Nutritional Support in Liver Disease

Module 13.2

Nutritional Support in Chronic Liver Disease

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Learning Objectives

• The consequences of malnutrition in liver cirrhosis;
• How to diagnose malnutrition in liver cirrhosis;
• How to treat malnutrition in liver cirrhosis.

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Key Messages

• Patients with liver cirrhosis are often malnourished.
• This malnutrition by itself worsens the prognosis.
• Nutrition support improves survival in patients with low dietary intake.
• Existing or developing hepatic encephalopathy is not a contraindication to nutrition support with an adequate protein supply.
• Patients with cirrhosis have specific metabolic disturbances, but in most patients the usual routes of feeding with standard food or products can be used.

1. Introduction

Most studies presented here deal with alcoholic liver cirrhosis since rather few studies have been done in patients with other etiologies.

Malnutrition is a complication of liver cirrhosis that should be treated together with the other complications. There is no specific meta-analysis available to use as a guide. The latest systematic review of nutrition support in patients with cirrhosis (1) aimed at defining more precisely in clinical terms when nutrition support is indicated in these patients. These studies dealt with the effect of nutrition on mortality. It was concluded that nutrition support is indicated in patients (improves survival) with a low spontaneous intake, i.e. below 50 g protein per day, for example due to reduced appetite from complications of the disease e.g. infections, tense ascites, bleeding, encephalopathic episodes. It is obvious that nutrition support only worked in the studies where the spontaneous intake was low in the control group. This recommendation was included in the consensus report of ESPEN on nutrition support in liver disease (2).

2. Pathophysiology

Patients with chronic liver cirrhosis experience 3 main clinical problems: malnutrition, ascites and hepatic encephalopathy.

2.1 Malnutrition

Malnutrition is caused by several factors: loss of appetite, malabsorption, increased requirements.

2.1.1 Loss of appetite

Many studies have shown that patients with cirrhosis have a low dietary intake, and also that the low dietary intake is associated with impaired clinical outcome (3, 4). As discussed by Davidson et al. (5), 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. In addition, the mechanical effect of ascites and intestinal oedema may play a role. Davidson et al. (5) reported that patients with cirrhosis had a hedonistic preference for low fat, moderate carbohydrate food (ice cream being tested), or high fat, high carbohydrate food in comparison to healthy controls who preferred high fat, moderate carbohydrate food. These changes paralleled the changes in macronutrient oxidation rates in the fasting state, showing higher fat oxidation in patients with cirrhosis. The spontaneous intake of patients with cirrhosis is characterized by a high proportion of energy from carbohydrate (6, 7), believed to reflect their low hepatic glycogen stores (8), which it is suggested leads to their high rate of fat oxidation during fasting.

The reduced dietary intake in patients with cirrhosis, in a clinically stable condition, balances with their reduced requirements, caused by low body weight/low lean body mass and decreased physical activity (6). Either the patients had reduced body size and physical activity secondary to their reduced appetite or they had reduced their intake to match their diminished body size and physical activity. During refeeding, they increased body size at normal rates (9), suggesting that intake is the primary limiting factor.

Few studies have tested ways of improving appetite and intake. Marchesini et al. (10) observed that a supplement with branched chain amino acids did improve appetite ratings in patients with cirrhosis. The possible mechanism for this was recently discussed in detail by Laviano et al. (11)
2.1.2 Malabsorption

Malabsorption may occur in patients with bile obstruction cirrhosis, especially in biliary cirrhosis. With this disease, there may be severe malabsorption of fat as well as fat soluble vitamins.

In other forms of chronic liver disease, neither fat nor protein are malabsorbed (12, 13) and faecal energy excretion was found to be normal (9). Malabsorption does not therefore seem to be a major problem without co-existing biliary or pancreatic disease or severe ongoing alcohol abuse.

In patients given lactulose, however, faecal mass and nitrogen increase, probably due to bacterial proliferation, leading to apparent malabsorption (13). Accordingly, cirrhotic patients given a high-fibre vegetable diet have an increased faecal bacterial nitrogen excretion (14).

2.1.3 Increased requirements

2.1.3.1 Energy

The average REE was found to normal in a study of 473 patients, as compared to values predicted by the Harris-Benedict equation, but 34% of the patients had an REE >120% of the expected value. In these hypermetabolic patients, total body potassium was lower, suggesting an association between increased REE and malnutrition, at least in some patients (15). Exercise-induced increase in oxygen uptake is normal in patients with cirrhosis (16-18). Energy intake matches REE in stable malnourished patients with cirrhosis (6, 18). Therefore, hypermetabolism may contribute to the development of malnutrition, but once the state of malnourishment is reached, it appears that in most patients a new steady state is also reached, i.e. that REE is adapted to the new condition.

2.1.3.2 Protein

Protein requirement is increased in clinically stable patients with cirrhosis, to an average requirement of about 0.8 g/kg per day. With the customary addition of 2 SD’s, this gives a recommended intake of about 1.2 g/kg per day (9, 19, 20).

Protein requirement can be increased due to:
1) decreased absorption;
2) decreased synthesis of body protein;
3) increased degradation of body protein;
4) increased hepatic urea production with increased urinary nitrogen excretion and/or
5) increased intestinal protein loss.

In the studies mentioned, faecal nitrogen excretion was not increased, i.e. neither malabsorption nor increased intestinal protein loss was responsible for the increase in protein requirements. Investigations with stable isotopes suggested, however, that there is an increased rate of endogenous protein degradation both in the fasting state (21) and in the diurnal fasting/fed state (22). This increase in breakdown of body protein was associated with a rise in the level of plasma amino acids, suggesting that the primary event is increased protein breakdown rather than increased hepatic urea formation (22). Based on the observations in Owen’s study (8), this increased degradation of protein in the fasting state may be due to low glycogen reserves, prompting an early switch to gluconeogenesis from amino acids derived from body protein stores (21). Preliminary data suggests that increased protein breakdown in the diurnal fasting/fed state may be due to a relative lack of branched-chain amino acids (BCAA - see further on BCAA below), e.g. for removal of ammonia (23), based on the observations in the study by Hayashi (24). A single meal does not increase whole body protein synthesis in patients with cirrhosis, in contrast to the increase seen in healthy volunteers (25). This defect was suggested to be due to the insulin-insensitivity also observed in the study.

Taken together, these studies indicate that the increased protein requirement is due to both a defect in meal-induced protein synthesis and increased protein degradation during feeding as well as fasting.
Despite the increased requirement for protein (per kg body weight), stable malnourished patients with cirrhosis are in nitrogen balance at an intake (per person) lower than that of the healthy population (9), suggesting that they have reached a steady state with the low intake.

In situations when acute exacerbations further decrease the intake, e.g. due to infections, tense ascites, bleeding, encephalopathic episodes, the possible increase in REE and the increase in protein requirement will of course aggravate the nutritional status rapidly.

**Protein intolerance**

It is a commonly held belief that hepatic encephalopathy may develop after excess protein intake, despite the absence of any documented evidence in the literature to support it or even to show how often excess protein intake is the suspected cause of an encephalopathic episode. It is likely that protein intolerance does exist in some cases, but it is a mistake to believe that protein restriction should be a routine part of the treatment (see further below). In the literature analysis mentioned above (1) there was no indication that an adequate dietary intake, including protein, aggravated existing hepatic encephalopathy.

### 2.1.4 Prevalence and diagnosis of malnutrition

In an Italian multicentre study of more than 1400 patients with cirrhosis, the prevalence of low body weight relative to height was only 5%, but 20% of the patients had recent weight loss >10% of usual body weight, and malnutrition, as measured by mid-arm-muscle-area (MAMA) or mid-arm-fat-area, was present in 30% of the patients (26). In a follow-up to that study, it was found that, within the Child-Pugh classes A and B but not in class C, survival was related to MAMA, suggesting that nutritional status is more important in patients with a better prognosis (27).

Nutritional status is also associated with impaired physiological function. Knee and ankle muscle strength were decreased in alcoholic cirrhosis, related to decrease in Lean Body Mass, as measured by 24 creatinine excretion, rather than to Child-Pugh score or polyneuropathy (28). Hand grip strength was related to Body Cell Mass (BCM), as determined by measurement of total body water and extracellular water (29). In a study of mainly Child-Pugh class A patients, all patients who were malnourished according to SGA (Subjective Global Assessment) also had decreased hand grip strength (30).

There is no “Gold Standard” for routine clinical screening or assessment of nutritional status in patients with cirrhosis. BMI taken literally may be unreliable for nutritional evaluation, since weight gain due to fluid accumulation can cause a falsely elevated or normal BMI. In most cases, a clinical judgment of the amount of ascites is possible and this estimate can be subtracted from the measured body weight. Patients with ascites and a low BMI are of course malnourished. As an alternative to BMI, simple methods, such as SGA or anthropometrics methods including MAC do provide information on which to base a correlation between clinical course and nutritional status (see above).

The use of bioimpedance analysis for calculating body cell compartments by equations that are impossible to validate in cirrhotic patients is of dubious value. It has been shown; however, that phase angle obtained by bioimpedance analysis is more closely related to survival than MAMA, total body potassium or lean body mass, estimated from 24 h creatinine, in patients with cirrhosis (31).

For nutritional screening purposes, the NRS-20002 recommended by ESPEN can be used (32).

### 2.2 Ascites

The pathophysiology of ascites is complex with involvement of portal hypertension, peripheral vasodilation, central hypovolemia and sodium & water retention. Strict restriction of sodium intake (20-40 meq/day) has no role in therapy today, since modern medical treatment to help eliminate excess salt is much more efficient and such a diet is very unpalatable. Moderate sodium restriction (about 2 g or 90-100 meq/day) is still recommended (33, 34), although the evidence for clinical benefit is scarce (33). Sodium overload, e.g. from i.v. fluids, is contraindicated.
2.3 Hepatic encephalopathy

The aetiology of hepatic encephalopathy is also complex. Current views are that the main mechanisms are accumulation of intracerebral ammonia & glutamine and disturbances in GABA receptors (35). Ammonia is believed to inhibit astrocyte TCA cycle activity, leading to a severe energy deficit which, together with other effects of glutamine and ammonia, causes astrocyte swelling and cerebral oedema (36). Treatment is focused on removal of precipitating factors and administration of non-absorbable disaccharides or antibiotics. It is now generally accepted that protein should not be restricted in malnourished patients with hepatic encephalopathy (2, 37-41). Iatrogenic protein restriction aggravates malnutrition, particularly since protein requirements are increased in cirrhotic patients.

3. Metabolic response

The metabolic response to chronic liver failure is characterized by changes in glucose, fat and amino acid metabolism.

3.1 Glucose metabolism

Many patients with cirrhosis have glucose intolerance or frank diabetes. A frequency of 20-30% has been reported (42). Glucose intolerance seems not to be related to clinical or biochemical indices of the disease (43, 44), nor to the aetiology (45). The glucose intolerance is due to a decrease in meal-induced insulin secretion (46), a higher meal-induced systemic appearance of glucose (47) and decreased peripheral glucose utilization (48), associated with hyperinsulinaemia and decreased sensitivity to insulin (44). The decreased peripheral utilization is reflected in decreased glucose membrane transport and decreased non-oxidative glucose disposal, i.e. glycogen synthesis, (49) in the periphery but not in the liver (50). Blood glucose should be monitored closely during nutrition therapy in cirrhosis, since hyperglycemia is probably as detrimental for patients with cirrhosis as it is for ICU patients (51).

3.2 Lipid metabolism

After an overnight fast, patients with cirrhosis have an elevated rate of fat oxidation, similar to that seen in healthy volunteers after a 3 day fast. Concomitantly, there is a decrease in glucose oxidation. The increase in fat oxidation has been explained as a more rapid switch to a prolonged fasting pattern because of low hepatic glycogen stores (8). In agreement with this, rates of fat oxidation normalize after 1 month’s refeeding (7).

When infusing an LCT emulsion intravenously, fat oxidation, plasma free fatty acids, and plasma triglycerides were the same in patients with cirrhosis as in controls. However, the increase in ketone bodies was less in the patients. This indicates that whole body removal of exogenously administered LCT is unaltered in cirrhosis, while hepatic ketogenesis is reduced, probably secondary to decreased liver function (52).

A study of oral fat intake (12) showed that patients with cirrhosis, as compared to healthy controls, accumulate less fat in chylomicrons and VLDL postprandially and exhibit a more rapid rise in plasma free fatty acids. These changes were more pronounced in patients with ascites (portal hypertension). These data seem to indicate that more fatty acids derived from fat in food are absorbed via the portal route.

3.3 Amino acid metabolism

In the fasting state, plasma amino acid composition is characterized by an increase in aromatic amino acids and a decrease in branched-chain amino acids (53-55). The increase in aromatic amino acids is probably due to reduced capacity of the liver to remove them and the decrease in branched-chain amino may reflect their increased use for removal of ammonia (24).

After a protein meal, plasma concentrations of aromatic amino acids, tryptophan and branched-chain amino acids increased more in patients with cirrhosis than in healthy controls (56). Insulin and glucagon also increased more in the patients. The increase in branched amino acids was closely correlated to the increase in insulin levels and to the insulin insensitivity observed. The rise in aromatic amino acids and tryptophan is probably due to reduced hepatic removal while the increase in branched amino acids, which are primarily
metabolized in muscle, may be due to the insulin insensitivity.

4. Energy, and substrate requirements

4.1 Energy requirements

It is recommended to give malnourished patients with liver cirrhosis 35–40 kcal/kg/day. This will cover their energy requirement to maintain body weight and meet the needs of physical activity as well as allowing for weight gain (2, 37). This recommendation also agrees with the amounts of energy given in randomized trials which have shown clinical benefit (reviewed in (1)).

4.2 Protein requirements

As described above, clinically stable patients with cirrhosis have elevated protein requirements. It is therefore recommended to administer about 1.2 g/kg per day to stable patients and 1.5-1.8 g/kg per day in clinical conditions with increased demands (2, 37): this is also in agreement with earlier intervention trials.

4.2.1 Branched chain amino acids

BCAAs are still under investigation as a nutritional supplement to improve nutritional status and clinical outcome. For recent reviews, see (11, 57-59). A large multicentre 1-year trial investigated the role of BCAA as a nutritional supplement (10). The 174 cirrhotic patients were included on the basis of severe liver disease, defined as a Child-Pugh score B or C, and evidence of portal hypertension. The patients included were not malnourished as determined by MAC or bioimpedance nor overtly encephalopathic. The patients were randomized to 3 groups given different supplements containing either BCAA or isonitrogenous + isoenergetic lactalbumin (nitrogen & energy control) or isoenergetic maltodextrin. BCAA reduced rate of death, further severe progression of liver disease, and rate of hospital admission, as well as improving appetite rating and Quality of Life. The main problem with the study was the rather large drop-out rate in the BCAA group, mainly due to palatability/acceptance issues. This led to a non-significant intention-to-treat analysis for the main outcome variable. The study does suggest, however, that BCAA has a positive effect on outcome, which was greater than the lactalbumin-based supplement, the composition of which was similar to a standard oral supplement.

BCAAs have also been investigated as a treatment of hepatic encephalopathy (HE), in order to reduce brain uptake of tryptophan (58, 59). In a meta-analysis of studies using BCAA for treatment of HE, BCAA was significantly effective only when all studies were included. When low quality studies (unknown randomization method, unknown blinding) were excluded, the effect was not present (60).

One of the first studies to employ BCAA was carried out in patients who were protein-intolerant, i.e. tolerating less than 40 g of protein. They were randomized to increase their protein intake to 70 g, either in the form of casein or with a BCAA supplement (61). When encephalopathy worsened, it was considered a treatment failure and the patient was withdrawn from the study. Seven out of 12 patients in the casein group were treatment failures, but only 1 out of 14 in the BCAA group was a treatment failure. This study combines the two potential uses of BCAA, firstly nutritional treatment and secondly prevention of HE in malnourished patients who cannot be refed because of protein-intolerance. This is the only study available with this design, and was the basis of the ESPEN recommendation to use BCAA in this particular situation (2) Plauth, 2006 #4161}. The results of this study, of course, need confirmation from other centres, but until such studies are available, this situation, i.e. protein intolerance, remains the only clear indication for the use of BCAA in the treatment of patients with cirrhosis.

4.3 Lipid requirements

There are no special requirements in terms of amount, type of lipids, or composition of fatty acids. Intravenous lipid emulsions are not contraindicated in patients with liver disease.
4.4 Carbohydrate requirements

There are no special recommendations concerning glucose intake, although it is important to monitor blood glucose to avoid the clinically important side effect of hyperglycemia (51, 62).

4.5 Micronutrient requirements

Patients with liver cirrhosis often have low plasma levels of vitamins and minerals, but the specific functional or clinical implications of these abnormalities are not known in detail.

Thiamine deficiency is common in alcoholism and in alcoholic cirrhosis, and, surprisingly, it was found to be equally frequent in hepatitis C virus related cirrhosis (63). The deficiency was not due to decreased erythrocyte phosphorylation of thiamine in that study, and other potential causes were not investigated (e.g. reduced dietary intake). It was therefore recommended that all patients with cirrhosis should receive thiamine. Deficiency of fat-soluble vitamins is observed in patients with steatorrhea due to cholestasis and bile salt deficiency and in alcohol abusers (2).

Magnesium depletion is common in end stage liver disease (64). Zinc deficiency is also common and seems to be caused by decreased absorption as well as a diuretic-induced increase in urinary excretion (65). Supplementation with zinc improves glucose tolerance (66, 67) whereas any possible effect on encephalopathy remains unproven (68, 69).

To cover any possible deficiency it is advised to prescribe a standard vitamin/mineral tablet (2).

5. Route of feeding

The preferred route of feeding follows the usual recommendations: food > supplements > tube feeding > intravenous nutrition. Use of PEG tubes is not recommended in patients with ascites. In most cases, standard formula feeds can be used. In patients showing worsening of encephalopathy during refeeding, branched-chain amino acids should be tried (2).

Evening meals

Following Owen’s observations (8) that, after an overnight fast, splanchnic metabolism in patients with cirrhosis was similar to that of healthy volunteers after a 3 day fast, and in particular that gluconeogenesis from peripherally derived amino acids was increased, further studies were carried out (70) which showed that nitrogen balance was improved when the daily protein intake was split between 4-6 meals rather than the usual 3. The same group later reported that a similar improvement could be achieved by giving a late evening oral dose of glucose (71). This approach has been extended to giving BCAA at night, resulting in decreased urinary excretion of 3-methylhistidine, indicating lower muscle protein breakdown (72). It has also been found that one late evening snack with carbohydrate and BCAA improves glucose tolerance to the same degree as the same snack given twice during the daytime (73). These studies all point to the importance of reducing the length of the evening and night time period of starvation in patients with cirrhosis. Further studies are needed to compare the relative effects on clinical outcome of the methods described, i.e. meal, carbohydrate alone, or carbohydrate with BCAA.

6. Monitoring

In addition to the usual monitoring of food intake, body weight and electrolytes when artificial feeding is administered, it is advised also to monitor mental status to detect the development or worsening of hepatic encephalopathy in the rare patient with protein intolerance. This can be done clinically or by measuring continuous reaction time twice weekly (9).

7. Summary

Patients with chronic liver disease often present with malnutrition including deficiencies in vitamins and minerals. Treatment of this malnutrition improves clinical outcome, including survival. Patients with cirrhosis
have disturbances in macronutrient metabolism and have increased protein requirements. Standard routes of feeding using standard formulae can be used in most patients. Hepatic encephalopathy is not a contraindication to nutrition support with a high protein intake. In patients with worsening encephalopathy, judged to be protein intolerant, branched-chain amino acids should be tried. In patients with ascites, moderate but not severe sodium restriction should be employed.

8. References