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REVIEW ARTICLE

Nutrition and Chronic Liver Disease

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Abstract
Malnutrition is common in chronic liver diseases and worsens the patient's prognosis. Many liver disorders are associated with nutritional deficiencies. Some of the main factors that can lead to malnutrition in patients with chronic liver disease include decreased lipid absorption and reduced albumin production. In addition, these patients are sometimes candidates for a liver transplant that requires nutritional intervention after surgery to improve their prognosis. Thus, it is very important to recognise malnutrition in patients with liver failure in order to resolve it, mainly by a complete history of the patient, dietary survey, determination of muscle mass and a subjective assessment. To ensure a good nutritional status, exercise and lifestyle changes are considered, including dietary modifications, especially with a Mediterranean pattern. This article reviews these topics, including dietary modifications before and after liver transplantation. Additionally, nutritional recommendations are offered to patients with metabolic hepatic steatosis.

Key Points

Hepatic alterations cause nutritional deficiencies. In turn, malnutrition and obesity are associated with liver disease. To assess nutritional status and identify malnutrition in advanced liver disease, a subjective global assessment and determination of anthropometric parameters are recommended.

Before liver transplantation, caloric requirements are 1.2–1.5 times the basal energy expenditure. Protein intake should not be restricted in this situation.

After liver transplantation, an adequate nutritional intake improves postoperative evolution, controlling hypercatabolism, maintaining a correct electrolyte balance and adequate glycaemia, and avoiding excessive weight gain.

Metabolic Hepatic steatosis is related to an unhealthy diet and has become the main cause of chronic liver disease. Lifestyle changes based on diet, preferably a Mediterranean diet, and physical exercise avoiding sedentary lifestyles are the key to the treatment of this condition.

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1 Introduction

The liver is the first station where nutrients are stored after being absorbed in the gut. In this organ, the metabolism of carbohydrates, fats and proteins is carried out; vitamins are activated and stored; and the detoxification and excretion of endogenous and exogenous products occurs [1]. This close relationship between the liver and nutrition means that a hepatic alteration could cause nutritional deficiencies; thus, different states of malnutrition or obesity are associated with liver diseases.

Because of the worldwide increase in the prevalence of obesity, type 2 diabetes mellitus and dyslipidaemia, metabolic hepatic steatosis is becoming very important. Considering that patients with this disease are mostly obese, appropriate nutritional treatment and lifestyle changes to achieve weight loss are required. Weight loss has proven to be effective in the regression of liver fibrosis, the main factor conditioning the survival of these patients [2].

However, malnutrition is often a burden in patients with liver cirrhosis. It is present in 20% of those with compensated cirrhosis and in 50% of those with decompensated cirrhosis [3]. Malnutrition is a poor prognostic factor in patients with chronic liver disease, as it is associated with many other factors such as anorexia, early satiety, nausea, vomiting, and problems of malabsorption and poor digestion. In addition, the nutritional status may worsen if the patient is on a restrictive diet. As a consequence of malnutrition, metabolic disturbances also occur, usually

due to baseline hypercatabolism, altered functioning of certain drugs and even increased energy expenditure [4].

In this article, we review some of the main hepatic causes and risk factors that can lead to malnutrition in patients with chronic liver disease. We also review the main dietary recommendations that can be offered to a patient before and after liver transplantation, and what nutritional recommendations can be given to a patient with metabolic hepatic steatosis.

2 Metabolic Changes in Patients with Chronic Liver Disease

The main metabolic disturbances observed in patients with chronic liver disease are: variations in energy expenditure; alterations in glucose metabolism; changes in protein metabolism; and impairments in lipid metabolism. Regarding changes in energy expenditure, although most patients are normometabolic, one-third have hypercatabolism, resulting in a net negative energy balance. Because of alterations in glucose metabolism, there is a decrease in glycogen reserves, hyperinsulinemia (due to insulin receptor blockade), decreased glucose oxidation in the liver, glucose intolerance and an increased risk of type 2 diabetes mellitus. Altered protein metabolism leads to increased protein catabolism and accelerated gluconeogenesis from amino acids. Finally, altered lipid metabolism leads to increased lipid oxidation that generates reactive oxygen species, resulting in hepatic lipotoxicity and a deficiency in essential fatty acids [5].

3 Factors Contributing to Malnutrition

From the lipid metabolism point of view, when the liver is damaged there is a decrease in the production of bile salts, which alters the absorption of fats and fat-soluble vitamins, and leads to a decrease in essential and polyunsaturated fatty acids. Regarding proteins, there is a decrease in the production of albumin in the liver. This hypoalbuminemia produces oedema in the intestinal mucosa that hinders the absorption of nutrients. In addition, given the need of proteins for energy, there is a depletion of muscle mass. Sarcopenia is commonly observed in patients with chronic liver disease [4].

4 Assessment of Nutritional Status

The assessment of nutritional status in these patients is complex. Because of hydrosaline retention, body weight determination is not useful because most of it will correspond to water in the form of ascites or oedema. In addition, both protein kinetics and other analytical parameters commonly used to assess nutritional status are altered. Protein concentration is decreased because of impaired hepatic activity and the lymphocyte count is lower because of hypersplenism. Thus, determination of the serum protein level, measurement of prothrombin time, or erythrocyte, lymphocyte or platelet counts are also not useful to assess malnutrition [6].

The best way to assess nutritional status is to perform a complete clinical history of the patient; a dietary survey of at least 2 days (one daily and one at the weekend) to detect micronutrient and vitamin deficiencies; a physical examination; anthropometry; measurement of skinfold thickness; and measurement of arm muscle circumference to determine the amount of muscle mass; and finally, a global subjective assessment [7]. There are several tools to classify patients at risk of malnutrition, but most have not been validated in cirrhotic patients and are biased by hydrosaline retention. The Royal Free Hospital-Nutritional Prioritizing Tool correlates with clinical deterioration, severity of liver disease, and with clinical complications such as ascites, hepatorenal syndrome and episodes of hepatic encephalopathy [8]. The predictive role of skeletal muscle mass assessed by computed tomography in liver transplant candidates has also been studied, but is rarely used in routine clinical practice [9].

5 Dietary Modifications Before and After Liver Transplantation

A summary of all nutritional recommendations before and after liver transplantation is shown in Table 1.

5.1 Dietary Modifications Before Transplantation

The caloric requirements to maintain the patient in a correct nutritional situation are 1.2–1.5 times the basal energy expenditure (i.e. 30–35 kcal/kg/day). If the patient's weight needs to be increased because of malnutrition, the requirements would be 1.5 times (i.e. 40 kcal/kg/day). In overweight patients, it is recommended to decrease energy expenditure by 500–1000 kcal/day, reaching 25–35 kcal/kg/day in obese patients and 20–25 kcal/kg/day in morbidly obese patients [10]. Both cases would improve the prognosis of patients after transplantation.

Although there is a tendency to restrict protein intake to control weight, it is not necessary to do so in patients with hepatic insufficiency or chronic liver disease. These patients should ingest between 1.2 and 1.5 g/kg/day of protein. If protein repositioning is desired to reach an adequate level, 1.5 g/kg/day should be achieved. Depending on the patient's tolerance, the recommended protein intake in patients with hepatic encephalopathy is 1.2–1.5 g/kg/day to

prevent sarcopenia, with a predominance of branched-chain over aromatic amino acids [11]. In protein-intolerant cirrhotic patients, replacing meat with vegetable proteins plus branched-chain amino acid supplementation is likely to be preferable to a reduction in total protein intake [12].

Fat should not account for more than 25–40% of total calories. It is suggested to use medium-chain triglycerides that do not require hydrolysis for their absorption, especially if steatorrhoea is present, which is common in these patients [13].

Regarding carbohydrates, it is necessary to avoid the consumption of fructose and sugar-sweetened beverages as they can be converted into fats by de novo lipogenesis in the liver. Instead, it is recommended to consume complex carbohydrates that are absorbed more slowly. If glucose intolerance is present, it is also recommended to avoid consumption of simple sugars [14].

A normal diet contains between 2 and 4 g/day of sodium. If patients are not responding to diuretics, sodium consumption should be restricted (2 g/day) whenever the patient begins to retain fluid or develop oedema. However, strict restriction is not recommended, as the patient will tend to eat less if the food is tasteless and will lose weight. Fluids should be restricted to 1000–1500 mL/day only if hyponatraemia (sodium levels below 120 meq/L) is present. Otherwise, it would not be necessary to restrict fluid intake [14].

The most frequent vitamin deficiency in these patients is vitamin D; therefore, it is recommended to provide supplements of this vitamin, together with A, E and K. Because vitamin E can cause long-term adverse effects, including higher mortality, it is only recommended for short periods of time and in patients with advanced disease, but not in cirrhotic or diabetic patients [15]. It is also necessary to give a vitamin B complex supplement to patients with alcohol-use disorder. Because of the consumption of diuretics, minerals such as zinc, potassium, magnesium and phosphorus are lost, thus supplements of these should be provided. It is also necessary to monitor calcium levels, trying to reach 800–1000 mg/day to avoid the increased risk of bone density loss and pathological fractures. In contrast, because manganese can accumulate, it is not necessary to offer it as a supplement as it could be harmful [13, 14, 16].

Taking all these considerations into account, the nutritional support of a patient before undergoing liver transplantation should consist of multiple meals (five to seven), with one of them being before bedtime to decrease

Table 1 Nutritional recommendations before and after liver transplantation

Pre-transplant recommendations	
Weight control	To increase weight → 40 kcal/kg/day To reduce weight → 25–35 kcal/kg/day in obese, 25 kcal/kg/day in morbidly obese
Proteins	1.2–1.5 g/kg/day Restriction of aromatic amino acids in hepatic encephalopathy 12 g/day of branched-chain amino acids in patients with sarcopenia
Fat	<25–40% of total calories Use of medium-chain triglycerides
Carbohydrates	Avoid fructose and sugar-sweetened beverages Use complex carbohydrates
Sodium	2 g/day if ascites and oedema not responding to diuretics 1000–1500 mL/day fluids if hyponatremia (sodium <120 meq/L)
Vitamins and minerals	Vitamin D, A, E and K supplementation Vitamin B complex in patients with alcohol-use disorder Zinc, potassium, magnesium and phosphorous supplementation if diuretics are received Calcium 800–1000 mg/day
Nutrition type	5–7 meals per day, one of them before bedtime Nasogastric tube or enteral route if oral administration is not tolerated Total parenteral nutrition if enteral nutrition is contraindicated No gastrostomy or jejunostomy to avoid infection of ascitic fluid Malabsorption → oligomeric formulas with medium-chain triglycerides Pancreatic enzymes deficiency → enzyme replacement therapy
Post-transplant recommendations	
Protein	1.5–2 g/kg/day
Nutrition type	Enteral or oral nutrition in the first 24–48 hours after surgery Polymeric enteral formulas enriched in proteins Malabsorption → semi-elemental formulas with small peptides and medium-chain triglycerides Hepatic encephalopathy → formulas enriched with branched-chain amino acids

nocturnal gluconeogenesis. When a patient is expected to be unable to maintain an adequate oral intake in 5–7 days, they should receive nutritional support, preferably by the enteral route. Enteral nutrition should be initiated at a low dose when acute metabolic disorders are life threatening and cannot be controlled with hepatic support strategies. So far, there are no published studies comparing enteral formulas in patients with acute liver failure [17].

Neither gastrostomy nor jejunostomy is recommended in patients because of the high risk of infection of ascitic fluid. In patients with malabsorption, oligomeric formulas with medium-chain triglycerides can be used, and, in situations of pancreatitis and pancreatic enzyme deficiency, enzyme replacement therapy could improve the nutritional status of patients. Total parenteral nutrition should only be used if enteral nutrition is contraindicated [18]. It is important to note that parenteral nutrition has no clear advantage over enteral nutrition and may increase infectious complications [19].

5.2 Dietary Modifications After Transplantation

One of the main objectives of nutritional support after liver transplantation is to avoid sarcopenic obesity and metabolic syndrome, as they are poor prognostic factors in these patients [20]. It is also necessary to control the acute catabolic situation that occurs immediately after the operation, to maintain a correct electrolyte balance and adequate blood glucose, and to promote a correct post-surgical healing process by means of a nutritional supply of proteins, vitamins and collagen precursors.

The main recommendation in these patients is to administer enteral or oral nutrition in the first 24–48 hours after surgery. Polymeric enteral formulas enriched in protein, semi-elemental formulas with small peptides and medium-chain triglycerides if malabsorption is present, or formulas enriched in branched-chain amino acids in patients with hepatic encephalopathy can be used [21].

The preferred energy source in the first 6 hours post-surgery is lipids, as glucose is not well processed. Subsequently, glucose administration can be started. In addition, as a result of surgical stress, infections, or the use of steroids or immunomodulatory drugs, hyperglycaemia is often observed. Protein hypercatabolism is also frequent because of the use of steroids and the surgical intervention itself. Therefore, administration of 1.5–2 g/kg/day of protein is recommended. This dose should be increased if there are fistulas, surgical drains, or a loss of phosphorus, potassium and magnesium owing to the use of diuretics or re-feeding syndrome triggered by the rapid reintroduction of nutritional support [21].

The main problems that can arise after transplantation are excessive weight gain and hyperlipidaemia. After the intervention, there is usually a mean gain of 6.5 kg in 1 year, with an obesity rate of 43% at 18 months, and altered liver function tests because of hepatic steatosis. Moreover, weight gain is more frequent with the use of immunosuppressants such as cyclosporine. After transplantation, hypertension is also frequent, with an incidence of 81%; it is more frequent in obese and cyclosporine-treated patients and type 2 diabetes may occur in 9% of cases. In addition, there may be a decrease in bone mineral density related to the use of glucocorticoids [22]. Thus, appropriate assessments and supplementation should be provided for every patient, including the involvement of a multidisciplinary team to improve a patient's long-term outcome and survival.

6 Nutrition in Metabolic Hepatic Steatosis

Metabolic hepatic steatosis is the main cause of non-alcoholic fatty liver disease. Because of the increase in obesity, diabetes or dyslipidaemia, its prevalence has been increasing in recent years [23]. The treatment of hepatic steatosis consists of lifestyle modifications through diet, physical activity and exercise, and avoidance of sedentary behaviour. If all these strategies fail, pharmacological treatments would have to be used, but none of these is currently available.

In overweight or obese patients, it is necessary to use a restrictive hypocaloric diet to achieve a 5–10% weight reduction. Isocaloric diets are indicated for those who do not need to lose weight. It is important to emphasise the use of polyunsaturated and monounsaturated fats and to follow a Mediterranean diet pattern rather than a low-fat or low-carbohydrate diet. In a recent meta-analysis, despite the heterogeneity of results, omega-3 polyunsaturated fatty acids supplementation may decrease liver fat, although its optimal dose is currently not known. Thus, more randomised controlled trials are needed to quantify the magnitude of effect of omega-3 polyunsaturated fatty acids supplementation on liver fat [24]. An isocaloric diet enriched in monounsaturated fatty acids compared with a diet higher in carbohydrate and fibre has been associated with a clinically relevant reduction in hepatic fat content in type 2 diabetic patients independent of an aerobic training programme. Therefore, it should be considered for the nutritional management of hepatic steatosis in people with type 2 diabetes [25].

In patients with normal weight, as there is no need to reduce caloric intake, a review of their dietary composition is recommended to reduce added sugar, avoid sugar-sweetened beverages and have moderate use of complex carbohydrates, preferably high in fibre, reduce saturated/trans fats and cholesterol, and increase polyunsaturated fatty acids (omega-3) and monounsaturated fatty acids. All in all, fast food should be minimised and it is preferable to follow a Mediterranean diet [26]. Another important issue is to insist on aerobic and anaerobic physical activity. Aerobic

exercises allow lipid oxidation and calorie consumption, and reduce weight. Anaerobic resistance exercises increase muscle mass in relation to fat mass and increase the patient's basal metabolism. Nutraceuticals (e.g. coffee, antioxidants and probiotics) also can be recommended [26].

The Mediterranean dietary pattern is most often recommended. It is based on the consumption of olive oil, nuts, oily fish, legumes, fruits, vegetables and predominantly monounsaturated and polyunsaturated fats (omega-3). Conversely, consumption of soda drinks, sweets, red and processed meats, and refined carbohydrates should be reduced to only 40% of total kilocalories [27–30]. Some studies have evaluated the usefulness of the Mediterranean diet in these patients. They compared a Mediterranean diet with a low-fat and low-carbohydrate diet, and found that the Mediterranean diet resulted in a greater decrease in intrahepatic lipids and better glycaemic control [30, 31].

The best recommendation that can be given to these patients is to reduce body weight through lifestyle changes. A prospective study of 293 patients with metabolic hepatic steatosis who were encouraged to adopt recommended lifestyle changes to reduce their weight over 52 weeks was conducted [2]. Liver biopsies were collected when the study began and at week 52 of the diet and were analysed histologically. A weight loss of 5% improved steatosis, a 7% weight loss improved inflammation and a 10% weight loss improved fibrosis. Among those who underwent lifestyle changes for 52 weeks, 25% achieved resolution of steatohepatitis, 47% had reductions in the non-alcoholic fatty liver disease activity score and 19% had regression of fibrosis [2].

7 Patients with Acute Liver Failure, Encephalopathy and Hyperammonemia

Because of the partial loss of hepatocellular function and the resulting multi-organ dysfunction in acute liver failure, there is severe impairment of carbohydrate, protein and lipid metabolism. There is hypoglycaemia, release of free fatty acids and ketogenesis is reduced [32, 33].

Patients with hyperacute liver failure and sustained elevated arterial ammonia levels (>150 mmol/L) may be at an increased risk of cerebral oedema and the development of intracranial hypertension [34]. In this specific context, the administration of proteins may further elevate ammonia levels and increase the risk of cerebral oedema. Its administration can be delayed or for a short period (24–48 hours) while liver function improves and when started, arterial ammonia should be monitored.

Plasma levels of amino acids are altered. There is a decrease in branched-chain amino acids and an increase in tryptophan and sulphur-containing amino acids. This leads to hepatic encephalopathy and malnutrition. Parenteral nutrition with a solution enriched in branched-chain amino acids, together with a low-protein diet, can correct the specific metabolic abnormalities in patients with chronic liver failure and help restore quality of life and survival [35].

8 Conclusions

Malnutrition is common in chronic liver diseases and worsens the prognoses. Many of these liver disorders are associated with nutritional deficiencies, such as vitamins and minerals. In addition, metabolic hepatic steatosis is related to an unhealthy diet and has become the leading cause of chronic liver disease.

The recommended protein intake in patients with hepatic encephalopathy is 1.2–1.5 g/kg/day to prevent sarcopenia and has a predominance of branched-chain over aromatic amino acids. As body weight can be altered by the pathology itself, to assess nutritional status and detect malnutrition in advanced liver disease, subjective global assessment and determination of anthropometric parameters are recommended.

Both before and after liver transplantation surgery, an adequate nutritional intake is necessary to improve the evolution of patients. Lifestyle changes based on dietary modifications, preferably with a Mediterranean pattern, and physical exercise avoiding sedentary lifestyles, are the key to the treatment of metabolic hepatic steatosis.

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