Nutritional Support in Liver Diseases

Module 13.2

Nutritional Support in Chronic Liver Disease

Mathias Plauth,
Chair Department of Internal Medicine,
Community Hospital Dessau,
Auenweg 38, 06847 Dessau-Roßlau,
Germany

Learning Objectives

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

Contents

1. Introduction
2. Nutritional risk in chronic liver disease patients
3. Effect of nutritional state on liver disease
   3.1. Undernutrition
   3.2. Overnutrition
4. Effect of chronic liver disease on nutritional status
   4.1. Cirrhosis
   4.2. Surgery and transplantation
5. Pathophysiology and nutrient requirement in chronic liver disease
   5.1. Energy
      5.1.1. Cirrhosis, ASH & NAFLD
      5.1.2. Surgery and transplantation
   5.2. Carbohydrate metabolism
      5.2.1. Cirrhosis
      5.2.2. Surgery and transplantation
   5.3. Fat metabolism
      5.3.1. Cirrhosis
      5.3.2. Surgery and transplantation
   5.4. Protein and amino acid metabolism
      5.4.1. Cirrhosis
      5.4.2. Surgery and transplantation
   5.5. Vitamins and minerals
6. Nutrition therapy in chronic liver disease
   6.1. Alcoholic steatohepatitis (ASH)
   6.2. Non-alcoholic steatohepatitis (NASH)
   6.3. Liver cirrhosis
   6.4. Perioperative nutrition
   6.5. Liver transplantation
7. References
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; 1.3 x resting energy expenditure);
- Use indirect calorimetry if available;
- Provide enough protein (1.2-1.5 g kgBW⁻¹ d⁻¹);
- Use BCAA after GI-bleeding and in HE III°/IV°;
- Use fat as fuel;
- Use enteral tube or sip feeding;
- Use parenteral nutrition if enteral feeding alone is not sufficient;
- Avoid refeeding syndrome or vitamin/trace element deficiencies.

1. Introduction

Nutrition has long been recognized 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 relevant in the management of their patients. In this module the scientific and evidence base of nutrition management of patients with liver disease is reviewed to give recommendations for nutrition therapy.

2. Nutritional Risk in Liver Disease Patients

Adequate nutrition can be viewed as a complex action by which a healthy organism responds to various challenges in a flexible adaptive manner. Therefore, the assessment of nutritional risk of patients must include a measure 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 is stronger when available with a dynamic view (e.g. weight loss in a given 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). NRS-2002 and MUST are validated tools to screen hospitalized patients for risk of malnutrition (14, 15) and are recommended by ESPEN (16). The Royal Free Hospital Nutrition Prioritization Tool (RFH-NPT) has been developed as a screening tool for malnutrition in liver disease patients (17, 18). In a head-to-head comparison the RFH-NPT was more sensitive than the NRS-2002 to identify liver patients at risk for malnutrition (19). NRS-2002 was considered helpful in identifying malnourished cirrhotic patients with hepatocellular carcinoma (HCC) (20).

In cirrhosis (LC) or alcoholic steatohepatitis (ASH), poor oral food intake is a predictor of an increased mortality. In nutrition intervention trials, patients with the lowest spontaneous energy intake showed the highest mortality (21-28). In clinical practice, the plate protocol of Nutrition Day (29) 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 (25, 30). Simple bedside methods like the “Subjective Global Assessment” (SGA) or anthropometry have been used to identify malnutrition (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 (21-23). 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. The accurate quantitative measurement of nutritional status is difficult in chronic liver disease patients with fluid overload (31, 32) and/or impaired hepatic protein synthesis (e.g. albumin) (33, 34) and requires sophisticated methods such as total body potassium count (35, 36) or in vivo neutron activation analysis (37, 38) or isotope dilution (32).

For the assessment of nutritional state of ASH patients in the VA trials a composite scoring system was used (21-23). This scoring system has been modified repeatedly; one of the later publications of this series also reported a prognostic significance of the absolute CD8+ count and hand grip strength (23). The authors observed a close association between low food intake and high mortality (22). Plasma levels of visceral proteins (albumin, prealbumin/transthyretin, retinol-binding protein) are highly influenced by liver synthesis, alcohol intake or acute inflammatory conditions (39, 40). Immune status, which is often considered a functional test of malnutrition, may be affected by hypersplenism, abnormal immunologic reactivity and alcohol abuse (40).

In LC, nutritional status can be assessed using bedside methods, such as the SGA (32, 41, 42) or the modified Royal-Free-Hospital SGA (RFH-SGA) combining SGA and anthropometry (43). The RFH-SGA proved to be a strong predictor of morbidity and mortality but it is time consuming and requires a trained dietician (11, 43, 44). Anthropometry of midarm circumference and triceps skinfold thickness are non-invasive bedside methods (4, 6) but suffer from great inter-observer variability. Handgrip strength is lower in protein depleted LC patients (45, 38) and is a good predictor of the rate of complications within the next year (46-48) but is an insensitive measure of fatigue (49). Handgrip strength is better preserved in LC of viral as opposed to alcoholic or cholestatic aetiology (38). Handgrip strength is a valuable tool to measure efficacy of nutritional intervention (50).

In LC, patients’ reactance and resistance readouts from bioelectrical impedance analysis (BIA) can be used to calculate phase angle as a measure of cell mass and cell function or body cell mass (BCM) for the assessment of nutritional state (36, 51-53). In LC, low phase angle is associated with increased mortality as in many other disease entities (42, 51, 54, 55).

3. Effect of Nutritional State on Liver Disease

3.1 Undernutrition

Severe malnutrition in children can cause fatty liver (56-58) which in general is fully reversible upon refeeding (58). In children with kwashiorkor, there seems to be a maladaptation associated with less efficient breakdown of fat and oxidation of fatty acids (59, 60) compared to children with marasmus. An impairment of fatty acid removal from the liver could not be observed (61). Malnutrition impairs specific hepatic functions like phase-I xenobiotic metabolism (62, 63), galactose elimination capacity (64) or plasma levels of c-reactive protein in infected children (65, 66). In nutritional intervention trials in cirrhotic patients, quantitative liver function tests improved more, or more rapidly in treatment groups. This included

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antipyrine (26, 68), or aminopyrine (69) clearance, as well as galactose elimination capacity (68, 69). It is unknown, whether 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 versus reduced liver function due to 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.

3.2 Overnutrition

Both undernutrition (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 (70-73). 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 (72, 73). In this patient group, the presence and extent of ascites seem to increase with the degree of obesity. The subtraction of the amount of ascitic fluid removed by the surgeon can be used to calculate “dry BMI” (73, 74). Some investigators found that severe obesity was associated with increased morbidity and mortality even when patients were classified according to “dry BMI” (73) while others found the amount of ascites but not BMI to increase mortality risk (74) or did not address this issue (72). Also, in chronic liver disease obesity is an independent risk factor for a worse clinical outcome (75, 76).

Intensive lifestyle intervention achieving > 10 % weight loss was associated with a 24 % reduction in hepatic venous pressure gradient (77). Nonalcoholic fatty liver disease (NAFLD) is defined by the presence of hepatic steatosis when causes for secondary fat accumulation in the liver have been excluded, such as alcohol consumption, HCV infection, drug-induced or hereditary liver disease (78, 79). NAFLD is histologically further categorized into non-alcoholic fatty liver (NAFL) characterized by steatosis alone without hepatocellular injury and nonalcoholic steatohepatitis (NASH) which is characterised by the combination of steatosis and inflammation and hepatocyte injury that may progress to fibrosis, cirrhosis and hepatocellular carcinoma (HCC) (78, 79). The definition of significant alcohol consumption has been inconsistent and ranges from 10-40 g·d\(^{-1}\) (78-80). In NAFLD, overall and cardiovascular mortality are increased compared to the general population (81-83). NAFLD is associated with an increased standardized mortality ratio compared with the general population (84) and liver disease ranks third after cardiovascular disease and cancer as cause of death. 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 (72, 73). Diabetes risk and overt type 2 diabetes are associated with more severe NAFLD, progression to NASH, advanced fibrosis and the development of HCC (85, 86) independently of liver enzymes (87). Vice versa, NALFD patients are facing an increased risk (up to 5-fold) of developing overt type 2 diabetes after adjustment for several lifestyle and metabolic confounders (88). Therefore, European guidelines recommend that persons with NAFLD should be screened for diabetes and that in patients with type 2 diabetes the presence of NAFLD should be looked for irrespective of liver enzyme levels (79).
4. Effect of Chronic Liver Disease on Nutritional State

4.1 Cirrhosis

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 (89). Sarcopenia is the key feature of malnutrition in LC patients and should be diagnosed by radiologic methods (DXA, CT) so as to detect loss of muscle mass or by tests of muscle function such as exercise test or the 6-minute walk distance. Sarcopenia can be diagnosed when there is loss of muscle mass or muscle function (90). On CT images at the level of lumbar vertebra 3 (91) or lumbar vertebra 4 (92) skeletal muscle area can be measured and normalized for stature by calculating the skeletal muscle index (SMI) (93). The skeletal muscle area at L3 has been shown to be linearly correlated to whole body muscle mass (93). Loss of skeletal muscle mass on CT has been shown to indicate an increased mortality in LC patients (91, 94), obese LC patients (95), and liver transplant (OLT) recipients (96-98). After porto-systemic stent shunt (TIPS), failure to reverse sarcopenia was associated with poorer survival (92) and after transplantation, new-onset sarcopenia was associated with a trend for higher mortality (99). Also in NASH patients, a progressive loss of muscle mass has been observed (100).

A French group has shown that transverse psoas muscle thickness measured at the level of the umbilicus was inversely correlated with death on the waiting list for transplantation (101). Low psoas muscle area at lumbar vertebra 3 level was associated with increased mortality and morbidity (44). In order to obviate costly and invasive radiologic imaging, ultrasound based protocols for the assessment of muscle mass have been proposed (102) and await further validation.

Recently, attempts have been made to establish SMI cut-off values for cirrhosis in a North-American population (103). Since cut-off values vary according to region and ethnicity (104) more work is needed to establish appropriate age, gender, BMI and ethnicity matched reference values. A French group has published a comparison of the SMI and the transverse psoas thickness approach (105).

Two studies in LC patients on the wait list reported muscle function (in terms of 6-min walk distance, grip strength and the short physical performance battery), but not loss of muscle mass (in terms of CT derived skeletal muscle index), to be associated with increased mortality (106, 107). In LC patients, frailty experienced as a functional decline in grip strength, gait speed, chair stands or the short physical performance battery has been shown to be associated with increased risk for complications requiring hospitalisation (108), death on the wait list or removal from the wait list (109, 110).

In LC patients, there is a profound reduction in exercise capacity, and this reduction is only moderately ameliorated after transplantation as reviewed in great detail by Williams & McKenna (111). LC patients with a VO_{2,max} < 60 % of normal had only a 50 % one-year survival when transplanted (112, 113). Actively exercising transplant recipients, however, can bring their VO_{2,max} back to normal (114).

Recovery from this loss in body cell mass can be achieved by the control of complications such as portal hypertension and by adequate nutrition (115, 116). The aetiology of the liver disease per se does not seem to influence the prevalence and degree of malnutrition and protein depletion (38, 89, 117) and the higher prevalence and more profound degree of malnutrition in alcoholics obviously result from unhealthy life style and low socio-economic conditions.

In hospitalized cirrhotics, fatigue, somnolence, or psychomotor dysfunction often lead to insufficient oral nutrition even in the absence of overt HE (26, 118-120). 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 (119). Moreover, taste acuity and thresholds for salty, sweet and sour are impaired (121) and these disturbances can be
aggravated 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 do occur in cholestatic liver disease, such as primary biliary cholangitis or cystic fibrosis leading to severe malabsorption of dietary fat as well as of fat soluble vitamins. In other forms of chronic liver disease fat or protein malabsorption are not common (122, 123) and faecal energy excretion was found to be normal (30). Upon administration of lactulose, however, faecal mass and nitrogen excretion increase, most likely due to increased bacterial protein synthesis (123). Likewise, a high-fibre vegetable diet for the treatment of hepatic encephalopathy is associated with an increased faecal nitrogen loss (124).

4.2 Surgery & Transplantation

Plank and coworkers reported a loss of 1.0 kg of total body protein (equivalent to 5.0 kg of skeletal muscle), mainly from skeletal muscle, immediately after surgery, and this loss was not replenished within 12 months thereafter (125). In follow-up using total body potassium counting for 24 months after liver transplantation an initial postoperative loss but no subsequent gain in body cell mass was observed (126). As a functional equivalent, Selberg and coworkers (127, 128) demonstrated that glucose uptake and non-oxidative glucose disposal by skeletal muscle had still not normalized within 12 months and longer after liver transplantation. Not surprisingly, respiratory muscle function still has not returned to normal one year after transplantation (125).

Long term survivors after liver transplantation are at considerable risk of becoming overweight or even obese and to develop related morbidity due to the metabolic syndrome (129-131). More attention should be paid to avoiding the problem of sarcopenic obesity (132, 133). Already while on the wait list LC patients suffer from a stage dependent loss of quality of life and exercise capacity (134), have fatigue (135), and exhibit a very low activity level (136) and a progressive loss of muscle mass. Participants in a structured 12-week exercise protocol achieved an improvement in 6-min walk distance and quality of life (137). After transplantation, activity level, quality of life and exercise capacity in general do not improve to a normal level (111, 135, 138). Transplant recipients participating in a structured exercise and nutrition protocol however had a significantly better gain in VO_{2max} and quality of life (139).

Taken together, these observations indicate that upon the restoration of hepatic function and cessation of portal hypertension full nutritional rehabilitation is possible.

5. Pathophysiology and Nutrient Requirement in Chronic Liver Disease

5.1 Energy

5.1.1 Cirrhosis, ASH & NAFLD

Measurement of REE in LC and in controls showed no difference when REE was related to body surface area (140-143) or body mass (LC: 22-27 kcal·kgBW^{-1}·d^{-1}) (142, 144-146). REE showed increased values in LC when REE was related to lean body mass in terms of urinary creatinine excretion (142, 143, 147) or in terms of body cell mass (142).

In ASH patients, the relationship between measured and predicted REE was not different from healthy individuals (150, 151) or patients with LC (150). However, when related to their reduced muscle mass, REE in ASH patients was up to 55% higher than in healthy controls (148, 149). In alcoholics without biochemical evidence of liver disease but not in patients with alcoholic LC an increased REE (25.8 vs 20.8 kcal·kgBW^{-1}·d^{-1}) was observed (140). Likewise,

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in alcoholics with fatty liver, ASH or LC alcohol abuse was associated with increased REE (26%); a decrease in REE consistently occurred four days after abstinence from alcohol (151). After adjustment for body mass, REE was higher by 11% in alcoholics with or without liver disease compared to healthy social drinkers (152).

In NAFLD it is difficult to draw a clear picture, because patient populations studied vary with regard to the presence or absence of overweight/obesity, chronic inflammation and Metabolic Syndrome. In severely obese men with NAFLD and Metabolic Syndrome REE was higher by 17% than in those without Metabolic Syndrome (153). Comparing individuals with less difference in BMI (NAFLD 27.7 kgBW·m⁻²; controls 25.3 kgBW·m⁻²) Kotronen et al. (154) found no difference in REE (77.4±1.4 vs 75.6±1.0 J-kgFFM⁻¹·min⁻¹) after adjustment for fat-free mass. On average measured REE is of the same magnitude as energy expenditure predicted by use of formulae (Harris & Benedict, Schofield, etc.) (155-157). The question of hypermetabolism has been addressed in cirrhosis and ASH patients. ASH patients may be considered hypermetabolic when measured REE is related to their reduced muscle mass (148). Measured REE is higher than predicted REE in up to 35% of cirrhotic patients (hypermetabolism), and below the predicted value in 18% of the patients (155-157). In cirrhosis, hypermetabolism has been shown to be associated with reduced event-free survival and unfavourable outcome after transplantation (10, 157) and seems to regress with improvement of body composition (116) and after liver transplantation (158). For the diagnosis of hypermetabolism, however, indirect calorimetry is required so that in daily practice most clinicians cannot use this approach.

Measurements of total energy expenditure indicate that the 24 h energy requirement of cirrhosis patients amounts to about 130% of the basal metabolic rate (30,159). Diet-induced thermogenesis (160-162) and the energy cost of defined physical activity in stable cirrhotic patients (163-165) also show no deviation from values obtained in healthy patients. However, the spontaneous physical activity level is considerably lower in patients with cirrhosis (111, 136). Obviously, the increased energy requirement in advanced illness is balanced by diminished physical activity reflecting the poor physical condition (27, 165). In cirrhotics without ascites the actual body weight should be used for the calculation of the basal metabolic rate using formulae such as that proposed by Harris & Benedict. In underweight or normal weight patients with ascites actual weight and in overweight/obese patients 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 (166), that ascites mass should not be omitted when calculating energy expenditure by use of body weight.

5.1.2 Surgery & Transplantation

Liver transplant patients on average have the same energy requirements as the majority of patients undergoing major abdominal surgery. In general, non-protein energy provision of 1.3 x REE is sufficient (167, 168). In a longitudinal study, postoperative hypermetabolism peaked on day 10 after the transplantation at 124% of the predicted REE (79). By six to 12 months post transplant there was no longer a difference between the measured and predicted REE (125, 146).

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) (141, 143, 155, 169). In the postabsorptive state, glucose oxidation rate is reduced and hepatic glucose production rate is low despite increased gluconeogenesis due to a depletion of hepatic glycogen (170). 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 (127, 161, 171). It is not known to what extent glucose deposition as glycogen is impaired just in skeletal muscle or in both muscle and liver (172, 173). Some 15–37 % of patients develop overt diabetes, indicating an unfavourable prognosis (174, 175).

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 (176).

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 in healthy subjects (177). Lipids are oxidized as the preferential substrate and lipolysis is increased with active mobilisation of lipid deposits (141, 178). There is insulin resistance with regard to its antilipolytic activity.
After a meal, the suppression of lipid oxidation is not uniformly impaired (142, 162). Plasma clearance and lipid oxidation rates are not reduced and thus the net capacity to utilize exogenous fat does not seem to be impaired (178, 179). Plasma levels of essential and polyunsaturated fatty acids are decreased in cirrhosis and this decrement correlates with nutritional status and severity of liver disease (180, 181).

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 mainly focused on the presence of increased protein breakdown, while others suggest that a reduced protein synthesis plays the main role (182). Albumin but not fibrinogen synthesis rates correlate with quantitative liver function tests and clinical stages of cirrhosis (33, 34). Nevertheless, stable cirrhotics apparently are capable of efficient nitrogen retention and significant formation of lean body mass from increased protein intake during oral refeeding (30). Protein catabolism influences the amino acid imbalance of cirrhosis and indirectly causes nitrogen overload in the liver leading to hyperammonaemia (181-183). 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 or nocturnal feeding of ONS were associated with improved protein metabolism in cirrhotic patients (186-189). Insulin resistance apparently is without effect on amino acid disposal (190).
An explicit and systematic determination of the protein requirement of patients with 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 (27, 30, 64, 191).
Cirrhotic patients exhibit an altered pattern of plasma amino acids characterized, on the one hand, by the elevation of aromatic (phenylalanine, tyrosine) and sulfur containing amino acids (methionine) and tryptophane, and on the other by a decrease in BCAA (leucine, isoleucine, valine) (192, 193). Decreased metabolic clearance (194) by the failing liver of aromatic and
sulfurous amino acids and increased breakdown in skeletal muscle of BCAA due to portal systemic shunting (195) and hyperammonemia (183, 196-198) 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 hemorrhage (199). 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 comagenic potential. Moreover, this antagonism leading to hyperammonaemia could be overcome by the infusion of just isoleucine (200).

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 (125, 167, 201) 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 (37, 38) goes hand-in-hand with salt retention, which therefore does not usually lead to hyponatraemia. 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 (202-205). An impressive association between HE and zinc deficiency has been described in case reports (206, 207). A deficiency in water soluble vitamins, mainly group B vitamins, is common in cirrhosis, especially that of alcoholic origin (208, 209). Deficiency in fat soluble vitamins has been observed in cholestasis-related steatorrhoea, bile salt deficiency, and more generally in alcoholics (210, 211). Patients with hypophosphataemia after paracetamol/acetaminophen-induced liver damage have a better prognosis. Severe hypophosphataemia, however, results in respiratory insufficiency and dysfunction of the nervous system and erythrocytes (212), 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 like ileus. Clinical trials (21-24, 213, 214) in ASH patients showed 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.

Severely malnourished ASH patients who achieve an adequate intake of oral nutrition supplements have an improved survival, regardless of whether or not additional anabolic steroids are used (22). 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 (214). In a randomized trial of patients with severe ASH treated with corticosteroids, enteral tube feeding for 14 days was withdrawn prematurely in 49 % of patients (median duration 5 d; range 25-10 d) and did not increase survival. Regardless of group, patients with a low calorie intake
(<21.5 kcal·kgBW\(^{-1}\)·day\(^{-1}\)) had a higher cumulative infection rate and a 6-month mortality as high as 66 % compared to 33 % (p<0.001) in patients with an energy intake ≥21.5 kcal·kgBW\(^{-1}\)·day\(^{-1}\), and the authors concluded that adequate nutritional intake should be a main goal for treatment (28). In the tube fed group 3 cases of aspiration pneumonia occurred. 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 (25, 26, 215). Placement of a PEG is associated with a higher risk of complications (due to ascites or varices) and is not recommended (216). 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\(^{-1}\) (216-218). 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 (216). 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 like in cirrhotics, a low protein intake can worsen HE (26, 219).

Parenteral nutrition should be commenced immediately in ASH patients with moderate or severe malnutrition who cannot be fed sufficiently either orally or enteraly. Parenteral nutrition supplemental to oral nutrition ad libitum did not improve survival but did not negatively affect mental state (67-69, 213, 220-223). 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 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 PN or even i.v. glucose in alcoholic patients. 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 (224). 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)

Weight loss generally reduces hepatic steatosis, irrespective of how it is achieved (78, 79, 225). However, longitudinal studies of patients with NAFLD clearly show that fibrosis stage, but no other histological features of steatohepatitis, is associated independently with long-term overall mortality, liver transplantation, and liver-related events (226). Results from the evaluation of paired biopsies in NASH patients achieving weight loss indicate that only substantial weight loss (> 9-10 %) is accompanied by improvement in fibrosis but this can even achieve full resolution of NASH (227-235). A less pronounced weight loss is associated with improvement in steatosis and inflammation and liver enzymes, but not in fibrosis (234, 236-239).

A meta-analysis of a total of 15 studies reporting findings from 766 paired liver biopsies of patients losing weight after bariatric surgery shows improvement or resolution in steatosis in 91.6% (95% CI, 82.4-97.6%), in steatohepatitis in 81.3% (95% CI, 61.9-94.9%), and in fibrosis in 65.5% (95% CI, 38.2-88.1%) (240). NASH resolved completely in 69.5 (95% CI, 42.4-90.8%). In this pooled sample mean BMI reduction ranged from 19.1 to 41.7 %. The potential of bariatric surgery to improve fibrosis of NASH is underscored by another meta-analysis (241). A less invasive procedure, endoscopic placement of a duodeno-jejunal bypass

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liver for 6 months, resulted in 10.9% weight loss accompanied by a decrease in liver enzymes (242).

Life style change resulting in moderate weight loss (<5 %) was shown to improve hepatic fat accumulation as detected by \(^{1}\text{H}-\text{MRS}\) when a hypocaloric diet and exercise were combined, but not when a hypocaloric diet alone was implemented (243, 244). Lifestyle change resulting in weight loss of 5-10 % was shown to improve histology when both hypocaloric diet and exercise were implemented (232, 234, 238, 245, 246). Subgroup analyses indicate that the extent of weight loss seems to be correlated with the extent of histological improvement. Profound improvement of steatosis, inflammation and ballooning was observed already when weight loss of 7-9 % was achieved (232, 238, 246) while only a weight loss > 10% was associated with improvement in fibrosis (234). In a systematic trial, shifting energy balance to the same degree by either reduced intake alone or a lesser caloric restriction combined with increased energy expenditure (exercise) yielded the same weight loss (-10 %) and the same improvement in hepatic fat, ALT and insulin sensitivity (247).

Available data indicate also, that each of the two interventions alone is effective when the other variable - either weight or daily physical activity - is kept constant. Non-invasive measurements using \(^{1}\text{H}-\text{MR}-\text{spectroscopy}\) convincingly demonstrate a reduction of intrahepatic and visceral triglycerides in subjects just exercising without losing weight (248-250) or following intensive lifestyle intervention by moderate caloric restriction and exercise (251). Conversely, weight loss by either a low carbohydrate or a low fat diet in subjects maintaining their sedentary lifestyle was associated with a substantial loss of intrahepatic lipid (239).

Readiness for behaviour changes, however, is low in overweight/obes patients with NAFLD with only 10 % actively working on or preparing to change (252).

The efficacy of Vitamin E as an anti-oxidant to ameliorate biochemical and/or histological abnormalities of NASH has been investigated in a number of trials (246, 253-262). There is, however, a great heterogeneity among these trials regarding study power, entry criteria, dosage of vitamin E, formulations of vitamin E used, additional use of other anti-oxidants or other drugs, and histological data to assess outcomes. Despite these limitations, the following conclusions can be drawn regarding adults with NASH (78, 79): 1) the use of vitamin E is associated with an improvement of liver enzymes (decrease in ALT, AST), 2) trials evaluating NASH features in paired liver biopsies show improvement in steatosis, inflammation, and ballooning and resolution of steatohepatitis in patients treated with vitamin E when compared to controls, and 3) vitamin E has limited or no effect on hepatic fibrosis. In the largest RCT (PIVENS trial) the predefined primary endpoint was achieved in a significantly greater number of participants receiving oral vitamin E (800 IU·d\(^{-1}\) for two years) compared to placebo (42% vs. 19%, p<0.001, number needed to treat = 4.4)(260). Re-analysis of the PIVENS trial showed that ALT responses were more frequent in the vitamin E recipients and were associated with NAS, but not fibrosis scores (263). Interestingly, vitamin E had an added effect on the improvement of ALT, NAS, and fibrosis scores obtained by weight loss > 2.0 kg (263).

The authors of a meta-analysis of 19 trials (135 967 participants) studying a variety of populations in whom the presence or absence of NASH was not specifically addressed came to the conclusion that vitamin E dosage > 400 IU·d\(^{-1}\) was associated with an increased risk for all-cause mortality and should be avoided (264). This issue is also discussed in the in the light of more recent findings (78). The Cochrane Hepato-Biliary Group’s meta-analysis of 20 randomized trials (1225 participants) studying the effect of anti-oxidant supplements in patients with liver disease of various aetiologies included 15 trials supplementing vitamin E (265). The authors found no significant treatment effect of antioxidants on all-cause mortality or liver-related mortality. In another meta-analysis no beneficial effect of anti-oxidant treatment on liver biochemistry and histology was reported (81). In their meta-analysis Ji et al. report an effect of vitamin E on ALT and AST in NASH but not in NAFLD (266). Of the two
large and well controlled trials (PIVENS, TONIC) in NASH patients with neither diabetes nor cirrhosis the abstract of the PIVENS trial was included in one meta-analysis only (81) and the TONIC trial (261) in none. When targeting insulin resistance by use of insulin-sensitizing drugs like pioglitazone or rosiglitazone, the beneficial effects on liver histology (267, 268) seem to be offset by a considerable gain in body weight and body fat mass (267, 269).

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

6.3 Liver Cirrhosis

In patients with cirrhosis the primary goal is to ensure a quantitatively adequate nutrient intake (23-26, 270-272). Increasing protein intake by nutrition therapy can decrease mortality (25), and adequate nutrition after successful treatment of portal hypertension by transjugular intrahepatic portosystemic stent-shunt (TIPS) has the potential to improve body composition (115, 116).

Regarding the method of nutritional intervention, nutritional counselling alone (270) or in combination with oral nutrition supplements (23, 24, 272) will often prove successful. Supplemental enteral nutrition should be given when patients with liver 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 therapeutic gain (25, 26, 118, 119) from the timely use of tube feeding is missed. Due to somnolence and psychomotor dysfunction oral nutrition is often insufficient even in no or mild HE (I°-II°) (118, 119). 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 porto-systemic collateral circulation due to portal hypertension have been reported as contraindications to PEG placement (273).

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\(^{-1}\) (216-218) 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 (274). Patients with liver cirrhosis suffer from a depletion of hepatic glycogen stores and thus are less prepared to adequately master periods of even short term food deprivation. A late evening carbohydrate snack can improve protein metabolism in cirrhotics (186-188). Recently, it has been shown that nocturnal oral supplements, (i.e. given after 21:00 h), are more efficient in improving total body protein status of cirrhotic patients than isonitrogenous and isocaloric amounts given during the daytime (189).

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 (275). In stable patients with cirrhosis long-term (12 and 24 months) supplementation with BCAA-rich oral nutrition supplements has the potential to slow the progression of hepatic failure and prolong event-free survival (276-278), but this treatment is not reimbursed in many countries. When patients develop HE during enteral nutrition BCAA-enriched formulae should be used (216).

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 (279-281), despite encouraging case reports (206, 207). Urea production capacity increased after oral zinc application when previously subnormal plasma levels were normalised (282). Supplementing zinc and vitamin A may indirectly improve food intake and nutritional state by improving dysgeusia (283, 284). 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 cholangitis; oestrogen substitution proved to be much more effective in female patients (210, 211, 285). 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. By analogy with 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 PN 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 (218).

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. 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 the 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 (286). Plasma clearance and oxidation of infused lipids are normal in cirrhosis patients (178, 179). Regarding the optimal composition of i.v. oxidative fuels - fat and carbohydrate - only limited information is available (287, 288). 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 soybean oil emulsions (218). Compared to the traditional soy bean-based long-chain triglyceride (LCT) emulsions, new 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 (289-293).

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 (294). 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 (24-26, 68, 69, 220-223, 295). 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 sulfur-containing amino acids were developed (296-298). Such solutions help to correct the amino acid imbalance seen in cirrhosis. The efficacy of BCAAs in the treatment of hepatic encephalopathy has been studied (287, 288, 299-303) and a meta-analysis showed an improvement in mental state by the BCAA-enriched solutions, but no definite benefit in survival (294). 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 (304). 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 (199). This antagonism leads to hyperammonaemia but HE could be overcome by the infusion of just isoleucine (200). Isoleucine solutions for i.v. infusions, however, are not commercially available. 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 (218).

### 6.4 Perioperative Nutrition

Nutrition therapy prior to elective surgery should be managed according to the recommendations given for the underlying disease (cirrhosis in the majority of cases). In malnourished LC patients, the risk of postoperative morbidity and mortality is increased after abdominal surgery (12, 13). Liver glycogen is depleted in LC 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 (141, 170, 186-189). Also in liver surgery, adoption of ERAS protocols improves morbidity and length of stay when among other measures patients are given carbohydrate-containing clear liquids until two hours preoperatively, early postoperative feeding and mobilization (305-307). Sarcopenic LC patients undergoing non-transplant surgery such as resection for HCC have an increased mortality risk (308, 309). In LC patients undergoing non-transplant visceral surgery, complication rates and nitrogen economy can be improved when nutrition support instead of just fluid and electrolytes is provided (310-312). It may safely be assumed that EN in the early postoperative period would yield at least equal results. There are, however, no studies comparing the two regimens in LC 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 (312). In LC 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·d⁻¹) was used for postoperative PN instead of a BCAA-enriched amino acid solution (40 g·d⁻¹) (310). Tang and colleagues reported improved immune function and preserved gut mucosal integrity when PN supplemented with glutamine and hGH was used in LC patients (313).

### 6.5 Liver Transplantation

Numerous descriptive studies have shown higher morbidity and mortality in LC patients with protein malnutrition when such patients undergo liver transplantation (3-5, 7, 8, 10, 35, 41). Recently, sarcopenia and frailty have been shown to carry an increased risk of morbidity and mortality for patients on the waiting list and after transplantation (44, 91, 94, 96-99, 101, 106-110). Patients on the wait list are at risk due to an inadequately low food intake (120) and those consuming a low protein diet (< 0.8 g·kgBW⁻¹·d⁻¹) have an increased wait-list mortality (314). Nevertheless, there are no formal trials showing that preoperative nutritional...
intervention improves clinical outcome. Data from a pilot study suggest that preoperative nutrition support improves total body protein status and reduces postoperative infection rates (201). In less advanced and predominantly cholestatic LC, nutritional counselling plus ONS improved mid-arm muscle circumference and grip strength compared to nutritional counselling alone while there was no difference in mortality (270). In one pilot study, 5 days of pre-operative immunonutrition changed laboratory findings but not nutritional variables or outcomes (315). In another pilot study, ONS enriched with ω-3 fatty acids, arginine and nucleotides appeared to reduce infectious complications (201). In the subsequent randomized trial, perioperative immunonutrition did not provide significant benefits in terms of preoperative total body protein status or postoperative outcome compared to standard ONS (316) and another trial was stopped (317). A combined meta-analysis of different interventions like glutamine or ω3 fatty acids by parenteral or enteral route reported overall beneficial effects regarding morbidity and liver function (318) but this methodological approach seems questionable.

Kaido and colleagues observed less risk of postoperative infection in their transplanted patients who received preoperative BCAA-enriched ONS (319). Interestingly, BCAA supplementation conferred better survival only to sarcopenic patients on the waiting list but not to non-sarcopenic individuals (94). Paediatric transplant patients with predominantly cholestatic liver disease show a better increase in BCM if they are given a BCAA-enriched formula (320).

For the growing subgroup of obese surgical patients, recent guidelines recommend basing the provision of energy (25 kcal·kgIBW⁻¹·d⁻¹) and protein (2.0 g·kgIBW⁻¹·d⁻¹) on ideal body weight (321).

After transplantation, postoperative PN (322) or EN (323) are superior to just infusing fluid and electrolytes regarding time on the ventilator and length of stay in the ICU (322) or bacterial infections and bile duct complications (323). Early EN (12 hours after the operation) is associated with fewer viral infections and better nitrogen retention than parenteral nutrition (324). 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 the complication rate and cost (325). For early EN in adult liver transplant recipients, whole protein formulae with (326) or without pre- and probiotics (324, 325) or peptide-based formulae via catheter jejunostomy (327, 328) have been used. Formulae were administered via nasogastric or nasoduodenal tubes after endoscopic placement (325) or via catheter jejunostomy (312, 327, 328) placed during laparotomy. According to a European survey (168) the combination of EN and PN was used in 10/16 centres, while 3/16 stated use of PN or EN alone.

After liver transplantation, there is a considerable nitrogen loss and patients remain in negative nitrogen balance for a prolonged period (125, 167, 201) necessitating an increase in the provision of protein or amino acids. Protein or amino acid provision of 1.0-1.5 g·kgBW⁻¹·d⁻¹ has been reported (8, 322) which is slightly lower than recommended for hospitalized or critically ill patients (329-331). No difference was observed between the effects of a standard and a BCAA-enriched amino acid PN solution after liver transplantation (322).

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 as in other surgical patients (307). In the first 48 h a lower provision of energy (<18 kcal·kgBW⁻¹·d⁻¹) (332) may be advisable in the light of the growing recognition of autophagy as a source of endogenous substrate supply. Less postoperative morbidity and shortened length of stay was reported, seemingly in duplicate, when ω-3 fatty acids were used for PN (333, 334). Hepatic RES function was reported to show better recovery when an MCT/LCT combination as compared to a pure LCT emulsion was given for PN after liver transplantation (335).

Chronic dilutional hyponatraemia is not infrequent in LC patients and should be corrected carefully after transplantation in order to avoid pontine myelinolysis (336). Magnesium levels

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need to be monitored not least in order to detect and treat ciclosporin- or tacrolimus-induced hypomagnesaemia (337). The simultaneous administration of enteral feeding with tacrolimus did not interfere with tacrolimus absorption (338).

At present, no specific recommendations can be made with regard to optimal organ donor conditioning. Fatty liver is 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 (339). 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. Postoperative hypophosphataemia and its possible relation to PN following right hemihepatectomy in living donors has been reported by some but not all study groups (340-342).

7. References


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