipitated by serious and life-threatening complications such as infection or haemorrhage which are more potent determinants of survival than HE. Therefore, it is not surprising that BCAA-based parenteral nutrition failed to improve short-term survival. Likewise, in a Cochrane analysis of seven randomised controlled trials studying 397 patients with acute HE, the parenteral BCAA administration had a significant, positive effect on the course of HE, but not on survival (199). A BCAA-enriched complete amino acid solution should be given in more severe HE (III° - IV°).

Blood from gastrointestinal haemorrhage is a protein source of low biologic value leading to BCAA antagonism (135). This antagonism leads to hyperammonaemia but HE can be overcome by the infusion of isoleucine on its own (136). Isoleucine solutions for i.v. infusions, however, are not commercially available, but the special hepatic formula amino acid solutions (c.f. above) contain high amounts of isoleucine and of the other BCAAs, leucine and valine.

For parenteral nutrition, water, electrolytes, water- and fat-soluble vitamins and trace elements should be given daily in order to cover daily requirements. Trace elements should be administered daily in a standard PN dose. In a pragmatic approach routine administration of twice the normal daily requirement of zinc (= 2 x 5 mg·d⁻¹) is
recommended. Malnourished cirrhotic patients are in danger of developing refeeding syndrome and additional phosphate, potassium and magnesium may be required (154).

6.4. Perioperative Nutrition

Nutrition therapy prior to elective surgery should be managed according to the recommendations given for the underlying disease which most likely is cirrhosis in the majority of cases. Cirrhotic patients have a reduced rate of complications and an improved nitrogen economy after abdominal surgery if they receive nutritional support instead of just fluid and electrolytes (200-202). It may safely be assumed that enteral nutrition in the early postoperative period yields even better results; however no studies have compared the two regimens in cirrhosis. A beneficial effect on gut permeability of sequential parenteral/enteral nutrition (via jejunostomy) as compared to parenteral nutrition alone or no postoperative nutrition has been reported (202). Cirrhotic patients should receive early postoperative (additional) parenteral nutrition after surgery if they cannot be nourished sufficiently by the oral/enteral route. In cirrhotic patients undergoing liver resection, oesophageal transection and splenectomy or splenorenal shunt, the rate of HE was not increased when a conventional rather than a BCAA-enriched amino acid solution was used (201).

6.2.5. Liver transplantation

Although the prognostic relevance of undernutrition in transplant candidates is well recognized, it has not yet been shown that preoperative nutritional intervention improves clinically relevant outcomes. However, nutritional therapy in undernourished cirrhotic patients is clearly indicated as outlined above. In the only randomized trial addressing this question there was no advantage of oral nutrition supplements over nutritional counselling and normal food in adults (164). Since normal food and nutritional counselling lead to the same adequate intake as when oral nutrition supplements are added, both regimens are considered similarly effective. Paediatric transplant patients with predominantly cholestatic liver disease show a better increase in body cell mass if they receive BCAA-enriched formula (203).

After liver transplantation, normal food and/or enteral nutrition should be initiated within 12-24 hours postoperatively in order to achieve lower rates of morbidity and complications and cost than during parenteral nutrition (204,205). Whole protein formulae with (206) or without pre- and probiotics (205,207) or peptide-based formulae via catheter jejunostomy (208,209) have been used for early enteral nutrition of adult liver transplant recipients. Nasogastric or nasoduodenal tubes after endoscopic placement (207) or via catheter jejunostomy (202,208,209) placed during laparotomy are used.

In hepatic transplant patients the principles of parenteral nutrition are no different from those in abdominal surgery. In the early postoperative phase hyperglycaemia due to disturbed glucose metabolism and insulin resistance should be managed mainly by reducing glucose intake because higher insulin doses are unable to increase glucose oxidation (110). The diabetogenic potential of the immunosuppressant tacrolimus can be lowered by reducing its dose, aiming for trough levels of 3-8 ng·ml⁻¹ without undue risk of rejection (210). Regarding lipid emulsions, an improved functioning of the reticuloendothelial system was observed when using MCT/LCT emulsions which have a lower content of n-6 unsaturated fatty acids than pure soy bean oil emulsions (211).

After transplantation there is a considerable nitrogen loss and patients typically remain in negative nitrogen balance for up to 28 days (79,99,137) necessitating an increase in the provision of protein or amino acids. Protein or amino acid intakes of 1.0-1.5 g·kgBW⁻¹·d⁻¹ have been suggested (8,204). There is no need to use a BCAA-enriched amino acid solution after liver transplantation (204).
In transplanted patients, the commonly seen pre-existing chronic dilutional hyponatraemia should be corrected carefully in order to avoid central pontine myelinolysis (212). Magnesium levels need to be monitored in order to detect and treat ciclosporin or tacrolimus induced hypomagnesaemia (213). Postoperative hypophosphataemia and its possible relation to parenteral nutrition following right hemihepatectomy in living donors has been reported by some but not all study groups (214-216).

At present, no specific recommendations can be made with regard to optimal organ donor conditioning. Fatty liver is however known to be a risk factor for primary graft malfunction. No data are available addressing the role of nutritional management of the organ donor. Animal data indicate that the balanced nutrition of a brain dead liver donor, using moderate amounts of carbohydrate, lipid (long-chain fatty acids and possibly fish oil) and amino acids, is associated with improved function of the transplanted organ (217). The value of donor or organ conditioning which aims at reducing ischaemia/reperfusion damage in man by provision of high doses of arginine or glutamine is unclear.

7. Summary

Nutritional status and liver disease influence each other. Liver function is compromised by malnutrition and this impairment can be overcome by nutritional intervention. Depending on disease severity chronic liver disease leads to malnutrition which is an independent indicator of a poor prognosis, also in patients undergoing liver transplantation. Both the presence and the degree of malnutrition can be diagnosed clinically without the need for technical equipment. In chronic liver disease, spontaneous food intake is often inadequate and frequently there is protein malnutrition. In a stepwise approach individualized dietary counselling, supplemental oral sip feeding, enteral tube feeding or parenteral nutrition should be implemented. In patients with hepatic encephalopathy protein restriction is not advantageous and may be harmful to the patient. Trace element and vitamin deficiency is common in patients with liver cirrhosis and appropriate supplementation is recommended. Nutritional therapy ensuring adequate provision of energy and protein can improve morbidity and mortality.

8. References

6. Merli M, Riggio O, Dally L, and PINC. What is the impact of malnutrition on survival in liver cirrhosis Does malnutrition affect survival in cirrhosis?. Hepatology 1996, 23: 1041-1046
53. Sanyal AJ. AGA Technical review on nonalcoholic fatty liver disease. Gastroenterology 2002, 123:1705-1725
62. Dixon JB, Bhathal PS, O'Brien PE. Weight loss and non-alcoholic fatty liver disease: falls in gamma-glutamyl transferase concentrations are associated with histologic improvement. Obes Surg 2006, 16:1278-86
69. Plauth M, Schütz T, Buckendahl DP et al. Weight gain after transjugular intrahepatic portosystemic shunt is associated with improvement in body composition in malnourished patients with cirrhosis and hypermetabolism. J Hepatol 2004, 40: 228-233

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89. Madden AM, Morgan MY. Resting energy expenditure should be measured in patients with cirrhosis, not predicted. Hepatology 1999, 30:655-64

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122. Olde Damink SWM, Jalan R, Redhead D, Hayes PC, Deutz NEP, Soeters PB. Interorgan ammonia and amino acid metabolism in metabolically stable patients with liver cirrhosis and a TIPSS. Hepatology 2002, 36:1163-1171

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149. Calvey H, Davis M, Williams R. Controlled trial of nutritional supplementation, with and without branched chain amino acid enrichment, in treatment of acute alcoholic hepatitis. J Hepatol 1985, 1:141-51

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