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ESPEN guidelines for nutrition in liver disease and transplantation

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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 devised by Child and Turcotte (2). Despite the increase in knowledge from research in the fields of metabolism, clinical nutrition and intervention, there is no generally accepted or standardized approach for the diagnosis and classification of malnutrition in these patients. Similarly, there is no general agreement on the criteria for when or how to implement nutritional intervention. Even among clinical trials, criteria for patient classification and study endpoints are heterogeneous and have been used inconsistently. Therefore, ESPEN commissioned the work of a group of hepatologists and nutritionists to prepare a consensus document on nutrition in liver disease and liver transplantation. The aim of this consensus was to disseminate current knowledge, propose common terminology, agree consensus definitions and diagnostic and therapeutic standards to be adopted in clinical practice and research, and to stimulate cooperative European studies. The present paper is the result of meetings on the occasions of the annual ESPEN and EASL meetings in Rome 1995 and Geneva 1996, a consensus group meeting in Berlin in 1996 and repeated discussions of circulars at various stages of the work.

Effect of liver disease on metabolism and nutritional status

Protein–energy malnutrition

Acute liver disease induces the same metabolic effects as any disease associated with an acute phase response. The effect on nutritional status depends on the duration of the disease and on the presence of any underlying chronic liver disease which may have already compromised the patients' nutritional status.

Malnutrition in chronic liver disease is better defined as protein–energy malnutrition (PEM) because kwashiorkor-like malnutrition and marasmus frequently coexist (3, 4). The prevalence and severity of PEM are related to the clinical stage of chronic liver disease: When diagnosed by anthropometric criteria, PEM may be present in 20% of patients with well compensated liver cirrhosis and in more than 60% of patients with severe liver insufficiency (5). The prevalence is even higher when body composition is assessed by more sensitive methods (4, 6). The presence of muscle wasting indicates an advanced stage and apparently is associated with poorer survival (7) particularly following shunt surgery (8). The prevalence and degree of PEM do not appear to relate to the etiology of liver disease per se (4, 5). The higher prevalence of malnutrition in patients with alcoholic liver disease is generally restricted to skid row alcoholics and patients from low socio-economic classes.

Conclusion. PEM is common in chronic liver disease and positively correlated with functional severity of the liver injury.

Substrate metabolism in chronic liver disease

Decreased glucose but increased lipid oxidation are observed in postabsorptive cirrhotic patients. This modified substrate utilization does not depend on the nutritional status (9–11).

Glucose. The majority of patients with cirrhosis have impaired glucose tolerance with hyperinsulinemia and insulin resistance. In 15–37% of patients overt diabetes may occur and this represents a risk factor for long-term survival (12, 13). In the postabsorptive state, due to a depletion of hepatic glycogen stores the glucose oxidation rate is reduced and the hepatic glucose production rate is low despite the increase in gluconeogenesis (14).

Under conditions of a euglycemic hyperinsulinemic clamp, glucose oxidation is normalized, while non-oxidative glucose disposal is impaired due to reduced glucose transport and uptake into skeletal muscle (15, 16). After a meal, insulin resistance is overcome to a degree because of high insulin and glucose levels and cirrhotics utilize the ingested carbohydrate as immediate fuel (17). At present, it is unknown whether glucose deposition as glycogen is impaired just in skeletal muscle or in both muscle and liver (18, 19).

Lipid. In the fasting state, plasma free fatty acids as well as glycerol and ketone bodies are increased. Lipids are oxidized as preferential substrate, and lipolysis is increased with active mobilisation of lipid deposits (10, 20). Insulin apparently does not suppress lipolysis to the same degree as in healthy controls, when plasma free fatty acid and glycerol concentrations are measured during low insulin infusion rates (21). There are controversial findings regarding maintenance (22) or loss (17) of suppression of postprandial lipid oxidation. Plasma clearance and lipid oxidation rates are not reduced (23, 24) and therefore, the net capacity to store exogenous lipid does not seem to be impaired in cirrhotics.

Essential and polyunsaturated fatty acids are decreased in cirrhosis and this decrement correlates with nutritional status (25) and the severity of liver disease (26).

Protein. The effect of insulin on protein metabolism and amino acid disposal does not seem to be impaired in patients with insulin resistance (27). Protein turnover in cirrhotic patients has been found to be normal or increased. Some authors have suggested that protein breakdown is increased, while others suggest that protein synthesis is reduced (28). Nevertheless, stable cirrhotic patients apparently are capable of efficient nitrogen retention and significant formation of lean body mass during oral hyperalimentation (29). Protein catabolism influences the amino acid imbalance of cirrhosis and indirectly causes nitrogen overload to the liver leading to hyperammonemia. Albumin but not fibrinogen synthesis rates correlate with quantitative liver function tests and clinical stages of cirrhosis (30, 31).

Conclusions. Substrate metabolism in chronic liver disease is characterized by insulin resistance which affects glucose transport and non-oxidative glucose disposal by skeletal muscle, but does not affect amino acid disposal. Protein turnover occurs at normal or increased rates with an increase in protein degradation in some patients. Metabolic clearance and oxidaton of lipids are normal in cirrhosis.

Assessment of nutritional status

For complete assessment of nutritional status information on energy balance, body composition and tissue function is essential.

Energy balance. From analysis of spontaneous dietary intake in control groups of nutritional intervention studies it has become clear that a low intake is associated with a poor outcome (32–35). Despite limitations of the various methods dietary intake should be assessed. In clinical practice a systematic dietary recall obtained by a skilled dietitian will provide adequate information in most cases. For metabolic studies in hospitalized patients, a food diary should be completed, weighing the food consumed, and appropriate tables for food composition should be used for calculaton of proportions of different nutrients. Regarding total energy intake, food analysis by bomb calorimetry may be utilized as a 'gold standard' (29, 36).

Energy expenditure should be measured by indirect calorimetry, especially in patients with decompensated cirrhosis. In these patients, no validated factors for estimating resting energy expenditure are available. Indirect calorimetry should be used in all metabolic studies. When this method is not available energy expenditure may be calculated from Harris and Benedict's equation (37) as an auxiliary method with a mean deviation of 11% from measured values (9). It remains controversial, however, whether actual, ideal or 'dry' body weight should be used for calculation, since ascites apparently is not an inert compartment regarding energy expenditure (38, 39). Both, actual weight in severe hydropic decompensation or errors in estimates of 'dry' weight may lead to erroneous values deviating to the extremes and therefore, ideal body weight may be accepted as a safe approach.

Body composition. In clinical practice, body composition of cirrhotic patients is assessed by indirect techniques, such as anthropometry, urinary creatinine excretion or bioelectric impedance analysis which are inaccurate, due to the combination of reduced body cell mass and a variable degree of extracellular fluid retention (6, 40). Therefore, it would be desirable to directly assess fat mass and fat free mass components total body water, extracellular water and body cell or muscle mass.

Anthropometry is a reasonably accurate bedside tool to detect the protein depleted status of cirrhotic patients when used by a single trained examiner (5, 40–42) and four site skinfold anthropometry has been considered the best indirect method of assessing body fat stores in these patients (43).

The value of urinary creatinine excretion as a basis to estimate muscle or body cell mass has been questioned since creatine is synthetized by the liver (44). In more recent studies, however, this method has been considered adequate (29) depending more on renal than on hepatic function (45). Total body potassium can be measured precisely and accurately when a whole body counter is available (46, 47). This non-invasive method is regarded as a reliable tool to estimate body cell mass in general, but has not been validated in cirrhotic patients yet.

The use of bioelectrical impedance analysis (BIA) is controversial in patients with ascites (4, 48, 49), but caution should also be exerted in patients without clinical signs of fluid overload (50, 51). In two studies a good correlation was found between fat free mass or body cell mass by BIA and muscle mass or body cell mass assessed by total body potassium counting (9, 13). However, BIA was found unable to accurately reflect changes in body composition due to cirrhosis when direct methods were used (40).

Clearly, for metabolic studies a multi-compartmental approach using direct methods, such as in vivo neutron activation analysis, dual energy X-ray absorptiometry or deuterium oxide dilution for determination of total body nitrogen, total body fat or total body water is a prerequisite for accurate quantification of changes in body composition. These methods, however, are expensive and not generally available. Therefore, the combination of anthropometry

and assessment of body cell mass by an appropriate method may serve as a useful approach (40).

Tissue function. Circulating concentrations of many visceral plasma proteins (albumin, prealbumin, retinol-binding protein) are highly affected by the presence of liver disease, excessive alcohol consumption and inflammatory states (53, 54). Immune status, which is often considered a functional test of malnutrition, may be affected by hypersplenism, abnormal immunologic reactivity and alcohol abuse (54). At present, total lymphocyte count and CD8 cell count seem to be of prognostic value in malnourished patients with alcoholic liver disease (55). In nutrition intervention trials, results from lymphocyte PHA stimulation index (56) or skin anergy test (3, 35, 55, 57, 58) were not useful for the detection of nutritional changes.

In patients with alcoholic liver disease, muscle function as monitored by handgrip strength was an independent predictor of outcome (55) and, therefore, tests of skeletal muscle function that respond to nutrition (59), may be useful also in patients with chronic liver disease.

Subjective global assessment. Subjective global assessment (SGA) when compared with anthropometry shows an agreement of 77% (5). SGA may prove a useful tool for screening for malnutrition but this approach fails to provide a sensitive quantitative measure of nutritional changes.

Composite scores. Various modifications of the protein calorie malnutrition score (60) have been used by the Veteran's Administration study group investigators (3, 35, 55, 57). In this scoring system, however, variables like midarm muscle area, skinfold thickness, creatinine excretion, lymphocyte count, recall antigen testing and muscle function have been combined with variables such as ideal body weight or circulating levels of visceral proteins that are of questionable value in chronic liver disease. The prognostic nutritional index (61) was of no value in identifying cirrhotic patients at risk of complications following liver transplantation (62).

Conclusions. At present, there is no general consensus on which technique should be used to assess nutritional status in patients with chronic liver disease. Composite scores are used in clinical trials in order to maximise information. At present, a reliable evaluation of the spontaneous nutrient intake appears to allow selection of patients at high risk. Accurate anthropometric measurements with expression of the results as percentiles of age- and sex-matched healthy volunteers probably represent an acceptable evaluation of nutritional status for enrollment of patients into clinical studies. More systematic studies of body composition and tissue function are needed.

Consequences of protein-energy malnutrition for the liver

Effect on liver morphology and function

PEM may affect liver morphology in animals although this has not been demonstrated to any convincing degree in humans (63). Rats, deprived of essential nutrients, develop liver fibrosis and, occasionally, fibrosis is observed in the livers of children with kwashiorkor. In both cases, fibrosis is readily reversed by administration of an adequate diet. Obese humans subjected to total starvation, or a severely energy deficient diet, develop transient degenerative changes with focal necrosis (63, 64).

PEM may affect liver function. In cirrhotic patients, an association between nutritional status and quantitative liver function, i.e. galactose elimination capacity and caffeine clearance, has been found by some (36), but not by all investigators (9). Thus, in nutritional intervention trials in cirrhotic patients, quantitative liver function tests improved more, or more rapidly in treatment groups. This included antipyrine (34), aminopyrine (65) and ICG clearance (66), as well as galactose elimination capacity (67, 68).

Quantitative liver function tests seem to be useful for following 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 impaired liver function due to a reduction in functional hepatic mass as opposed to impaired liver function secondary to inadequate nutrition.

Conclusions. PEM impairs liver function but rarely causes morphological alterations. Quantitative liver function tests can be used as global indicators of functional impairment but are not capable of separating between malnutrition-induced and disease-induced liver malfunction.

Association with clinical course

PEM is associated with an unfavourable clinical outcome. In cirrhotic patients in general, there is an association between nutritional status and mortality (4). Furthermore, within Child groups A and B, there is an association between nutritional status and mortality (7). Malnutrition when defined by low dietary intake is associated with high mortality (35). Malnutrition has been shown to be an independent predictor of both the first bleeding episode and survival in cirrhotic patients with oesophageal varices (69). Malnutrition also is associated with the presence of refractory ascites or the persistence of ascites (4). Preoperative nutritional status is related to postoperative morbidity and mortality in patients with cirrhosis (70).

In controlled trials, the rate of complications (ascites, gastrointestinal bleeding, encephalopathy, infection and mortality) tended to respond favourably to nutritional intervention that successfully increased nutrient intake in treated patients over controls (32–34, 66, 68, 71, 72).

Conclusions. Malnutrition negatively affects clinical outcome in terms of survival and complications. The relative contribution to clinical outcome of either PEM associated liver dysfunction or PEM associated malfunction of extrahepatic tissues cannot readily be differentiated. Apart from

improvement of nutritional status and/or liver function, a beneficial effect of nutritional intervention should be demonstrated on clinical outcome.

Ways to influence the nutritional status in liver disease

Tools and strategies to influence nutritional status

Nutritional status can be influenced by manipulations in the delivery of macro- and micronutrients with regard to composition and quantity in order to ensure an adequate supply with nutritious substrates. Secondly the regulation of substrate metabolism may be modified by use of special substrates and/or mediators or hormones. In another strategy, poor nutrient intake due the loss of appetite could be corrected by modifiers of the central nervous regulation of appetite. Effective treatment of anorexia certainly would have a major impact on nutritional state and prognosis of these patients (35). At present, however, it is not known which mechanisms are involved in the loss of appetite in cirrhotic patients.

Nutritional intervention by means of increased nutrient supply, modified eating patterns or administration of nitrogenous substrates such as branched chain amino acids (BCAA) can improve a number of static variables of nutritional status such as nitrogen balance, serum protein concentrations, anthropometric measures, or mortality (29, 33–36, 57, 73). Other investigators have studied the effect of nutritional interventions on dynamic variables such as substrate utilisation, energy expenditure and extra-hepatic tissue function (17, 55, 74–79), and their observations are discussed elsewhere in this paper.

Conclusion. Nutritional status may be influenced by altering substrate availability, use of special substrates, manipulation of metabolic regulation or treatment of anorexia.

Nutritional intervention

All patients who are eating not enough to cover their estimated/measured caloric needs should be offered systematical nutritional/dietary surveillance, advice and therapy aimed at provision of adequate nutrient intake. All interventions by dietary counselling or nutritional supplementation require cooperative and willing patients.

Eating pattern. A modified eating pattern with four to seven small meals including at least one late evening meal improves nitrogen economy and substrate utilisation in stable cirrhotic patients (73, 78).

Dietary supplements. Oral supplementation may provide the patient with the desired amount of a particular substrate, while permitting the continuation of an oral diet. Short-term supplementation with BCAA enables protein-intolerant patients with cirrhosis to attain positive nitrogen balance without increasing the risk of encephalopathy (80, 81). Long-term BCAA supplementation seems to be associated with better nitrogen accretion and liver function, while anthropometric measures are not clearly improved (82, 83).

Vegetable protein diets. Such diets do not consistently improve nitrogen economy. The apparent increase in nitrogen retention as judged by urinary excretion apparently may result from a nitrogen shift to increased incorporation and elimination in fecal bacteria (84).

Artificial feeding. Many malnourished cirrhotic patients are anorexic and cannot meet their nutrient requirements by oral intake 'ad lib'. This has been demonstrated in intervention trials when artificial feeding by use of liquid formulae proved to be more effective in providing adequate amounts of nutrients than normal oral nutrition 'ad lib'. Moreover, in patients with predominantly alcoholic liver disease the magnitude of daily caloric intake in general is positively correlated with survival (35).

Intervention by enteral nutrition using liquid formulae to supplement spontaneous oral nutrition is associated with improved survival and liver function (33–35, 57). Improvement of nutritional state, however, is not attained unequivocally when judged by improvement in serum proteins (albumin, transferrin, retinol binding protein), immunoreactivity (lymphocyte count, recall antigen test) and anthropometric variables (32–35, 57). In these trials, a protein intake of up to 1.3–1.5 $g \cdot kg^{-1} \cdot d^{-1}$ was tolerated by many patients without adverse effects on mental state (33–36, 57, 77, 79, 85).

Tube feeding. The decision, when to initiate tube feeding is debated. While tube feeding yields superior results over 'ad lib' oral feeding due to inadequate voluntary intake (33, 34), others are hesitant because of the risk of variceal bleeding. From the evidence of published trials, however, there is no suggestion that enteral tube feeding increases the incidence of variceal bleeding (33, 34). Slow or intermittent gastrointestinal (GI) bleeding is not an absolute contraindication to enteral feeding. In any case, patients must not be fasted and thus the introduction of tube feeding should not be delayed.

There is no general agreement as to whether enteral feeding should be intermittent (common clinical practice) or continuous (33, 34). Liquid enteral formulae for cirrhotic patients should preferably be of high energetic density (1.5 kcal/ml) with a low sodium content (40 mmol/d) so that they can be used in patients with fluid retention (33). Questions like optimal composition of non-nitrogenous caloric substrates or the nutritional efficacy of increased BCAA content in patients without encephalopathy have not been adressed in controlled trials.

Parenteral nutrition. Parenteral nutrition should be reserved for those not capable or willing to participate in oral nutrition or enteral tube feeding. Regarding energy and nitrogen provision the same guidelines should be followed as given for enteral nutrition.

Liver-adapted amino acid solutions. Solutions with an increased content of BCAAs (40–45%) and reduced amounts of aromatic amino acids and methionine have been introduced for the treatment of patients with liver disease (86). While they may have some value in the treatment of hepatic encephalopathy (vide infra) they have no documented effect on nutritional state. In some countries 'coma-solutions' are marketed containing only BCAAs and other compounds believed to be effective in hepatic encephalopathy. These are unbalanced solutions and not recommended as a nitrogen source for parenteral nutrition.

Special substrates. Ammonia lowering compounds such as arginine, ornithine-aspartate or ornithine-α-ketoglutarate have no effect on the nutritional status of patients with liver disease. Likewise, the nutritional value of special substrates like glutamine, nucleotides or ω-3-fatty-acids and of 'super-nutrients' such as phosphatidylcholine or S-adenosyl-L-methionine remains to be established.

Micronutrients. Apart from correcting established nutritional deficiency states no effect on nutritional state is obtained by administration of the micronutrients zinc, selenium, vitamin A/carotenoids, or vitamin E/tocopherols. Both, vitamin A and zinc supplementation, however, may indirectly alter nutritional state by improving gustatory function (87, 88) and thereby probably also volitional food intake. Also, hepatic urea production capacity has been shown to increase following oral zinc supplementation when accompanied by normalization of previously low plasma zinc levels (89). Since trace element deficiency may be difficult to diagnose, oral supplementation may be instituted liberally. In chronic cholestasis supplementation with fat soluble vitamins either by parenteral route (Vitamin ADEK) or orally using d-a-tocopheryl polyethylene glycole 100 succinate (TPGS) as a vehicle for vitamines E and D (90, 91) can prevent or correct deficiency states.

Anabolic hormones. Only moderately malnourished patients may benefit from anabolic steroids such as oxandrolone (40–80 mg/day) provided their caloric intake is adequate, whereas in severely malnourished patients this regimen is not effective (35).

Growth hormone (GH) has been successfully given for promotion of protein accretion, prevention of loss of intracellular water, and improvement in clinical outcome of patients with gut, renal, or pulmonary failure (92–95). In patients with cirrhosis, plasma levels of GH and IGFBP-1 are elevated, whereas IGF-1 and IGFBP-3 levels are decreased (96–98) suggesting possible GH resistance (99). Data from preliminary trials in patients given GH document an increase in IGF-1 and IGFBP-3 in patients with cirrhosis but no change in liver function, body weight or body mass index (100).

Intravenous IGF-1 (a potent mediator of biologic GH effects) promotes protein anabolism as efficiently as subcutaneous GH in human volunteers made catabolic by caloric restriction (101). No data are available yet on the effects of IGF-1 on nutritional state in cirrhotic patients, although it is not clear as to whether this compound will be available in the near future because of its side-effects.

Conclusions. Nitrogen economy can be improved in the majority of patients by frequent small meals and by special dietary supplements in those who are intolerant of protein. Nutrient intake can be increased by supplemental enteral nutrition and nutrient intake can be ensured by tube or parenteral feeding. Anabolic steroids may improve nutritional state, but only in moderatly malnourished cirrhotics who also receive adequate oral or enteral nutritional supplementation. The role of anabolic hormones GH and IGF-1 remains to be established.

Effect of nutritional therapy on outcome

Oral diet

In general, patients with liver disease tolerate a normal diet. The majority of patients do not need any dietary restrictions and they may even be harmed by them. A decrease in dietary fat may be useful to reduce symptoms of steatorrhea in patients with cholestatic liver disease, but it is associated with the risk of inadequate energy intake and is not supported by appropriate clinical trials.

If patients are able to eat more than 70 g protein·d^{-1} without deterioriation of mental status, no modification of their diet is necessary or effective. The definition of intolerance to dietary protein, however, depends on the methods used to document changes in mental status. In patients with borderline protein intolerance (60–70 g protein·d^{-1}) a vegetable diet (102, 103), or a diet rich in fibre (84) may help to prevent hepatic encephalopathy.

Salt restriction is of potential value in patients with ascites not responding to diuretic treatment.

Supplements to oral nutrition

Supplementation of a normal oral diet is necessary only when daily requirements of energy, protein, electrolytes, trace elements or vitamins are not met by actual intake.

Energy. At present, it can safely be assumed that patients with compensated cirrhosis do not require modification of their intake of non-nitrogenous substrates. In patients with severe hepatic insufficiency, frequent carbohydrate feedings may help to avoid hypoglycemia and counteract the metabolic situation of advanced liver failure (104).

Protein. Besides pharmacological methods to improve mental status (disaccharides, antibiotics) supplementation of a low protein diet with BCAA may be useful. Patients with stable cirrhosis improved in psychometric testing when their normal diet was supplemented with BCAA (0.25 g·kg^{-1}·d^{-1}) rather than with isonitrogenous amounts of casein (82, 83). It is unclear what minor improvements of psychometric tests mean for the quality of life of

patients. Patients with abnormal psychometric tests may do quite well when their performance in daily life is tested (105).

In patients intolerant of a daily protein intake of 1.0 $g \cdot kg^{-1} \cdot d^{-1}$ dietary protein may need to be reduced to an intake of 0.5 $g \cdot kg^{-1} \cdot d^{-1}$, but this should be avoided at all cost. In this situation, positive nitrogen balance and improvement in nitrogen intake can be achieved by oral supplementation of BCAA at 0.25 $g \cdot kg^{-1} \cdot d^{-1}$ without undue risk of encephalopathy (80–82). It should be recognized, however, that protein intolerance may present as a transient phenomenon and that patients may later be tolerant of a higher protein intake when the increment in daily dietary protein has been slow (106). Generally, periods of protein restriction should be kept as short as possible.

Micronutrients, electrolytes. While an association between encephalopathy and zinc defidiency could be demonstrated (107, 108), three randomized controlled trials of oral supplementation (600 mg zinc daily) produced conflicting results in patients with subclinical encephalopathy (109–111). Improved zinc status, however, may be associated with improvement of liver function as discussed above. Supplementation with calcium and vitamin D has been recommended for treatment of patients with osteopenia in chronic liver disease, although these measures failed to improve bone mineral density in patients with primary biliary cirrhosis; estrogen replacement was more effective (112, 113).

Conclusion. Supplements to oral nutrition are of value in the small subgroup of protein-intolerant patients (BCAA) and in patients with documented deficiencies of micronutrients (zinc, vitamin A).

Enteral nutrition

There are several controlled trials of enteral nutrition involving a substantial number of patients (32–34, 57, 114–116) with predominantly or exclusively alcohol related liver disease. Most patients had either stable liver disease or acute alcoholic hepatitis, but no patients were protein-intolerant and protein restriction was not necessary. Since many patients had reduced volitional oral intake, the observed beneficial effects seem to be arisen because energy and nitrogen intake increased in the treatment groups. No information is available on the effects of enteral nutrition in patients with non-alcoholic liver disease.

In general, the observed results reflect effects of nutritional supplementation in treatment groups. A significant effect on mortality was observed only in association with longer nutritional support (> 3 weeks) and low spontaneous nutrient intake (33). In addition, in a trial comparing oxandrolone with placebo a drug effect was only observed when adequate nutrition was provided (35). Beneficial results have been obtained with standard as well as with BCAA-enriched formulae and therefore standard formulae may be used except in cases of protein intolerance.

Conclusions. Supplementary enteral nutrition is of documented value in cirrhotic patients resulting in an improvement in nutritional status and possibly mortality. Liver function as well as hepatic encephalopathy may improve.

Parenteral nutrition in patients with alcoholic hepatitis

Parenteral nutrition using conventional amino acid solutions has been given as a nutritional supplement in addition to oral nutrition ad lib in seven controlled trials. Parenteral energy and nitrogen supply were in the range of 200–3000 $kcal \cdot d^{-1}$ and 35–130 g $protein \cdot d^{-1}$, while oral intakes ranged from 13 to 39 $kcal \cdot kg^{-1} \cdot d^{-1}$ (58, 66–68, 71, 72, 115–118).

Using this approach, mortality remained unaffected most likely due to the inclusion of patients with only moderately severe disease. No detrimental effects of the increased nitrogen intake were observed as far as neuropsychiatric status was concerned, although this was not optimally monitored. Improvement in visceral protein status was demonstrated by a majority of studies. Also, an improvement in liver function (galactose elimination capacity, serum bilirubin) was found.

Conclusions. Parenteral nutrition provides a useful therapeutic option for the treatment of malnutrition in alcoholic hepatitis patients not suitable for or not tolerating enteral nutrition. It seems to have a beneficial effect on liver function, but in these patients studied it is difficult to separate the effects of nutritional therapy from those of cessation of alcohol abuse and liver disease. There are no published randomized trials comparing enteral vs parenteral nutrition in patients with alcoholic hepatitis or cirrhosis.

Perioperative parenteral nutrition in chronic liver disease

Patients with stable cirrhosis probably do not need any specific treatment preoperatively, but no well-designed prospective studies are available which have addressed this topic. Malnourished cirrhotic patients undergoing non-shunt laparotomy are at higher risk of postoperative complications including death than those who are not malnourished (119). In cirrhotic patients undergoing hepatic resection, esophageal transection with splenectomy or distal splenorenal shunting procedures no difference in the frequency of encephalopathy was observed during 14 days postoperative parenteral nutrition with a conventional or a BCAA-enriched solution (120).

In patients having surgery for hepatocellular cancer pre- and postoperative parenteral nutrition has a beneficial effect on mortality and nutritional status as assessed by visceral protein concentrations (56). More detailed information on liver function and mental state were not available and it should be noted, that only 10% of the patients were malnourished. The treatment group received parenteral nutrition with increased BCAA-content whereas controls received isotonic glucose and electrolyte solutions.

Conclusions. Cirrhotic patients benefit from immediate

postoperative nutrition and, in the absence of encephalopathy, there is no need to use BCAA-enriched rather than conventional amino acid solutions. Most likely, early enteral nutrition may be at least as effective as parenteral nutrition, but this has not been formally investigated.

Parenteral nutrition in cirrhosis

Compensated cirrhosis. If patients with compensated cirrhosis require parenteral nutrition then this can be supplied by standard solutions.

Cirrhosis with encephalopathy. Most of the controlled studies performed 10–15 years ago adressed the question of the value of BCAA in the treatment of hepatic encephalopathy (121–127). Their results are conflicting (for review see 128). Studies cannot be compared directly because of differences in design, patient selection, treatment schedules and study endpoints. The effect on hepatic encephalopathy is not readily discernable if complications of cirrhosis such as GI bleeding, sepsis, or renal failure are present which determine the final outcome. A meta-analysis (129) found a trend in favour of beneficial effects of BCAA-enriched solutions on hepatic encephalopathy, but the authors concluded that more and better designed studies are needed to definitively prove or disprove the role of this treatment. From these short-term interventional studies no meaningful data regarding the effect of BCAA-enriched solutions on nutritional status or liver function are available.

Less information is available on the optimal formulation and composition of the energy-yielding substrates carbohydrate and fat. In certain patients, the increase in fat intake to cover 50% of non-protein calories may aid in reaching an adequate energy intake.

Conclusions. Adequate nutrition per se counteracts hepatic encephalopathy; parenteral nutrition is only indicated, when oral or enteral nutrition (including tube feeding) is not possible. BCAA may improve mental state in patients with hepatic encephalopathy provided that liver function does not further deteriorate and major clinical complications are absent. The improvement of encephalopathy by BCAA is not necessarily a result of better nutrition alone. The use of BCAA-enriched solutions has no effect on survival.

Parenteral nutrition in fulminant hepatic failure

There are no controlled studies in these patients. It is unknown whether such patients can appropriately metabolize amino acids or fat at all. Glucose administration is mandatory to prevent or treat hypoglycemia. In clinical practise, plasma levels of lactate, glucose and triglycerides may be used as a guide to monitor substrate utilisation.

Chronic cholestasis

From the point of nutrition, the basic defect in these conditions is impaired fat digestion and impaired absorption of fat soluble vitamins. At present, only the role of vitamin D has been investigated to any greater extent as referred to in the section on supplements. In the presence of vitamin deficiency the respective vitamins should be given parenterally.

Nutrition in liver transplantation

Impact of preoperative nutritional status on outcome of liver transplantation

Malnutrition is uncommon in individuals transplanted for fulminant hepatic failure, whereas it is often observed in those suffering from advanced chronic liver disease (62, 130, 131). Subjective global assessment of variables such as muscle wasting, loss of subcutaneus fat, dietary intake, and functional capacity and physical activities have been recommended for assessing nutritional state in transplant candidates (132, 133). Composite scores to identify high risk patients have been used with some success in one (130) but not in another study (62). In one large study bioelectrical impedance analysis was used to estimate body cell mass and fat free mass and in a subgroup of patients body cell mass was also determined by total body potassium counting showing a close correlation to fat free mass values obtained by BIA (9).

From these studies it can be concluded that poor nutritional state before transplantation is associated with prolonged stay in intensive care unit, on respirator therapy and in hospital and with increased mortality (9, 130, 133, 134). Also, hypermetabolism prior to transplantation seems to be associated with the persistence of hypermetabolism and an unsatisfactory course postoperatively (135). Judging from answers to a questionnaire European transplant centers do not regard malnutrition per se as a general contraindication to liver transplantation, since in cirrhosis it is part of the spectrum of clinical manifestations of the disease. In malnourished children, growth, in terms of height and body weight, prior to transplantation was observed only in those on oral BCAA supplementation but not in controls (136). In view of these findings, it would be desirable to have more information on the efficacy and impact of nutritional support prior to transplantion.

Conclusions. Malnutrition is not a contraindication to transplantation but may negatively affect outcome. Systematic evaluation of the effects of nutritional intervention prior to elective transplantation is needed with regard to substrate metabolism, body composition and clinical outcome.

Postoperative nutrition in liver transplantation

Reilly and colleagues (137) compared the effects of two parenteral nutritional regimens using either a standard or a BCAA-enriched amino acid solution with isotonic electrolyte or glucose infusions in postoperative transplant patients. Both groups of patients, who also received parenteral nutrition, had a better outcome in terms of shortened

ventilator and intensive care treatment than those without nutritional support and there was no difference between those receiving a standard and those receiving a BCAA-enriched solution.

Hasse and colleagues (138) compared early enteral feeding, commenced at 12 h after transplantation, with conventional intravenous electrolyte solutions until oral feeding was started. Significantly fewer viral infections and better nitrogen retention were found in patients who were enterally fed. Most frequently, nasogastric feeding tubes are used, but jejunostomy tubes, placed at the time of transplantation have been used without undue risk of serious complications (139).

Direct comparison of parenteral and early enteral nutrition revealed comparable efficacy of both strategies with regard to provision of nutrients and nutritional state on postoperative day 10 (140). At present, it may be concluded that early postoperative enteral nutrition is well tolerated (138, 140, 141) and may reduce complication rates and cost (140).

Considering long-term results, protein turnover seems to decrease but not normalized 12 months after transplantation (142). At that time body composition analysis reveals a decrease in total body water, an increase in total body fat but no change in body cell mass (135, 142). Despite supposedly normal dietary intake, excessive weight gain and hypercholesterolemia were observed within the first 18 months after transplantation (143, 144). This has been attributed to obesity prior to transplantation as well as to changes in energy expenditure and disturbance in cholesterol metabolism by immunosuppressive agents such as cyclosporine (143, 144). Therefore, after transplantation long-term metabolic and dietary evaluation and counseling may prove useful.

Conclusions. Early postoperative nutrition is clearly beneficial following liver transplantation in terms of morbidity. Nutrition should be given preferably by the enteral route as early as possible. Few data are available on substrate metabolism and body composition from long-term follow-up after transplantation.

Substrate requirements

Energy. In general, non-protein energy requirement in the graft recipient does not differ from other patients with abdominal surgery (145) and can be estimated from Harris and Benedict's equations (37) using ideal body weight plus 30% (141, 146). At present, there are insufficient data to delineate special patterns of substrate requirement and utilisation unique to patients with a liver graft. Some authors have used indirect calorimetry in the pre- and post-transplant period to estimate substrate requirements with particular regard to impairment of glucose utilization and compensation by fat emulsions (9, 141). In clinical practice, adequate substrate utilisation may be monitored by determination of glucose, lactate, and triglyceride levels in serum. In the early postoperative period glucose metabolism may be disturbed and insulin resistance may be observed. In preoperatively nondiabetic patients hyperglycemia should be treated by reducing glucose administration since in the presence of insulin resistance high doses of insulin fail to improve glucose oxidation (147).

Protein. Grafted patients may exhibit considerable nitrogen losses with a persistantly negative nitrogen balance for 28 days postoperatively (146); therefore, protein or amino acid requirements may be increased. In reported trials, however, a protein or amino acid intake of 1.0–1.5 $g \cdot kg^{-1} \cdot d^{-1}$ has been used (133, 137), which does not differ from recommendations for surgical patients in general. Monitoring of postoperative urinary urea excretion may help to determine actual nitrogen requirement. There seems to be no advantage in using BCAA-enriched amino acid solutions over conventional amino acid solutions (137).

Micronutrients and electrolytes. At present, no recommendations can be given on the basis of published trials. Caution should be exerted when attempting to rapidly correct chronic hyponatremia because of the risk for pontine myelinolysis (148). Magnesium levels should be monitored to look for cyclosporine or tacrolimus induced hypomagnesemia (149).

Conclusions. With the exception of potentially elevated nitrogen requirements transplanted patients do not differ from surgical patients in general with regard to macronutrient requirements. Micronutrient and electrolyte status should be monitored in order to identify and correct deficiency states.

Requirements and recommendations

Energy and substrate requirements

Energy. Measured energy expenditure has been found increased over controls (38, 150, 151) or predicted values (9, 152) in patients with cirrhosis who therefore have been classified as hypermetabolic. But this is not a uniform finding since hypometabolism as well as normometabolism have been observed in patients with cirrhosis (9–11, 17, 39, 150, 152). The diagnosis and the degree of hypermetabolism, however, are highly dependent not only the reference population (controls or predicted values), but also on the expression of energy expenditure in relation to either body weight (ideal, actual, or 'dry' weight), fat free mass or body cell mass and this is discussed in detail elsewhere (52, 153). When related to predicted energy expenditure among stable cirrhotics a subgroup of 15–20% may be considered as hypermetabolic, 25–30% as hypometabolic and the large majority as normometabolic (9, 152). Hypemetabolism may be an indicator of a high risk population characterized by more severe malnutrition, greater hemodynamic abnormalities and a poorer outcome after transplantation (52, 135) and, therefore, the diagnosis should be based on a sound assessment of body cell mass as a

major determinant of energy expenditure (153). Increased resting energy expenditure has also been observed during complications of liver disease, such as acute hepatic failure (154), high volume ascites (39), or presence of hepatoellular carcinoma (155).

Total energy expenditure in cirrhosis has been determined only occasionally and increased requirements appear to be offset by reduced physical activity. Diet-induced thermogenesis has been found normal in cirrhotics (15, 17, 156) and energy requirements for physical activity do not seem to be increased (157, 158).

Although resting energy expenditure is difficult to predict in patients with clinically stable liver cirrhosis, for practical purposes energy requirement may be calculated from the Harris and Benedict equation (52).

Protein. In clinical intervention trials protein or amino acids were given in amounts of 0.6–1.2 $g \cdot kg^{-1} \cdot d^{-1}$ in patients with cirrhosis and severe encephalopathy (129) and 0.5–1.6 $g \cdot kg^{-1} \cdot d^{-1}$ in patients with alcoholic hepatitis or cirrhosis with or without low grade encephalopathy (32–34, 57, 58, 66–68, 71, 72, 117, 118). In only a few studies, however, were protein requirements assessed systematically. From these findings, patients with stable cirrhosis appear to have increased protein requirements of 1.2 $g \cdot kg^{-1} \cdot d^{-1}$ to maintain nitrogen homeostasis as opposed to 0.8 $g \cdot kg^{-1} \cdot d^{-1}$ in normal individuals (29, 36, 106). The reasons for this phenomenon are not yet clear, but the increased protein requirement seems to be due to increased whole body protein degradation which may be due to low plasma levels of IGF-1 (159, 160).

Micronutrients. Deficiency of fat-soluble vitamins is observed in patients with steatorrhea due to cholestasis and bile salt deficiency und in alcohol abusers (112, 161). A depletion in water soluble vitamins is not uncommon in cirrhosis, particularly in alcohol induced cirrhosis (162, 163).

Zinc and selenium deficiency has been observed in both alcoholic and non-alcoholic liver disease (164–166) and may be associated with neurological symptoms (167). The causes are multiple: reduced dietary intake, malabsorption, increased metabolic demands, impaired conversion of vitamins into their active forms and reduced hepatic storage.

Conclusions. In patients with clinically stable chronic liver disease energy requirements are similar to healthy subjects. Energy expenditure is increased in patients with cirrhosis and complications. Protein requirements are increased in patients with cirrhosis. Micronutrient deficiencies are not uncommon in cirrhosis, but no data on requirements are available in this patient group.

Recommendations

In patients with chronic liver disease nutritional therapy is of documented value in those with malnutrition who are failing to maintain an adequate oral nutrient intake. Generally, nutrition should be provided by the oral or the enteral route. Parenteral nutrition should only be used when enteral feeding is not possible or impractable. For parenteral nutrition energy should be provided by glucose and fat in a ratio of 65–50 : 35–50% of non-protein calories. Parenterally administered fat is cleared from the blood and utilized efficiently by the majority of patients with cirrhosis (23, 24); MCT/LCT emulsions are well tolerated in transplanted patients (168). As a standard, nitrogen should be provided by conventional amino acid solutions for parenteral nutrition or high quality protein for enteral feeding in amounts to meet requirements as outlined above.

Recommendations for various clinical conditions are summarized in the Table. In patients with clinically stable cirrhosis, available data on energy and nitrogen balance suggest a recommended intake for maintaining body composition of 1.3 × REE or 25–30 $kcal \cdot kg^{-1} \cdot d^{-1}$ non-protein energy plus 1.0–1.2 $g \cdot kg^{-1} \cdot d^{-1}$ of protein. In malnourished patients requiring repletion, intakes should be higher.

According to the intervention studies available, malnourished patients who have an inadequate dietary intake and are at risk of fatal complications of liver cirrhosis (infection, bleeding, etc) should receive nutritional support. In the studies suggesting a positive effect on liver function and clinical outcome, non-protein energy was given in amounts of 35–40 $kcal \cdot kg^{-1} \cdot d^{-1}$ plus protein of up to 1.6 $g \cdot kg^{-1} \cdot d^{-1}$. In these patients, low grade encephalopathy (I–II) should not be considered a contraindication to nutritional support including an adequate protein supply.

In patients with encephalopathy as their main problem, other precipitating causes should be excluded before considering the patient protein-intolerant. Transient protein restriction can be instituted, but after a few days adequate nutrition should be reinstituted. In proven protein-intolerant patients, oral BCAA-supplementation may be helpful in

Table Nutrition in chronic liver disease – recommendations of the 1997 ESPEN consensus group

Clinical condition	Non-protein energy $kcal \cdot kg^{-1} \cdot d^{-1}$	Protein or amino acids $g \cdot kg^{-1} \cdot d^{-1}$
Compensated cirrhosis	25–35	1.0–1.2
Complications		
Inadequate intake Malnutrition	35–40	1.5
Encephalopathy I–II	25–35	Transiently 0.5, then 1.0–1.5 if protein intolerant: vegetable protein or BCAA supplement
Encephalopathy III–IV	25–35	0.5–1.2 BCAA-enriched amino-acid solution

Generally, the oral or enteral routes are preferred.

Parenteral nutrition should only be used when enteral feeding is not possible or impractable. For parenteral nutrition energy should be provided by glucose and fat with fat constituting 35–50% of non-protein calories. Nitrogen should be provided using conventional amino acid solutions unless indicated otherwise. For calculations ideal body weight should be used.

achieving an adequate nitrogen intake. Vegetable protein can also be tried, but the risk of inadequate protein assimilation should be kept in mind.

Patients in coma (encephalopathy III–IV°) can safely be given TPN regimens providing 25–30 $kcal \cdot kg^{-1} \cdot d^{-1}$ non-protein energy plus 1.0 $g \cdot kg^{-1} \cdot d^{-1}$ using BCAA-enriched amino acid solutions.

In addition to the clinical conditions given in the Table, it also seems advantageous to administer postoperative nutrition to patients undergoing major surgery, including transplantation. Fasting periods should not exceed 6 h due to the limited glycogen stores in malnourished cirrhotic patients.

References

1. Patek A J Jr, Post J. Treatment of cirrhosis of the liver by a nutritious diet and supplements rich in vitamin B complex. J Clin Invest 1941; 20: 481–505
2. Child C G, Turcotte J G. Surgery and portal hypertension. In: Child C G, ed. The Liver and Portal Hypertension. Philadelphia: Saunders, 1964: 50–51
3. Mendenhall C L, Anderson S, Weesner R E, Goldberg S J, Crolic K A. Protein calorie malnutrition associated with alcoholic hepatitis. Am J Med 1984; 76: 211–221
4. Lautz H U, Selberg O, Körber J, Bürger M, Müller M J. Protein calorie malnutrition in liver cirrhosis. Clin Invest 1992, 70: 478–486
5. Italian Multicentre Cooperative Project on nutrition in liver cirrhosis. Nutritional status in cirrhosis. J Hepatol 1994; 21: 317–325
6. Crawford D H G, Shepherd R W, Halliday J W et al. Body composition in nonalcoholic cirrhosis: the effect of disease etiology and severity on nutritional compartment. Gastroenterology 1994; 106: 1611–1617
7. Merli M, Riggio O, Dally L, P I N C. What is the impact of malnutrition on survival in liver cirrhosis. Hepatology 1996; 23: 1041–1046
8. Orloff M J, Charters A C, Chandler J G et al. Portocaval shunt as emergency procedure in unselected patients with alcoholic cirrhosis. Surg Gynecol Obstet 1975; 141: 59–68
9. Müller M J, Lautz H U, Plogmann B, Burger M, Körber J, Schmidt F W. Energy expenditure and substrate oxidation in patients with cirrhosis: the impact of cause, clinical staging and nutritional state. Hepatology 1992; 15: 782–794
10. Owen O E, Trapp, V E, Reichard J A et al. Nature and quantity of fuels consumed in patients with alcoholic cirrhosis. J Clin Invest 1983; 72: 1821–1832
11. Merli M, Riggio O, Romiti A et al. Basal energy production rate and substrate use in stable cirrhotic patients. Hepatology 1990; 12: 106–112
12. Bianchi G, Marchesini G, Zoli M, Bugianesi E, Fabbri A, Pisi E. Prognostic significance of diabetes in patients with cirrhosis. Hepatology 1994; 20: 119–125
13. Müller M J, Pirlich M, Balks H J, Selberg O. Glucose intolerance in liver cirrhosis: Role of hepatic and non-hepatic influences. Eur J Clin Chem Clin Biochem 1994; 32: 749–758
14. Petrides A S, De Fronzo R A. Glucose and insulin metabolism in cirrhosis. J Hepatol 1989; 8: 107–114
15. Müller M J, Willmann O, Rieger A et al. Mechanism of insulin resistance associated with liver cirrhosis. Gastroenterology 1992; 102: 2033–2041
16. Selberg O, Burchert W, van der Hoff J et al. Insulin resistance in cirrhosis. Positronemission tomography scan analysis of skeletal muscle glucose metabolism. J Clin Invest 1993; 91: 1897–1902.
17. Riggio O, Merli M, Romiti A et al. Early post prandial energy expenditure and macronutrient use after a mixed meal in cirrhotic patients. J Parent Enteral Nutr 1992; 16: 445–450
18. Kruszynska Y, Williams N, Perry M, Home P. The relationship between insulin sensitivity and skeletal muscle enzyme activity in hepatic cirrhosis. Hepatology 1988; 8: 1615–1619
19. Selberg O, Radoch E, Walter G F, Müller M J. Skeletal muscle glycogen content in patients with cirrhosis. Hepatology 1994; 20: 135–141
20. Merli M, Erikson S L, Hagenfeldt H, Wahren J. Splanchnic and peripheral exchange of FFA in patients with liver cirrhosis. J Hepatol 1986; 3: 348–355
21. Petrides S A, Groop L C, Riely C A, De Fronzo R A. Effect of physiologic hyperinsulinemia on glucose and lipid metabolism in cirrhosis. J Clin Invest 1991; 88: 561–570
22. Müller M J, Fenk A, Lautz H U et al. Energy expenditure and substrate metabolism in ethanol-induced liver cirrhosis. Am J Physiol 1991; 260: E338–E344
23. Müller M J, Rieger A, Willmann O et al. Metabolic responses to lipid infusions in patients with liver cirrhosis. Clin Nutr 1992; 11: 193–206
24. Druml W, Fischer M, Pidlich J, Lenz K. Fat elimination in chronic hepatic failure: long-chain vs medium-chain triglycerides. Am J Clin Nutr 1995; 61: 812–817
25. Cabré E, Nunez M C, Gonzalez-Huix F et al. Clinical and nutritional factors predictive of plasma lipid unsaturation deficiency in advanced liver cirrhosis: a logistic regression analysis. Am J Gastroenterol 1993; 88: 1738–1743
26. Cabré E, Abad-Lacruz A, Nunez M C et al. The relationship of plasma polyunsaturated fatty acid deficiency with survival in advanced liver cirrhosis: Multivariate analysis. Am J Gastroenterol 1993; 88: 718–722
27. Petrides A S, Luzi L, Reuben A, Riely C, DeFronzo R A. Effect of insulin and plasma amino acid concentration on leucine metabolism in cirrhosis. Hepatology 1991; 14: 432–441
28. McCullough A J, Tavill A S. Disordered Energy and protein metabolism in liver disease. Semin Liver Dis 1991; 11: 265–273
29. Nielsen K, Kondrup J, Martinsen L et al. Long-term oral refeeding of patients with cirrhosis of the liver. Br J Nutr 1995; 74: 557–567
30. Ballmer P E, Walshe D, McNurlan M A, Watson H, Brunt P W, Garlick P J. Albumin synthesis rates incirrhosis: correlation with Child-Turcotte Classification. Hepatology 1993; 18: 292–297
31. Ballmer P E, Reichen J, McNurlan M A, Sterchi A-B, Anderson S E, Garlick P J. Albumin but not fibrinogen synthesis correlates with galactose elimination capacity in patients with liver cirrhosis. Hepatology 1996; 24: 53–59
32. Bunout D, Aicardi V, Hirsch S et al. Nutritional support in hospitalized patients with alcoholic liver disease. Eur J Clin Nutr 1989; 43: 615–621.
33. Cabré E, Gonzalez-Huix F, Abad-Lacruz A et al. Effect of total enteral nutrition on the short-term outcome of severely malnourished cirrhotics. A randomized controlled trial. Gastroenterology 1990; 98: 715–720
34. Kearns P J, Young H, Garcia G et al. Accelerated improvement of alcoholic liver disease with enteral nutrition. Gastroenterology 1992; 102: 200–205
35. Mendenhall C L, Moritz T E, Roselle G A et al. A study of oral nutritional support with oxandrolone in malnourished patients with alcoholic hepatitis: results of a department of veterans affairs cooperative study. Hepatology 1993; 17: 564–576
36. Nielsen K, Kondrup J, Martinsen L, Stilling B, Vikman B. Nutritional assessment and adequacy of dietary intake in hospitalized patients with alcoholic liver cirrhosis. Br J Nutr 1993; 69: 665–679
37. Harris J A, Benedict F G. A biometric study of basal metabolism in man. Publication n° 270. Carnegie Institute of Washington DC, 1919
38. Schneeweiss B, Graninger W, Ferenci P et al. Energy metabolism in patients with acute and chronic liver disease. Hepatology 1990; 11: 387–393
39. Dolz C, Raurich J M, Ibanez J, Obrador A, Marsè P, Gayà J. Ascites increases the resting energy expenditure in liver cirrhosis. Gastroenterology 1991; 100: 738–744
40. Prijatmoko D, Strauss B J G, Lambert J R et al. Early detection of protein depletion in alcoholic cirrhosis: role of body composition analysis. Gastroenterology 1993; 105: 1839–1845
41. Mclntyre N. Undernutrition and malnutrition in cirrhosis. In: Tygstrup N, Orlandi F, eds. Cirrhosis of the Liver: Methods and Fields of Research. Amsterdam: Elsevier, 1987: 225–234
42. Mason J B, Roubenoff R. The unbearable lightness of being a cirrhotic Gastroenterology 1993; 105: 1911–1914
43. Bramley P, Oldroyd B, Stewart S et al. Body composition analysis in liver cirrhosis. The measurement of body fat by dual energy X-ray absorptiometry in comparison to skinfold anthropometry, bioelectrical impedance and total body potassium. In: Ellis K J, Eastman J D, eds. Human Body Composition. New York: Plenum Press, 1993: 11–214
44. Heymsfield S B, Arteaga C, McManus C, Smith J, Moffitt S.

Measurement of muscle mass in humans: validity of the 24-hour urinary creatinine method. Am J Clin Nutr 1983; 37: 478–494
45. Pirlich M, Selberg O, Böker K, Schwarze M, Müller M J. The validity of the creatinine approach to estimate skeletal muscle mass in patients with liver cirrhosis. Hepatology 1996; 24: 1422–1427
46. Roubenoff R, Kehayias J J. The meaning and measurement of lean body mass. Nutr Rev 1991; 46: 163–175
47. Forbes G B, Bruining G J. Urinary creatinine excretion and lean body mass. Am J Clin Nutr 1976; 29: 1359–1366
48. Guglielmi F W, Contento F, Laddaga L, Panella C, Francavilla A. Bioelectric impedance analysis: experience with male patients with cirrhosis. Hepatology 1991; 13: 892–895
49. Zillikens M C, van den Berg J W O, Wilson J H P, Swart G R. Whole body and segmental bioelectrical impedance analysis in patients with cirrhosis of the liver: changes after treatment of ascites. Am J Clin Nutr 1992; 55: 621–625
50. McCullough A J, Mullen K D, Kalhan S C. Measurements of total body and extracellular water in cirrhotic patients with and without ascites. Hepatology 1991; 14: 1102–1108
51. Zillikens M C, van den Berg J W O, Wilson J H P, Rietveld T, Swart G R. The validity of bioelectrical impedance analysis in estimating total body water in patients with cirrhosis. J Hepatol 1992; 16: 59–65
52. Müller M J, Böker K H W, Selberg O. Are patients with liver cirrhosis hypermetabolic? Clin Nutr 1994; 13: 131–144
53. Merli M, Romiti A, Riggio O, Capocaccia L. Optimal nutritional indexes in chronic liver disease. J Parenter Enteral Nutr 1987; 11: 130S–134S
54. Crawford D H G, Cuneo R C, Shepherd R W. Pathogenesis and assessment of malnutrition in liver disease. J Gastroenterol Hepatol 1993; 8: 89–94
55. Mendenhall C L, Moritz T E, Roselle G A et al. Protein energy malnutrition in severe alcoholic hepatitis: diagnosis and response to treatment. J Parenter Enteral Nutr 1995; 19: 258–265
56. Fan S-T, Lo C-M, Lai E C S, Chu K-M, Liu C-L, Wong J. Perioperative nutritional support in patients undergoing hepatectomy for hepatocellular carcinoma. N Engl J Med 1994; 331: 1547–1552
57. Mendenhall C, Bongiovanni G, Goldberg S et al. VA cooperative study on alcoholic hepatitis III: changes in protein-calorie malnutrition associated with 30 days of hospitalization with and without enteral nutritional therapy. J Parent Ent Nutr 1985; 9: 590–596
58. Naveau S, Pelletier G, Poynard T et al. A randomized clinical trial of supplementary parenteral nutrition in jaundiced alcoholic cirrhotic patients. Hepatology 1986; 6: 270–274.
59. Hill G L. Impact of nutritional support on the clinical outcome of the surgical patient. Clin Nutr 1994; 13: 331–340
60. Blackburn G L, Bistrian B R, Maini B S, Sclamm B A, Smith M F. Nutritional and metabolic assessment of the hospitalized patient. J Parenter Enteral Nutr 1977; 1: 11–22
61. Mullen J I, Buzby G P, Matthews D C, Smale B F, Rosato E F. Reduction of operative morbidity and mortality by combined preoperative and postoperative nutritional support. Ann Surg 1980; 192: 604–613
62. Di Cecco S R, Wieners E J, Wiesner R H, Southorn P A, Plevak D J, Krom R A F. Assessment of nutritional status of patients with end-stage liver disease undergoing liver transplantation. Mayo Clin Proc 1989; 64: 95–102
63. Conn, H O. Cirrhosis. In: Schiff L, Schiff E, eds. Diseases of the Liver. Philadelphia: Lippincott, 1982: 864–865
64. Drenick E J, Simmons F, Murphy J F. Effect on hepatic morphology of treatment of obesity by fasting, reducing diets and small-bowel bypass. N Engl J Med 1970; 282: 829–834
65. O'Keefe S J, El-Zayadi A R, Carraher T E, Davis M, Williams R. Malnutrition and immunoincompetence in patients with liver disease. Lancet 1980; ii: 615–617
66. Mezey E, Caballería J, Mitchell M C, Parés A, Herlong H F, Rodés J. Effect of parenteral amino acid supplementation on short-term and long-term outcomes in severe alcoholic hepatitis: a randomized controlled trial. Hepatology 1991; 14: 1090–1096
67. Achord J L. A prospective randomized clinical trial of peripheral amino acid-glucose supplementation in acute alcoholic hepatitis. Am J Gastroenterol 1987; 82: 871–875
68. Bonkovsky H L, Fiellin D A, Smith G S, Slaker D P, Simon D, Galambos J T. A randomized controlled trial of treatment of alcoholic hepatitis with parenteral nutrition and oxandrolone. l. Short-term effects on liver function. Am J Gastroenterol 1991; 86: 1200–1208
69. Møller S, Bendtsen F, Christensen E, Henriksen J H. Prognostic variables in patients with cirrhosis and oesophageal varices without prior bleeding. J Hepatol 1994; 21: 940–946
70. Helton W S. Nutritional issues in hepatobiliary surgery. Semin Liver Dis 1994; 14: 140–157
71. Nasrallah S M, Galambos J T. Amino acid therapy of alcoholic hepatitis. Lancet 1980 ii: 1276–1277
72. Diehl A M, Boinott J K, Herlong H F et al. Effect of parenteral amino acid supplementation in alcoholic hepatitis. Hepatology 1985; 5: 57–63
73. Swart G R, Zillikens M C, van Vuure J K, van den Berg J W O. Effect of late evening meal on nitrogen balance in patients with cirrhosis of the liver. Br Med J 1989; 299: 1202–1203
74. Holdsworth J D, Dionigi P, Clague M B, James O F W, Wright P D. Body protein metabolism and plasma amino acids in cirrhosis of the liver. The effect of varying the branched chain amino acid content of intravenous amino acid solutions. Clin Nutr 1984; 3: 153–162
75. Millikan W J, Henderson J M, Galloway J R et al. In vivo measurement of leucine metabolism with stable isotopes in normal subjects and in those with cirrhosis fed conventional and branched-chain amino acid-enriched diets. Surgery 1985; 98: 405–413
76. Weber F L, Bagby B S, Licate L, Kelsen S G. Effects of branched chain amino acids on nitrogen metabolism in patients with cirrhosis. Hepatology 1990; 11: 942–950
77. Swart G R, van den Berg J W O, Wattinema D L, Rietveld T, van Vuure J K, Frenkel M. Elevated protein requirements in cirrhosis of the liver investigated by whole body protein turnover studies. Clin Sci 1988; 75: 101–107
78. Verboeket-van de Venne W P H G, Westerp K R, van Hoek B, Swart G R. Energy expenditure and substrate metabolism in patients with cirrhosis of the liver: effects of the pattern of food intake. Gut 1995, 36: 110–116
79. Campillo B, Bories P N, Leluan M, Pornin B, Devanlay M, Fouet P. Short-term changes in energy metabolism after 1 month of a regular oral diet in severely malnourished cirrhotic patients. Metabolism 1995; 44: 765–70
80. Horst D, Grace N D, Conn H O et al. Comparison of dietary protein with an oral, branched chain-enriched aminoacid supplement in chronic portal-systemic encephalopathy: a randomized controlled trial. Hepatology 1984; 4: 279–287
81. Egberts E-H, Schomerus H, Hamster W, Jürgens. Branched chain amino acids in the treatment of latent portosystemic encephalopathy. A double blind placebo-controlled crossover study. Gastroenterology 1985; 88: 887–895.
82. Marchesini G, Dioguardi F S, Bianchi G P et al. Long-term oral branched-chain amino acid treatment in chronic hepatic encephalopathy. J Hepatol 1990; 11: 92–101
83. Plauth M, Egberts E-H, Hamster W et al. Long-term treatment of latent portosystemic encephalopathy with branched chain amino acids. A double-blind placebo-controlled crossover trial. J Hepatol 1993; 17: 308–314
84. Weber F L, Minco D, Fresard K M, Banwell J G. Effects of vegetable diets on nitrogen metabolism in cirrhotic subjects. Gastroenterology 1985; 89: 538–544
85. Morgan T R, Moritz T E, Mendenhall C L, Haas R, and V A. Cooperative study group. Protein consumption and hepatic encephalopathy in alcoholic hepatitis. J Am Coll Nutr 1995; 14: 152–158
86. Freund H, Dienstag J, Lehrich J et al. Infusion of branched-chain enriched amino acid solution in patients with hepatic encephalopathy. Ann Surg 1982; 196: 209–220
87. Weismann K, Christensen E, Dreyer V. Zinc supplementation in alcoholic cirrhosis. A double-blind clinical trial. Acta Med Scand 1979; 205: 361–366
88. Garrett-Laster M, Russell R M, Jacques P F. Impairment of taste and olfaction in patients with cirrhosis: the role of vitamin A. Hum Nutr Clin Nutr 1984; 38: 203–214.
89. Marchesini G, Fabbri A, Bianchi G, Brizi M, Zoli M. Zinc supplementation and amino acid-nitrogen metabolism in patients with advanced cirrhosis. Hepatology 1996; 23: 1084–1092
90. Sokol R J, Butler-Simon N, Conner C et al. Multicenter trial of d-α-tocopheryl polyethylene glycol 1000 succinate for treatment of vitamin E deficiency in children with chronic cholestasis. Gastroenterology 1993; 104: 1727–1735
91. Argao E A, Heubi J E, Hollis B W, Tsang R C. d-α-tocopheryl polyethylene glycol-1000 succinate enhances the absorption of

vitamin D in chronic cholestatic liver disease of infancy and childhood. Pediatr Res 1992; 31: 146–150
92. Suchner U, Rothkopf M M, Stanislaus G, Elwyn D H, Kvetan V, Askanazi J. Growth hormone and pulmonary disease. Metabolic effects in patients receiving parenteral nutrition. Arch Intern Med 1990; 150: 1225–1230
93. Gatzen C, Scheltinga M R, Kimbrough T D, Jacobs D O, Wilmore D W. Growth hormone attenuates the abnormal distribution of body water in critically ill surgical patients. Surgery 1992; 112: 181–187
94. Ziegler T R, Rombeau J L, Young L S et al. Recombinant human growth hormone enhances the metabolic efficacy of parenteral nutrition: a double blind, randomized controlled study. Clin J Endocrinol Metab 1992; 74: 865–873
95. Byrne T A, Morrissey T B, Nattakom T V, Scheltinga M R, Ziegler T R, Wilmore D W. Growth hormone, glutamine, and a modified diet enhance nutrient absorpti-on in patients with severe short bowel syndrome. J Parent Enteral Nutr 1995; 19: 296–302
96. Møller S, Juul A, Becker U, Flyvbjerg A, Skakkebaek N E, Henriksen J H. Concentrations, release, and disposal of insulin-like growth factor (IGF)-binding proteins (IGFBP), IGF-I, and growth hormone in different vascular beds in patients with cirrhosis. J Clin Endocrinol Metab 1995; 80: 1148–1157
97. Donaghy A, Ross R, Gimson A, Hughes S C, Holly J, Williams R. Growth hormone, insulinlike growth factor-1, and insulinlike growth factor binding proteins 1 and 3 in chronic liver disease. Hepatology 1995; 21: 680–688
98. Scharf J-G, Schmitz F, Frystyk J et al. Insulin-like growth factor-1 serum concentrations and patterns of insulin-like growth factor binding proteins in patients with chronic liver disease. J Hepatol 1996; 25: 689–699
99. Bucuvalas J C, Cutfield W, Horn J et al. Resistance to the growth-promoting and metabolic effects of growth hormone in children with chronic liver disease. J Pediatr 1990; 117: 397–402
100. Møller S, Becker U, Gronbaek M, Juul A, Winkler K, Skakkebaek N E. Short-term effect of recombinant human growth hormone in patients with alcoholic cirrhosis. J Hepatol 1994; 21: 710–717
101. Clemmons D R. Use of growth hormone and insulin-like growth factor I in catabolism that is induced by negative energy balance. Horm Res 1993; 40: 62–67
102. Greenberger N J, Carley J, Schenker S, Bettinger I, Stamnes C, Beyer P. Effect of vegetable and animal protein diets in chronic hepatic encephalopathy. Dig Dis 1977; 22: 845–855
103. Uribe M, Marquez M A, Ramos G G et al. Treatment of chronic portal-systemic encephalopathy with vegetable and animal protein diets. Dig Dis Sci 1982; 27: 1109–1116
104. Zillikens M C, van den Berg J W, Wattimena J L, Rietveld T, Swart G R. Nocturnal oral glucose supplementation. The effects on protein metabolism in cirrhotic patients and in healthy controls. J Hepatol 1993; 17: 377–383
105. Srivastava A, Mehta R, Rothke S P et al. Fitness to drive in patients with cirrhosis and portacaval shunting: a pilot study evaluating driving performance. J Hepatol 1994; 21: 1023–1028
106. Swart G R, van den Berg J W O, van Vuure J K, Tietveld T, Wattimena D L, Frenkel M. Minimum protein requirements in liver cirrhosis determined by nitrogen balance measurements at three levels of protein intake. Clin Nutr 1989; 8: 329–336
107. Grüngreif K, Abicht K, Kluge M et al. Clinical studies on zinc in chronic liver diseases. Z Gastroenterol 1988; 26: 409–415
108. van der Rijt C C D, Schalm S W, Schat H, Foeken K, DeJong G. Overt hepatic encephalopathy precipitated by zinc deficiency. Gastroenterology 1991; 100: 1114–1118
109. Reding P, Duchateau J, Bataille C. Oral zinc supplementation improves hepatic encephalopathy. Results of a randomized controlled trial. Lancet II 1984: 493–495
110. Bresci G, Parisi G, Banti S. Management of hepatic encephalopathy with oral zinc supplementation: a long-term treatment. Eur J Med 1993; 2: 414-416
111. Riggio O, Ariosto F, Merli M et al. Short-term oral zinc supplementation does not improve chronic hepatic encephalopathy. Results of a double-blind crossover trial. Dig Dis Sci 1991; 6: 1204–1208
112. Lindor K D. Management of osteopenia of liver disease with special emphasis on primary biliary cirrhosis. Semin Liver Dis 1993; 13: 367–373
113. Crippin J S, Jorgensen R A, Dickson E R, Lindor K D. Hepatic osteodystrophy in primary biliary cirrhosis: effects of medical treatment. Am J Gastroenterol 1994; 89: 47–50
114. Hirsch S, Bunout C, de la Maza P et al. Controlled trial on nutrition supplementation in outpatients with symptomatic alcoholic cirrhosis. J Parenter Enter Nutr 1993; 17: 119–124
115. Soberon S, Pauley M P, Duplantier R, Fan A, Halsted C H. Metabolic effects of enteral formula feeding in alcoholic hepatits, Hepatology 1987; 7: 1204–1209
116. Calvey H, Davis M, Williams R. Controlled trial of nutritional supplementation, with or without branched chain amino acid enrichement, in the treatment of acute alcoholic hepatitis. J Hepatol 1985; 1: 141–151
117. Simon D, Galambos J T. A randomized controlled study of peripheral parenteral nutrition in moderate and severe alcoholic hepatitis. J Hepatol 1987; 7: 200–207
118. Bonkovsky H L, Singh R H, Jafri I H et al. A randomized controlled trial of the treatment of alcoholic hepatitis with parenteral nutrition and oxandrolon. II: short-term effects on nitrogen metabolism, metabolic balance and nutrition. Am J Gastro 1991; 86: 1209–1218
119. Garrison R N, Cryer H M, Howard D A, Polk H C. Clarification of risk factors for abdominal operations in patients with hepatic cirrhosis. Ann Surg 1984; 199: 648–655
120. Kanematsu T, Koyanagi N, Matsumata T, Kitano S, Takenaka K, Sugimachi K. Lack of preventive effect of branched-chain amino acid solution on postoperative hepatic encephalopathy in patients with cirrhosis: a randomized, prospective trial. Surgery 1988; 104: 482–488
121. Rossi-Fanelli F, Riggio O, Cascino A et al. Branched-chain amino acids vs lactulose in the treatment of hepatic coma. A controlled study. Dig Dis Sci 1982; 27: 929–935
122. Wahren J, Denis J, Desurmont P et al. Is intravenous administration of branched chain amino acids effective in the treatment of hepatic encephalopathy? A multicentre study. Hepatology 1983; 3: 475–480
123. Cerra F B, Cheung N K, Fischer J E et al. Disease-specific amino acid infusion in hepatic encephalopathy: a prospective randomized, double-blind controlled trial. J Parent Enteral Nutr 1985; 9: 288–295
124. Michel H, Bories P, Aubin J P, Pomier-Layrargues G, Bauret P, Bellet-Herman H. Treatment of acute hepatic encephalopathy in cirrhotics with a branched-chain amino acids enriched versus a conventional amino acid mixture. A controlled study in 70 patients. Liver 1985; 5: 282–289
125. Fiaccadori F, Ginelli F, Pedretti G et al. Branched-chain enriched amino acid solutions in the treatment of hepatic encephalopathy: A controlled trial. Ital J Gastroenterol 1985; 17: 5–10
126. Strauss E, Dos Santos W R, Da Silva E C et al. Treatment of hepatic encephalopathy: a randomized clinical trial comparing a branched chain enriched amino acid solution to oral neomycin. Nutr Supp Svcs 1986; 6: 18–21
127. Vilstrup H, Gluud C, Hardt F et al. Branched-chain enriched amino acid versus glucose treatment of hepatic encephalopathy. A double blind study of 65 patients with cirrhosis. J Hepatol 1990; 10: 291–296
128. Ferenci P. Critical evaluation of the role of branched chain amino acids in liver disease. In: Thomas J C, Jones E S, eds. Recent Advances in Hepatology. Edinburgh: Churchill Livingstone, 1986; 137–154
129. Naylor C D, O'Rourke K, Detsky A S, Baker J P. Parenteral nutrition with branched chain amino acids in Hepatic encephalophathy: a metaanalysis. Gastroenterology 1989; 97: 1033–1042
130. Shaw B W, Wood R P, Gordon R D, Iwatsuki S, Gillquist W P, Starzl T E. Influence of selected patient variables and operative blood loss on six-month survival following liver transplantation. Semin Liv Dis 1985; 5: 385–393
131. Akerman P A, Jenkins R L, Bistrian B R. Preoperative nutrition assessment in liver transplantation. Nutrition 1993; 9: 350–356
132. Hasse J, Strong S, Gorman M A, Liepa G. Subjective global assessment: alternative nutrition-assessment technique for liver-transplant candidates. Nutrition 1993; 9: 339–343
133. Pikul J, Sharpe M D, Lowndes R, Ghent C N. Degree of preoperative malnutrition is predictive of postoperative morbidity and mortality in liver transplant recipients. Transplantation 1994; 57: 469–472
134. Moukarzel A A, Najm I, Vargas J, McDiarmid V S, Busuttil R W, Ament M E. Effect of nutritional status on outcome of orthotopic liver transplantation in pediatric patients. Transplant Proceed 1990; 22: 1560–1563
135. Müller M J, Loyal S, Schwarze M, Lobers J, Selberg O, Ringe B. Resting energy expenditure and nutritional state in patients with

liver cirrhosis before and after liver transplantation. Clin Nutr 1994; 13: 145–152
136. Chin S E, Shepherd R W, Thomas B J et al. Nutritional support in children with end-stage liver disease: a randomized crossover trial of a branched-chain amino acid supplement. Am J Clin Nutr 1992; 56: 158–163
137. Reilly J, Metha R, Teperman L et al. Nutritional support after liver transplantation. A randomized prospective study. J Parent Enteral Nutr 1990; 14: 386–391
138. Hasse J M, Blue L S, Liepa G U et al. Early enteral nutrition support in patients undergoing liver transplantation. J Parent Enteral Nutr 1995; 19: 437–443
139. Pescovitz M D, Mehta P L, Leapman S B, Milgrom M L, Jindal R M, Filo R S. Tube jejunostomy in liver transplant recipients. Surgery 1995; 117: 642–647
140. Wicks C, Somasundaram S, Bjarnason I et al. Comparison of enteral feeding and total parenteral nutrition after liver transplantation. Lancet 1994; 344: 837–840
141. Kuse E, Weimann A. Besonderheiten im Rahmen der Transplantationschirurgie. In: Hartig W, ed. Moderne Infusionstherapie- Künstliche Ernährung. München: W. Zuckschwerdt, 1993: 529–534
142. Swart G R, Metselaar H J, Hesselink E J, van den Berg J W O. Whole body protein turnover rates and body composition before and after liver transplantation. In: Capocaccia L, Merli M, Riggio O, eds. Advances in Hepatic Encephalopathy and Metabolic Nitrogen Exchange. Boca Raton: CRC Press; 1995, 76–80
143. Palmer M, Schaffner F, Thung S N. Excessive weight gain after liver transplantation. Transplantation 1991; 51: 797–800.
144. Munoz S J, Deems R O, Moritz M J, Martin P, Jarrell B E, Maddrey W C. Hyperlipidemia and obesity after orthotopic liver transplantation. Transplant Proceed 1991; 23: 1480–1483
145. Italian Society of Parenteral and Enteral Nutrition. Consensus statement – Perioperative nutrition: the rationale for nutritional support. Clin Nutr 1996; 15: 155–156
146. Plevak D J, DiCecco S R, Wiesner R J H et al. Nutritional support for liver transplantation: Identifying caloric and protein requirements. Mayo Clin Proc 1994; 69: 225–230.
147. Wolfe R R, Allsop J R, Burke J F. Glucose metabolism in man: responses to intravenous glucose infusion. Metabolism 1979; 28: 210–220
148. Lundbom N, Laurila S. Central pontine myelinolysis after correction of chronic hyponatremia. Lancet 1993; 342: 247–248
149. McDiarmid S V, Colonna J O 2d, Shaked A, Ament M E, Busuttil R W. A comparison of renal function in cyclosporine and FK-506-treated patients after primary orthotopic liver transplantation. Transplantation 1993; 56: 847–853
150. Shanbhogue R L K, Bistrian B R, Jenkins R L, Jones C, Benotti P, Blackburn G L. Resting energy expenditure in patients with end stage liver disease and in normal population. J Parent Enteral Nutr 1987; 11: 305–308
151. Green H J, Bramley P N, Losowsky M S. Are patients with primary biliary cirrhosis hypermetabolic? Hepatology 1991; 14: 464–472
152. Bosari S, Marradi C, Chiara O, Bevilacqua G, Nespoli A. Energy expenditure in cirrhotic patients. In: Kleinberger G, Ferenci P, Riederer P, Thaler H, eds. Advances in Hepatic Encephalopathy and Urea Cycle Diseases. Basel: Karger, 1984: 674–681
153. Heymsfield S B, Waki M, Reinus J. Are patients with chronic liver disease hypermetabolic? Hepatology 1990; 11: 502–505
154. Schneeweiss B, Pammer J, Ratheiser K et al. Energy metabolism in acute hepatic failure. Gastroenterology 1993; 105: 1515–1521
155. Merli M, Riggio O, Servi R et al. Increased energy expenditure in cirrhotic patients with hepatocellular carcinoma. Nutrition 1992; 8: 321–325
156. Campillo B, Bories P N, Sommer F, Wirquin E, Fouet P. The thermogenic and metabolic effects of food in liver cirrhosis: consequences on the storage of nutrients and the hormonal counterregulatory response. Metabolism 1992; 41: 476–482
157. Campillo B, Fouet P, Bonnet C, Atlan G. Submaximal oxygen consumption in liver cirrhosis. Evidence of severe functional aerobic impairment. J Hepatol 1990; 10: 163–167
158. De Lissio M, Goodyear L J, Fuller S, Krawitt E L, Devlin J T. Effects of treadmill exercise on fuel metabolism in hepatic cirrhosis. J Appl Physiol 1991; 70: 210–215
159. Kondrup J, Nielsen K, Juul A. Effect of long-term refeeding on protein metabolism in patients with cirrhosis of the liver. Br J Nutr 1996; in press
160. Kondrup J, Nielsen K. Protein requirement and utilization in patients with cirrhosis of the liver. Z Gastroenterol 1996; 34 (Suppl 5): 26–31
161. Lieber C S. Alcohol, liver, and nutrition. J Am Coll Nutr 1991; 10: 602–632
162. Shenker S, Halff G A. Nutritional therapy in alcoholic liver disease. Sem Liver Dis 1993; 13: 196–209
163. Mills P R, Shenkin A, Anthony R S et al. Assessment of nutritional status and in vivo immune responses in alcoholic liver disease. Am J Clin Nutr 1983; 38: 849–859
164. Aggett P J. Severe zinc defiency. In: Mills C F, ed. Zinc in Human Biology. Berlin: Springer, 1989: 259–274
165. Barry M, Keeling P W N, Feely J. Tissue zinc status and drug elimination in patients with liver disease. Clin Sci 1990; 78: 547–552
166. Thuluvath P J, Triger D R. Selenium in chronic liver disease. J Hepatol 1992; 14: 176–182
167. Halsted J A, Hackley B, Rudszi C, Smith J C. Plasma zinc concentration in liver diseases. Comparison with normal controls and certain other chronic diseases. Gastroenterology 1968; 54: 1098–1105
168. Kuse E, Kemnitz J, Kotzerke J et al. Fat emulsions in parenteral nutrition after liver transplantation: The recovery of the allografts RES function and histological observations. Clin Nutr 1990; 9: 331–336

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