27 Liver Disease

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CONTENTS

Objectives

1. Understand the pathogenesis of various liver diseases with an emphasis on how pathogenesis relates to nutrition and malnutrition.
2. Review the difficulty in assessing nutritional status in patients with liver disease and identify possible solutions to these problems.
3. Identify important micronutrient deficiencies and toxicities in patients with liver disease.
4. Determine the energy and protein requirements for patients with both acute and chronic liver diseases.
5. Identify and learn how to address barriers to the delivery of nutrition in patients with liver disease.

Test Your Knowledge Questions

1. Which of the following is an accurate marker of nutritional status in all patients with chronic liver disease with portal hypertension?
   A. Serum albumin
   B. Serum prealbumin
   C. Retinol-binding protein
   D. Anthropometry
   E. None of the above
2. Which of the following statement(s) is false regarding alcoholic hepatitis?
   A. Virtually all patients with alcoholic hepatitis have some degree of malnutrition.
   B. The severity of liver disease generally correlates with the degree of malnutrition.
   C. Caloric intake correlates with mortality.
   D. Protein delivery should be reduced to prevent portal systemic encephalopathy (PSE).
3. Which of the following statements is true regarding total parenteral nutrition (TPN) in the care of the inpatient with liver disease?
   A. There is no role for TPN in nutrition in liver disease.
   B. TPN should be initiated in all hospitalized patients with liver disease.
   C. In a patient unable to tolerate enteral feeding TPN can provide necessary nutrition, but should be discontinued in favor of enteral nutrition as soon as possible.
   D. Once a patient is unable to tolerate enteral nutrition they should continue on TPN for the duration of their hospitalization.

Test Your Knowledge Answers

1. The correct answer is E. There are no consistently accurate measures of malnutrition in patients with significant liver disease. Visceral proteins such as albumin, prealbumin, and retinol-binding protein are made in the liver and better correlate with the severity of liver disease rather than the degree of malnutrition. Anthropometry can be inaccurate in the setting of edema and/or ascites.
2. The correct answer is D. The Veterans Health Administration Cooperative Studies Program demonstrated that virtually all patients with alcoholic hepatitis have some degree of malnutrition. In addition, the severity of liver disease generally correlated with the degree of malnutrition. Study subjects consuming > 3000 kcal per day had near zero mortality, whereas those consuming less than 1000 kcal per day had > 80% mortality. Thus, food intake correlated with 6-month mortality. Protein requirements in patients with alcoholic hepatitis are increased and the delivery of protein is not a significant precipitant of PSE. Restriction of protein is not recommended in alcoholic hepatitis (or any other liver disease, for that matter) and should only be implemented in the setting of PSE refractory to medical treatment.
3. The correct answer is C. The goal should always be to provide enteral nutrition to patients with liver disease. In certain patients, such as those without a functional gut, it is necessary to provide nutrition in the form of TPN. This should be continued for the minimal period possible. Enteral feeding is always preferred to TPN when enteral feeding is possible.

Background

Nutritional support for patients with liver diseases is a complex topic. The liver is pivotal in many metabolic processes. It normally has considerable metabolic reserve. Despite this, patients with decompensated liver disease can develop significant nutritional deficiencies. A complicating factor for providing nutritional support is the tremendous variability in the causes and severity of liver disease among patients. In addition, traditional methods of assessing nutritional status are often unreliable. These issues make it difficult to provide a "blanket" recommendation for nutritional therapy in liver disease patients.

Perfused by both the portal vein and hepatic artery, the liver has a unique dual blood supply and consists of multiple cell types having differing functions. Hepatocytes make up over 80% of the total liver mass and play a critical role in the metabolism of amino acids and ammonia; in the detoxification of a variety of drugs, vitamins, and hormones; and in the biochemical oxidation reactions. Hepatic Kupffer cells, the largest reservoir of fixed macrophages in the body, play a protective role against gut-derived toxins that have escaped into the portal circulation. These cells are major producers of cytokines, which can markedly influence nutritional status. The liver also contains hepatic stellate cells, which play an important role in collagen formation following liver injury and are the major storehouse for vitamin A in the body. There are a host of additional cell types located in the liver, each with distinctive functions (eg, bile duct epithelium in bile flow, sinusoidal endothelial cells in adhesion molecule expression and endocytosis).

The liver plays an essential role in the metabolism of proteins, carbohydrates, and fats. Plasma proteins, nonessential amino acids, urea (for ammonia excretion), glycogen, and critical hormones such insulinlike growth factor-1 are synthesized in the liver. The liver is also a chief site for the metabolism of fatty acids. In addition, bile from the liver is needed for fat absorption from the intestine. Thus, a properly functioning liver is imperative for achieving and maintaining appropriate nutritional status.

Acute hepatitis is usually a self-limited liver disease characterized by the elevation of serum transaminases (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)). Acute hepatitis is most frequently caused by a viral infection, medication/toxicant, Wilson disease, or shock. Malnutrition and the presence of chronic liver diseases, such as nonalcoholic fatty liver disease (NAFLD), may predispose patients to acute liver injury. The functional reserve of the liver is so great that 80% to 90% of liver cells must be injured before physiologic functions are impaired. Destruction of a large proportion of the hepatocytes results in acute liver failure, which is characterized by deterioration in hepatic synthetic function (eg, jaundice, coagulopathy, hypoalbuminemia) and manifestations of portal hypertension (eg, ascites, hyponatremia, esophageal varices). Hepatic encephalopathy (HE) can range from subtle behavioral changes to disorientation and deep coma.

Two epidemics are fueling the most recent increase in the prevalence of chronic liver disease, namely, hepatitis C virus (HCV) and NAFLD/nonalcoholic steatohepatitis (NASH). Approximately 2% of Americans are infected with HCV. NAFLD, the hepatic manifestation of metabolic syndrome/insulin resistance, has become the most common liver disease in the United States. Both of these diseases can progress to cirrhosis in a significant percentage of patients. Cirrhosis, characterized by dense collagen accumulation, or fibrosis, may lead to end-stage (or decompensated) liver disease, which may also be accompanied by synthetic dysfunction and portal hypertension as well as hepatocellular carcinoma. However, in its early stages, chronic liver disease may be asymptomatic. Serologic tests may reveal abnormal liver enzymes in either a hepatocellular (AST/ALT) or a cholestatic pattern (alkaline phosphatase). Progressive fibrosis develops in some but not all patients with chronic liver disease resulting in cirrhosis.

Pathogenesis, Malnutrition, and Nutritional Aspects of Liver Disease

There are multiple etiologies of liver disease (Table 27-1). Although often difficult to diagnose, patients with advanced liver disease are often at risk for malnutrition.[1] Although the pathophysiology of how liver dysfunction causes malnutrition is unclear, local and systemic neurohormonal mechanisms are likely involved in causing delayed gastric emptying, small bowel dysmotility and bacterial overgrowth, and constipation.[2-6] Further complicating this picture are increased renal losses of micronutrients, such as zinc, in conditions such as alcoholic liver disease.[7]

TABLE 27-1 Causes of Liver Disease

Toxins
- Ethanol
- Medications
- Industrial chemicals (vinyl chloride)
- Aflatoxins
- Other (eg, *Amanita* sp. mushroom)

Metabolic causes
- Obesity (NAFLD)
- Wilson disease
- Hemochromatosis
- Alpha-1-antitrypsin deficiency

Infectious
- Viral (eg, hepatitis A, B, C, E)
- Bacterial

Immune mediated
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Sarcoidosis

Other
- Budd-Chiari syndrome

NAFLD, nonalcoholic fatty liver disease.

Maldigestion and malabsorption may occur in liver disease and may play an important role in causing malnutrition. Typical gastrointestinal disturbances in liver disease include dysgeusia, anorexia, nausea, and early satiety. Concomitant complications typical of liver disease such as upper gastrointestinal bleeding, portal systemic encephalopathy, and sepsis also cause prolonged periods of poor oral intake. Dietary management of fluid retention with salt and water restriction; and carbohydrate and lipid restrictions used in patients with diabetes mellitus, chronic pancreatic insufficiency, and cholestatic liver disease can all affect diet palatability and can severely restrict patients' food choices.

Impaired lipid metabolism is multifactorial in liver disease. Decreased intraluminal bile salts, small bowel bacterial overgrowth, coexistent pancreatic insufficiency or intestinal disease (inflammatory bowel disease, sprue), and mucosal vascular hypertension and edema can worsen maldigestion and malabsorption. Cholestatic liver disorders are associated with decreased intraluminal concentration of bile salts, resulting in lipid and lipid-soluble vitamin malabsorption.[8]

The loss of glycogen stores that occurs in patients with advanced liver disease predisposes them to enter a starvation state within a few hours of fasting.[9,10] This can lead to peripheral muscle proteolysis to provide amino acids for gluconeogenesis, thus contributing to protein malnutrition. Liver disease patients with portal hypertension and ascites and those with acute alcoholic hepatitis are at increased risk of developing a hypermetabolic state (resting energy expenditure > 110% of its expected value), which also contributes to overall malnutrition.[11-13]

Dysregulated cytokine metabolism (eg, elevated tumor necrosis factor [TNF]) is well documented in many forms of liver disease.[14] Low-grade endotoxemia, facilitated by portal hypertension and gut bacterial translocation, leads to increases in proinflammatory cytokines and further affects nutrient management and overall metabolism.[15] Increased levels of cytokines have been postulated to cause many of the metabolic and nutritional abnormalities observed in liver disease, especially in acute alcoholic hepatitis and in chronic decompensated liver disease.[14] Thus, abnormalities such as fever, anorexia, muscle breakdown, and wasting and altered mineral metabolism are likely to be at least partially cytokine mediated.

Despite the increased frequency of malnutrition in patients with alcoholic or viral liver disease, one cannot assume that all of these patients are at nutritional risk. Moreover, obesity and the metabolic syndrome are increasingly recognized as a major cause of abnormal liver enzymes and can also coexist with and worsen liver diseases of other etiologies. Consequently, both undernutrition and obesity play important roles in liver disease. For this reason, an accurate assessment of nutritional status in patients with liver disease is essential. Patients with alcoholic liver disease are also at risk for complications of alcohol use such as pancreatitis and myopathy. It is not clear, however, what contribution a diminished nutritional status plays in the incidence of these complications. Although the role of nutrition in the pathogenesis, progression, and treatment of specific forms of liver disease (Table 27-1) is clearly beyond the scope of this chapter, some etiologies clearly deserve special focus because they are prevalent or closely linked to nutrition. These include alcoholic liver disease, nonalcoholic fatty liver

disease, viral hepatitis, hemochromatosis, Wilson disease, and cholestatic diseases including primary sclerosing cholangitis and primary biliary cirrhosis.

Alcoholic Liver Disease

The liver is the main organ responsible for ethanol metabolism; other organs, such as the stomach, contribute to a much lesser degree. The pathogenesis is complex and involves numerous mechanisms that are variably well understood. Acetaldehyde (one of the metabolites of ethanol) is postulated to play an etiologic role in alcoholic liver disease (ALD). Other mechanisms such as oxidative stress (through both direct injury and cell signaling); mitochondrial dysfunction; hypoxia; impaired proteasome function; abnormal metabolism of methionine, *S*-adenosylmethionine (SAM), and folate; Kupffer cell activation; dysregulated cytokine production; immune responses to altered hepatocellular proteins; and genetic/. epigenetic mechanisms are all thought to be involved in the development and progression of ALD.[16] Importantly, many are directly modifiable through nutritional interventions (eg, oxidative stress).

The most extensive studies involving interactions between nutritional status and liver disease have been in patients with ALD. The most detailed of these studies derive from the Veterans Health Administration (VA) Cooperative Studies Program in patients with alcoholic hepatitis.[17–20] In these and other studies it is clear that malnutrition is a major complication of ALD. Importantly, malnutrition worsens clinical outcomes in ALD, and nutritional support improves nutritional status and may improve clinical outcome (Practice Scenario 27-1).

The first of the VA Cooperative Studies (Study #119) established that nearly every patient with alcoholic hepatitis had some degree of malnutrition.[19] This study categorized 284 patients with complete nutritional assessments into groups with mild, moderate, or severe alcoholic hepatitis (based on clinical and biochemical parameters). Mean alcohol consumption among all patients was 228 g per day, with almost 50% of energy intake coming from alcohol. As a result, although caloric intake for many patients was adequate, there was often a deficient intake of protein and critical micronutrients. The severity of liver disease generally correlated with the severity of malnutrition. Similar data were generated in a follow-up VA study on alcoholic hepatitis (Study #275).[21]

In both of these studies, patients were carefully monitored by a dietitian and encouraged to eat a balanced 2500-kcal hospital diet. In the second study, patients in the therapy arm of the protocol also received oxandrolone 80 mg per day and an enteral nutritional support product high in branched-chain amino acids (BCAAs). Caloric intake correlated in a stepwise fashion with 6-month mortality data. Those patients who consumed < 1000 kcal per day had > 80% 6-month mortality, whereas those who voluntarily consumed > 3000 kcal per day had virtually no mortality.[17] Furthermore, the degree of malnutrition correlated with the development of serious complications such as encephalopathy, ascites, and hepatorenal syndrome.[17] Although it is possible that nutrition prevented mortality, it is also possible that the inability to eat was simply a marker of disease severity. Nonetheless, many centers, including our own, provide enteral nutritional support to patients with severe acute alcoholic hepatitis who are unable to voluntarily consume sufficient calories.

In the VA Cooperative Studies, the chronic alcohol-consuming control population without liver disease also frequently had some degree of protein-energy malnutrition. This contradicts other data indicating that only alcoholics with underlying liver disease demonstrated significant protein-energy malnutrition. Although the VA studies evaluated patients with acute alcoholic hepatitis, patients with stable alcoholic cirrhosis without alcoholic hepatitis have been studied as well. One such investigation of patients with compensated alcoholic cirrhosis (not actively drinking) revealed indicators of malnutrition almost as severe as those in patients with alcoholic hepatitis (eg, a creatinine-height index of 71% of normal).[22] Supplemental micronutrients such as SAM and zinc have a potential therapeutic role in alcoholic liver disease and are subsequently discussed as CAM agents later in this chapter.

Practice Scenario 27-1

Question: How important is enteral nutrition in the management of acute alcoholic hepatitis?

Scenario: A 55-year-old male with a past medical history of alcoholism presents with a 2-week history of nausea, vomiting, increasing abdominal girth, and jaundice. Until 2 weeks ago the patient was drinking one-fifth of vodka per day, but since has been unable to tolerate anything by mouth. A physical examination reveals scleral icterus, jaundice, and a tense abdomen with a positive fluid wave consistent with ascites. The patient's memory is normal and there is no asterixis. His weight is 70 kg and his height is 68 in. Diagnostic studies, including laboratory and radiologic investigations, reveal severe alcoholic hepatitis, normal renal function, and new onset ascites. The original diet order is a 2 g sodium diet. Despite aggressive supportive care and corticosteroids, over the next 48 hours the patient develops worsening renal function consistent with hepatorenal syndrome, and an assessment of diet intake reveals the patient is consuming 10% of goal calories and protein.

Intervention: Given the inadequacy of the patient's caloric and protein intake, nasogastric access is obtained and the patient is started on a standard polymeric enteral formula. Enteral nutrition is increased slowly with close attention to his risk of refeeding syndrome. By day 5 of the hospitalization, the patient is receiving 40 kcal per kilogram per day and tolerating 1.5 g of protein per kilogram per day. Over the next several days, the patient begins tolerating oral feeding and is discharged in stable condition 1 week later.

Answer: Early and aggressive enteral nutrition improves outcomes in patients with alcoholic hepatitis. Nasoenteral access is generally required given the many obstacles to enteral feeding in patients with severe liver disease (eg, anorexia, nausea, vomiting). These patients are at risk of refeeding syndrome.

Rationale: The Veterans Health Administration Cooperative Studies Program demonstrated that virtually all patients with alcoholic hepatitis have some degree of malnutrition.[17–20] In addition, the severity of liver disease generally correlated with the degree of

malnutrition. Study subjects consuming > 3000 kcal per day had near zero mortality, whereas those consuming less than 1000 kcal per day had > 80% mortality. Thus, food intake correlated with 6-month mortality. A major multicenter study demonstrated that enteral nutrition, when compared to corticosteroids, has similar short-term mortality rates, improved 1-year mortality rates, and reduced infectious complications. Restricting protein is not recommended in alcoholic hepatitis (or any other liver disease, for that matter) and should only be implemented in the setting of PSE refractory to medical treatment.

Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

An estimated 65% of Americans are either overweight or obese. Some estimates predict that close to 100% of Americans will be overweight by the year 2030, placing them at increased risk for development of the metabolic syndrome (see Chapter 35).

NAFLD, the hepatic manifestation of the metabolic syndrome, is a consequence of inappropriate hepatic management of lipids resulting in the abnormal accumulation of fat in the hepatocytes. This phenomenon, although not completely understood, seems to be a consequence of increased free fatty acid delivery to the liver from visceral sources coupled with hyperinsulinemia-related inadequate formation and the export of very low-density lipoproteins (VLDL) out of the hepatocyte.

Although steatosis alone does not usually result in progressive fibrosis, approximately 10% to 20% of patients with NAFLD experience a "second hit," of unknown nature, that induces an inflammatory response to the fat-laden hepatocytes. This inflammation, in turn, can lead to liver cell injury, death, and replacement by scarring (fibrosis). As this necroinflammatory response progresses, it can and frequently does lead to cirrhosis. NASH-related cirrhosis can lead to liver failure and has been associated with the development of hepatocellular carcinoma.

Most NAFLD/NASH patients are obese. As with other obese patients, nutritional assessment is often difficult and complicated, and standard estimates of nutritional needs based on weight and anthropometric measurements are often misleading.[23–26] Additionally, patients with NAFLD/NASH are often diabetic (see Chapter 34) and have varying degrees of diabetic nephropathy and associated proteinuria, which can lead to low serum albumin levels.

When patients' fatty liver disease advances to cirrhosis with serologic hepatic dysfunction, hepatic production of proteins is often impaired. Furthermore, because cirrhosis often results in a catabolic state, a patient's nutritional needs, especially with respect to protein requirements, can be underestimated. Cirrhotic NASH patients are often malnourished and protein deprived despite being obese.

Evidence indicating that specific dietary components play a role in the development/progression of NAFLD is continually emerging. Mechanisms such as lipotoxicity, oxidative stress, endotoxemia, dysregulated cytokines/adipokines, and alterations in gut microflora appear to be involved in triggering both steatosis and steatohepatitis. These mechanisms are also linked with specific dietary habits (eg, obesity, high fat diets [HFDs], excess fructose, diets low in omega-3 fatty acids). HFDs have often been implicated in NAFLD. In fact, many animal models use a HFD (71% of energy from fat) to induce NAFLD.[27] Importantly, HFDs result in a number of metabolic derangements, including oxidative stress, alterations in postprandial triglyceride metabolism, increased TNF-α, circulating free fatty acids (FFAs), and insulin resistance that likely play an etiologic role in NAFLD.

Although the amount of dietary fat certainly appears to be important in the development of NAFLD, there is emerging evidence that the type and ratios of dietary fats can also contribute. An increased fat intake with an excessive amount of omega-6 fatty acids has been implicated in promoting necroinflammation.[28] On the other hand, a diet containing medium-chain triglycerides (MCTs) in the absence of long-chain triglycerides (LCTs) has been reported to be hepatoprotective.[29] There are also studies demonstrating the role of fructose in the pathogenesis of NAFLD.[30,31] Indeed, specific sources of fructose, such as soft drinks, have also been implicated. Recent animal studies have confirmed that high fructose diets induce the metabolic syndrome with intrahepatic accumulation of triglycerides. In these models, fructose-induced NAFLD was associated with intestinal bacterial overgrowth and increased intestinal permeability, subsequently leading to an endotoxin-dependent activation of hepatic Kupffer cells and increased monocyte chemotactic protein-1 (MCP-1) and tumor necrosis factor alpha (TNF-α).[32,33]

Diet and physical activity for weight reduction and weight loss surgery for extreme obesity are the current standard recommendations for the treatment of NAFLD. There is recent evidence that intensive lifestyle intervention in patients with type 2 diabetes can reduce steatosis and the incidence of NAFLD.[34] Caloric restriction can result in significant changes in both liver fat and volume within a few days. Another area of increasing interest is the use of low carbohydrate diets in NAFLD. A low carbohydrate, ketogenic diet in patients with NASH led to significant weight loss and histologic improvement of fatty liver disease at 6 months.[35] Dietary avoidance of lipogenic, simple sugars (ie, fructose) seems to be universally recommended. A reduction in the consumption of sweetened beverages can also lead to significant weight loss owing to a reduction in total calories consumed.[36] Regarding exercise, vigorous exercise may be most beneficial, because it appears that exercise intensity may be more important than duration.[37] Weight loss by bariatric surgery attenuates both steatosis and steatohepatitis, but data supporting improvements in fibrosis are limited.[38] Despite intensive research, there remains no U.S. Food and Drug Administration (FDA)-approved therapy for NAFLD. However, the PIVENS study demonstrated a benefit with vitamin E therapy (800 IU daily), which has become standard practice in many areas of the country. The PIVENS study is further discussed in the CAM section of this chapter.

Patients with NASH-related decompensated cirrhosis pose other challenges. Despite their often marked obesity and because of the catabolic nature of cirrhosis, these patients are often significantly malnourished with protein deficits.[39,40] Although weight reduction is still beneficial, all efforts should be made to ensure adequate protein needs are supplied. As is the case with cirrhotics in general, there is rarely, if ever, an indication to limit protein intake to subnormal levels in patients with NAFLD. In fact, there are emerging data that high protein intake may lead to better outcomes in patients with cirrhosis with liver failure.[41]

Viral Hepatitis

Viral hepatitis consists of five distinct entities (A to E). Hepatitis A is an RNA virus that is transmitted via the fecal–oral route. It is an uncommon infection in the United States, but has higher prevalence in areas of low socioeconomic status, such as Africa, Asia (excluding Japan), the Mediterranean basin, Eastern Europe, the Middle East, Mexico, Central and South America, and parts of the Caribbean. In the United States, this disease is most often encountered in individuals that have emigrated from or traveled to these locations without receiving appropriate vaccinations.[42] This virus does not cause chronic infection. Management of acute hepatitis A consists of supportive care; there are no specific recommendations for dietary restrictions or support, aside from abstinence from alcohol intake.[43]

Hepatitis B is a DNA virus that is transmitted most commonly via perinatal, percutaneous, and sexual routes. The disease is endemic in sub-Saharan Africa and Asia where as much as 25% of the population have an active hepatitis B infection. Rates of infection in the United States are substantially lower. It is estimated that 0.1% to 0.2% of the population has chronic hepatitis B infection, whereas 200,000 to 300,000 new cases of hepatitis B infection occur annually.[44] In the United States, the majority of cases can be attributed to intravenous (IV) drug use and high risk sexual practices. Low rates in developed countries are largely due to preventative measures, specifically, vaccination against the virus. In young, otherwise healthy individuals, the virus will be cleared with complete recovery 95% to 99% of the time. The infection is more likely to become chronic in newborns who contract the virus during birth and in young children who contract the virus. The disease will only become chronic in 1% to 5% of adults that contract the virus.[44] Chronic infection can lead to inflammation and fibrosis leading to cirrhosis. Chronic hepatitis B virus is associated with the highest risk for the subsequent development of hepatocellular carcinoma among viral hepatitis. Concomitant exposure to dietary aflatoxins, particularly in Asia, has been associated with a greater risk for the development of cirrhosis and hepatocellular carcinoma in patients with hepatitis B.[45] Preliminary liver cancer chemoprevention trials have been performed in these patients using broccoli extracts, which are shown to activate the antioxidant response element.[46]

Hepatitis C is the most common blood-borne infection in the United States with an estimated 3.2 million people suffering from chronic hepatitis C infection.[47] The peak incidence of the disease occurs in individuals between the ages of 40 and 49. Approximately 30,000 new cases are diagnosed each year with the vast majority of infections having been contracted decades prior to presentation.[47] Infection with hepatitis C is most commonly acquired via IV drug use, but also occurs in transfusion recipients (most often those who received transfusions prior to 1992), hemodialysis patients, Vietnam veterans, and in healthcare workers due to accidental sticks with infected needles. Sexual and perinatal transmission of the disease is far less common.[47] Hepatitis C usually results in chronic infection and cirrhosis develops over 20 to 25 years in an estimated 20% of patients. Acute hepatitis C is typically asymptomatic, although signs such as fever, nausea, and jaundice can occur 1 to 3 months after exposure.[48]

Supplement use is common with chronic hepatitis C infection. In the most rigorously designed study to date, highly purified silymarin (milk thistle) was recently found to have no effect on liver enzymes in patients with chronic hepatitis C, but the use of this over-the-counter supplement remains widespread.[49] In contrast, multiple studies demonstrate that vitamin D supplementation increases sustained virologic response (cure) rates in patients on HCV therapy with pegylated interferon (IFN) and ribavirin.[50] Likewise, preliminary studies indicate that SAM may lead to increased sustained viral response (SRV) rates, but its clinical use is uncertain given the recent introduction of HCV protease inhibitors.[51] St. John's wort, a CAM agent commonly used for depression, is absolutely contraindicated in patients taking HCV protease inhibitors because it may lead to increased metabolism and subsequent loss of efficacy of these medications.

Hereditary Hemochromatosis

Hereditary hemochromatosis is a genetic disorder of iron overload classically occurring as an autosomal recessive disorder in individuals heterozygous for the C282Y mutation in the human hemochromatosis (HFE) gene. The disease is common, with an incidence of 1 in 250 people. Penetrance is incomplete, with clinical disease presenting more commonly in Caucasian males.[52] The resulting iron accumulation affects the liver, as well as the heart, endocrine system, and musculoskeletal systems. The disease results in cirrhosis in its late stages. However, if the disease is caught before the onset of cirrhosis, it can essentially be cured. The most effective treatment for hemochromatosis is therapeutic phlebotomy, initially scheduled weekly, with maintenance phlebotomy performed as need based on serum ferritin levels.[53] It is essential to limit dietary iron intake in patients with a diagnosis of hereditary hemochromatosis. In addition, alcohol consumption should be limited in patients with hemochromatosis, because intake greater than 60 g per day is associated with increased rates of cirrhosis.[52] Excess vitamin C supplementation should also be avoided because this vitamin may lead to increased dietary iron absorption.

Wilson Disease

Wilson disease is an important, but rare, heterogeneous inborn disorder of copper metabolism occurring due to mutations in the *ATP7B* gene. Copper accumulation leads to hepatic and neurologic disease resulting from improper hepatocellular use and biliary excretion of copper. Wilson disease occurs in 1:30,000 people and usually becomes clinically apparent before the age of 40.[54] Wilson disease can also affect the eyes (Kayser-Fleischer rings) and kidneys and has been associated with hemolysis. The disease may present with either neuropsychiatric symptoms or liver disease (chronic liver disease and cirrhosis or acute liver failure). A variety of tests (serum ceruloplasmin, 24-hour urine copper, slit-lamp eye examination, and liver biopsy with hepatic copper quantification) are used to diagnose suspected Wilson disease.[55] Treatment involves the use of chelating agents to remove tissue copper and to allow excretion in the urine. The most commonly used chelating agents are penicillamine and trientine. Patients

receiving penicillamine therapy require the replacement of vitamin B6. Zinc acetate has also been approved by the FDA for the treatment of Wilson disease. Zinc induces metallothionein and reduces dietary copper absorption. A recent report demonstrated that there may be more "nonresponders" to zinc than chelation therapy.[56] The authors proposed that combination therapy with zinc plus a chelator could be considered, particularly if monotherapy fails to normalize liver enzymes. Wilson disease patients should also be instructed to avoid foods high in copper, including liver, chocolate, shellfish, and nuts.[55]

Cholestatic Liver Diseases

In contrast to the aforementioned hepatocellular liver diseases, primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are the most prevalent etiologies of chronic cholestatic liver disease. Cholestatic liver diseases pose unique challenges in nutrition. In PBC, the initial damage occurs in the biliary tree due to T-cell–mediated destruction of the intrahepatic bile ducts. Over time, the damage becomes severe enough to cause cholestasis, which results in a universal end point of cirrhosis and end-stage liver disease.[57] The disease most commonly presents with pruritus and alkaline phosphatase elevation in middle-aged women. Striking hypercholesterolemia may accompany PBC, but curiously, hypercholesterolemia in PBC has not been definitively linked to increased atherosclerosis. The only approved treatment in the United States for PBC is ursodeoxycholic acid (UDCA), which alters bile cholesterol composition.[58]

PSC is characterized by inflammation and sclerosis of the intrahepatic and/or extrahepatic bile ducts. PSC has a more rapid and severe course than PBC, however, with median time from diagnosis to time of death ranging between 9 and 12 years. As the disease progresses, complete obstruction of the biliary tree occurs, leading to cirrhosis and the development of end-stage liver disease.[59] PSC has been associated with both inflammatory bowel disease and autoimmune hepatitis (especially in children). PSC carries an increased risk of cholangiocarcinoma with estimates of risk between 8% and 15% over a patient's lifetime.[60] UCDA does not appear to be effective for PSC.[61] Endoscopic treatment (endoscopic retrograde cholangiography) of dominant biliary strictures may be performed to exclude cholangiocarcinoma and to relieve obstruction.

Regardless of its etiology, chronic cholestasis may cause calcium- and lipid-soluble vitamin malabsorption. Fat malabsorption is usually associated with a decrease in dietary calcium absorption and an increase in oxalate absorption. This is because FFAs bind to calcium in the digestive tract, making it unavailable for absorption. Calcium malabsorption may be worsened by vitamin D deficiency. The liver usually activates vitamin D into its active compound 1,25-dihydroxyvitamin D. Most patients with chronic cholestasis have osteoporosis, but osteomalacia is rare. These bone problems are known as metabolic bone disease and are responsible for significant morbidity. Calcium usually binds oxalates in the intestine, therefore fatty acid malabsorption results in an increase in free oxalates that are easily absorbed and predispose the patient to kidney stones. In PBC, 23% of patients have a decrease in their vitamin K plasma levels, which does not correlate with the prothrombin time (PT).[62] Vitamin A, D, and E deficiencies are usually present together with vitamin K deficiency. The prevalence of lipid-soluble vitamin deficiencies correlates with bilirubin levels.

In chronic cholestatic diseases, such as PBC and PSC, parenteral supplementation of lipid soluble vitamins (A, D, E, and K) may be necessary if steatorrhea greater than 10 g per day is present. Oral calcium supplements are also recommended. The progression of PBC-related osteodystrophy can be slowed by supplementing with calcium, 1,25-dihydroxyvitamin D, and calcitonin.[63] In patients with weight loss, supplements containing MCTs (MCT oil) can be given to provide extra calories because they do not need bile acids to be absorbed.

Malnutrition in Chronic Liver Disease

There is a high prevalence of protein-calorie malnutrition (PCM) in cirrhosis, which appears to correlate better with the severity rather than the etiology of the chronic liver disease.[64-68] The literature reports malnutrition in 34% to 82% patients with alcoholic cirrhosis.[20] In nonalcoholic cirrhosis, the prevalence of PCM ranges from 27% to 87%.[20] Because of the difficulties with nutrition assessment in cirrhosis, these prevalence figures are based on anthropometric data only.

In general, malnutrition in cirrhosis has many causes; these can be classified into three groups: (1) causes that limit oral intake; (2) causes that decrease the digestion and absorption of nutrients; and (3) causes that interfere with the metabolism of nutrients (Table 27-2). A majority of cirrhotic patients suffer

TABLE 27-2 Causes of Malnutrition in Cirrhosis

Decrease in oral intake
- Anorexia
- Nausea
- Vomiting
- Early satiety
- Taste abnormalities
- Alcohol abuse
- Iatrogenic due to restrictive diets or NPO status
- Medications

Maldigestion and malabsorption
- Fat malabsorption due to cholestasis or chronic pancreatitis
- Water-soluble vitamin malabsorption due to alcohol abuse
- Calcium and lipid-soluble vitamin malabsorption due to cholestasis

Metabolic abnormalities
- Glucose intolerance
- Increased protein and lipid catabolism similar to sepsis
- Trauma or other catabolic states

Associated renal diseases
- Urinary micronutrient losses
- Hepatorenal syndrome
- Viral hepatitis associated glomerulonephritis (MPGN in HCV, membranous glomerulonephritis in HBV)

NPO, nothing by mouth; MPGN, membranoproliferative glomerulonephritis; HCV, hepatitis C virus; HBV, hepatitis B virus.

from gastrointestinal symptoms such as anorexia, early satiety secondary to ascites, taste dysfunction, nausea, and vomiting, which limit their nutrient intake. The prevalence of weight loss, nausea, and anorexia among cirrhotic patients were reported to be 60%, 55%, and 87%, respectively.[69] Taste abnormalities have been associated with zinc and magnesium deficiencies.[70] Steatorrhea (fat malabsorption) has been reported in 40% of cirrhotics, and 10% have severe steatorrhea (more than 30 g per day), usually caused by concomitant pancreatic insufficiency. Side effects of medications and diets with excessive protein and salt restriction seem to be a common cause of malnutrition in cirrhosis, but studies evaluating the magnitude of this problem are not available.

Regardless of the etiology of cirrhosis, poor nutritional status is associated with a poor prognosis for survival. This has been shown in decompensated cirrhotic patients as well as those awaiting liver transplantation and undergoing abdominal surgery.[71,72] Whether PCM is an independent predictor of survival or just a reflection of the severity of liver insufficiency is still a subject of controversy.

Energy Expenditure in Chronic Liver Disease

Patients with chronic liver disease can develop serious metabolic abnormalities that mimic a state of catabolism similar to sepsis or trauma.[69] Measurements of the basal energy expenditure in cirrhotics have not shown a statistically significant difference from healthy controls when energy expenditure is expressed in calories per kilogram of body weight.[73–75] The prediction of the Resting Energy Expenditure (REE) by the Harris–Benedict equation (see Chapter 2) is not accurate in more than 50% of patients with cirrhosis.[74] The presence of ascites has been noted to increase the REE by 10%.[76] Given that body cell mass is decreased even in early stages of cirrhosis, the energy expenditure per unit of metabolically active tissue is thought to be increased.

Regardless of the absolute rates of energy expenditure, the type of fuel preferred by cirrhotic patients is altered. Cirrhotic patients have Respiratory Quotient (RQs) that are significantly lower than controls after an overnight fast. This indicates that cirrhotic patients are using more fat as a fuel, which is similar to what occurs to a normal subject after 72 hours of starvation.[75] In other words, the metabolism of cirrhotic patients, after an overnight fast, mimics that of starving controls. However, as opposed to a starving patient in whom the energy expenditure decreases over time, cirrhotic patients continue to have normal or increased energy expenditures, leading to progressive loss of muscle and fat mass, and resulting in PCM.

Metabolism in Chronic Liver Disease

Studies on carbohydrate metabolism in cirrhosis have shown that the prevalence of glucose intolerance in cirrhosis is high.[77] The pathogenesis of this abnormality is not well defined, but it seems to be caused by a postreceptor intracellular abnormality in both the liver and muscle. Associated with this insulin resistance are the decreased storage of glycogen in the liver and muscle and the early use of lipids and protein as fuel sources, manifested as a low RQ. Abnormalities in lipid metabolism have also been described in cirrhosis. The levels of fatty acids and ketone bodies are increased, and there is an increase in ketone body production.[69] There is evidence of impairment of fatty acid storage in the form of triglycerides, which is likely caused by lipoprotein lipase inhibition and a decrease in the availability of glycerol phosphate in the adipocyte. This imbalance between fat synthesis and catabolism results in depletion of the reserves in adipose tissue. In addition, leptin levels in cirrhotics are inappropriately elevated for their fat mass.[78] This excessive leptin production by the adipose tissue is postulated to decrease appetite and increase energy expenditure in these patients. Both insulin resistance and hepatic steatosis have been associated with HCV infection and with viral replication and resistance to antiviral therapy.

Perhaps the most remarkable metabolic abnormality of patients with end-stage liver disease is in amino acid metabolism. Urine nitrogen losses are increased in cirrhotic patients with a normal renal function, suggesting a catabolic state. The catabolism of protein is increased and fails to decrease normally in response to feeding.[79] In cirrhosis, the plasma levels of BCAAs (leucine, valine, and isoleucine) are low, and the levels of aromatic amino acids (phenylalanine, tyrosine, and tryptophan) are high. This serum amino acid imbalance is also seen in sepsis and trauma, and is probably mediated by an alteration in the balance between insulin and other regulatory hormones.

The role of skeletal muscle in amino acid metabolism has gained prominence. Skeletal muscle constitutes the largest metabolic organ of the body and actively takes up BCAAs that are used to synthesize glutamine and alanine. These amino acids are, in turn, released into the bloodstream and taken up by the liver to become the substrates for hepatic gluconeogenesis. Glutamine is a carrier for ammonia that is converted to urea by the liver and excreted by the kidneys. In cirrhosis, excessive glutamine is synthesized in the skeletal muscle, while hepatic urea synthesis is impaired. This leads to an increase in renal glutamine uptake and constitutes a back up mechanism for ammonia elimination through the kidneys. Studies have shown that cirrhotic patients with decreased skeletal muscle mass are more prone to develop hepatic encephalopathy.[80] This underscores the importance of preserving the skeletal muscle mass in cirrhotic patients as a means of preventing chronic hepatic encephalopathy.

In summary, cirrhotic patients have decreased carbohydrate use and storage capacity plus an increase in fat and protein catabolism, which lead to a chronic catabolic state resulting in the depletion of protein and lipid reserves. These abnormalities, combined with a decrease in food intake and nutrient absorption, constitute the basis of the pathogenesis of PCM in end-stage liver disease. Without question, dysregulated cytokine levels are intimately involved in many of the metabolic and nutritional abnormalities observed in liver disease, especially in acute alcoholic hepatitis and in more decompensated liver disease.[14] More specifically, cirrhotic patients have increased levels of TNF and interleukin(IL)-1 and -6, which have catabolic effects in muscle, adipose tissue, and the liver.[81] Endotoxin produced by intestinal gram-negative bacteria is often present in the blood of cirrhotic patients.[82] Cirrhotic patients have an increase in intestinal permeability that allows the leakage of endotoxin from the intestine to the lymphatics and the bloodstream.[83]

Endotoxin triggers the release of cytokines and nitric oxide, which may be mediators of the catabolic state as well as the hyperdynamic circulation of cirrhotics.[84]

Nutritional Assessment

All of the previous data suggest that a proper assessment of nutritional status in patients with liver disease is important. This helps to determine the goals for nutritional support. Although there is a common recognition of the importance of accurate nutrition assessments in patients with liver disease, there are several issues that make a nutritional assessment in these patients difficult (Table 27-3).

Anthropometrics

Height and weight are normally a good starting point for a nutritional assessment, but because of fluid abnormalities such as ascites, patients with liver disease may have a normal or greater than normal body weight in relation to their height and still have decreased protein and muscle mass. This is the result of excess fluid such as ascites, which increases weight without increasing protein stores. Because the excess fluid weight provides no structural protein for strength and activities of daily living, it makes a physical examination in a patient with liver disease essential. In this examination, the clinician must determine if the patient has muscle wasting in the extremities, the upper body, and the temporal areas despite a weight greater than the ideal weight.

Laboratory Measurements

Laboratory values can also be misleading in these patients. Because of ongoing liver disease, albumin and prealbumin may be moderately or very low, even in the presence of good nutritional status.[85] This is due to the decreased production by the diseased liver. One method of determining muscle mass is to collect a 24-hour urine sample for creatinine. A normal value of 18 mg per kilogram of ideal weight in females and 23 mg per kilogram of ideal weight in males would suggest normal muscle mass, and decreased values would suggest decreased muscle mass. This technique is limited to patients with normal renal function, and requires an accurate 24-hour urine collection, which can be challenging in an ambulatory setting.

TABLE 27-3 Nutrition Assessment in Advanced Liver Diseases

Method	Reliable	Unreliable
Weight for height		X
Plasma proteins: albumin, prealbumin		X
Delayed skin reactions and total lymphocyte count		X
24-h creatinine: height ratio	X (only with normal renal function)	
Bioelectric impedance		X
Anthropometry: triceps skinfold and mid-arm muscle area or Subjective Global Assessment	X	

Other Nutritional Assessment Tools

Other methods of nutrition assessment (see Chapter 9) may be more accurate in these patients, such as a subjective global assessment (Table 27-4). This method evaluates patient performance during daily activities and includes a physical exam and may provide a more accurate assessment of the nutrition status of a patient with liver disease.[85] A physical and functional examination is essential in assessing the nutritional status of patients with liver disease.

Provision of Nutrients

Patients with Compensated Liver Disease

Interest in nutritional therapy in cirrhosis began when Patek et al.[86] showed that a nutritious diet improved the 5-year outcomes compared to control subjects consuming an inadequate diet. Although these patients had alcoholic liver disease, several recent studies further support the concept of improved outcomes with nutritional support in patients with cirrhosis due to any cause. Hirsch et al.[87] demonstrated that outpatients supplementing their diet with an enteral nutritional support product (1000 kcal [4.2 MJ], 34 g protein) had significantly improved protein intake and significantly fewer hospitalizations. This group then provided an enteral supplement to outpatients with alcoholic cirrhosis and observed an improvement in nutritional status and immune function.[87] In the VA Cooperative Study on nutritional support in alcoholic liver disease using the anabolic steroid oxandrolone and an enteral nutritional supplement, an improvement in mortality was seen with the combination of oxandrolone plus nutritional supplementation in patients who had moderate protein-energy malnutrition.[17] Those with severe malnutrition did not significantly benefit from therapy. This was possibly due to their disease being so severe that no intervention could improve their outcome. Studies by Kearns et al.[88] showed that patients with alcoholic liver disease who were hospitalized for treatment and given an enteral nutritional supplement via a feeding tube had significantly improved serum bilirubin levels and liver function as assessed by antipyrine clearance. A multicenter randomized study of enteral nutrition versus steroids in patients with alcoholic hepatitis showed similar overall short-term results.[89] Moreover, those receiving enteral nutrition (rich in BCAAs) had a better long-term outcome with fewer infection-related deaths. Thus, nutritional supplementation clearly improved nutritional status and, in some instances, hepatic function and other indicators of outcome in cirrhosis.

An important component of the dietary management of the patient with advanced liver disease is to minimize periods without food intake because patients rapidly enter into starvation mode with decreased glucose oxidation and increased protein and fat catabolism.[90] To prevent this, the diet should, optimally,

TABLE 27-4 Subjective Global Assessment

(Select the appropriate category with a check mark, or enter numerical value where indicated by "#".)

A. History

1. Weight change
   Overall loss in past 6 mos: amount = # _____ kg; % loss = # _____
   Change in past 2 wks: _____ increase, _____ no change, _____ decrease
2. Dietary intake change (relative to normal)
   _____ No change
   _____ Change _____ duration = # _____ weeks
   _____ Type: _____ suboptimal solid diet _____ full liquid diet
   _____ hypocaloric liquids _____ starvation
3. Gastrointestinal symptoms (that persisted for >2 wks)
   _____ none _____ nausea _____ vomiting _____ diarrhea _____ anorexia
4. Functional capacity
   _____ No dysfunction (eg, full capacity)
   _____ Dysfunction _____ duration = # _____ wks
   _____ Type: _____ working suboptimally
   _____ ambulatory
   _____ bedridden
5. Disease and its relation to nutritional requirements
   Primary diagnosis (specify) _____
   Metabolic demand (stress): _____ no stress _____ low stress
   _____ moderate stress _____ high stress

B. Physical

(for each trait specify 0 = normal, 1+ = mild, 2+ = moderate, 3+ = severe)

_____ loss of subcutaneous fat (triceps, chest)
_____ muscle wasting (quadriceps, deltoids)
_____ ankle edema
_____ sacral edema
_____ ascites

C. SGA rating (select one)

_____ A = Well nourished
_____ B = Moderately malnourished (or suspected of being malnourished)
_____ C = Severely malnourished

SGA, Subjective Global Assessment. Reprinted from Detsky AJ, McLaughlin JR, Baker JP, et al. What is subjective global assessment of nutritional status? *J Parenter Enteral Nutr.* 1987;11:8–14.

be divided into three meals (the first of which should be early in the morning), three snacks, plus one bedtime supplement. The early breakfast improves cognitive function in patients with subclinical (minimal) hepatic encephalopathy and the bedtime supplement improves body protein stores.[91] Importantly, an improvement in muscle mass with nighttime supplements was demonstrated by Plank et al.,[9] who randomized 103 cirrhotic patients to receive two cans of Ensure Plus (710 kcal with 26 g of protein) or two cans of Diabetic Resource (500 kcal with 30 g of protein) either during the day or at bedtime, for a total of 12 months. Only the patients who received the supplements at bedtime gained lean muscle mass (2 kg) over 12 months (Practice Scenario 27-2). Unfortunately, there is a long tradition of protein restriction for patients with advanced liver disease who also have hepatic encephalopathy. This tradition has no solid scientific basis, and recent studies do not support this approach. Cordoba et al.,[92] in a prospective randomized study, treated 30 cirrhotic patients who suffered episodic overt hepatic encephalopathy with either a low-protein enteral formula (with increased protein every 3 days [0 g, then 12 g, 24 g, and 48 g]) or a normal protein formula (1.2 g per kilogram per day) from the first day. Both formulas provided 30 kcal per kilogram per day. The outcome of hepatic encephalopathy was similar with both formulas. In a second study, Gheorghe et al.[93] treated 153 consecutive cirrhotic patients with overt HE with a diet providing 30 kcal per kilogram per day with 1.2 g of protein per kilogram per day, divided into five meals from 8:00 AM to 10:00 PM. Most patients improved their HE, with the best results seen in the more severe HE patients.[93] The HE should be treated with FDA-approved medications such as lactulose or rifaximin, if needed. If the HE persists despite maximal medical therapy and an evaluation for other causes of changes in mentation, then protein intake can be decreased to the maximal tolerated, and a BCAA-enriched formula supplement can be administered to complete the nitrogen needs. These studies highlight the need to maintain caloric intake in patients with liver disease at 25 to 30 kcal per kilogram via enteral feeds and, more specifically, the importance of maintaining protein intake at 1.0 to 1.5 g per kilogram per day (Table 27-5).[94]

Practice Scenario 27-2

Question: What is the appropriate meal schedule to provide optimal nutrition to the outpatient with chronic liver disease?

Scenario: A 57-year-old female with a history of cirrhosis secondary to PBC presents to the clinic for consultation regarding her nutrition. The patient states that she has had trouble maintaining her weight despite her best efforts to eat an appropriate amount. The patient states that she feels progressively weaker and feels that she has been losing muscle mass. In addition, the patient reports that her husband notices that she tends to function more slowly in the mornings. The patient has never received any education regarding proper nutrition in the setting of her liver disease. She requests that some intervention be made to help her maintain or increase her weight and to improve her mentation.

Intervention: The patient is started on a diet consisting of three meals per day with one early morning meal. In addition, the patient begins to eat three snacks per day, as well as a late night snack before bed. Over the course of the next 6 months the patient gains 5 pounds and notes improvement in her strength and mentation.

Answer: Nutrition is essential to improve both lean muscle mass and overall function in patients with liver disease. This patient should be educated regarding the importance of consuming an appropriate number of calories. The emphasis should be on consumption of three meals per day beginning with an early morning breakfast. The patient should also be instructed to consume three small snacks in between meals. Additionally, the patient should be encouraged to consume a late night snack before bed. This will improve her overall functioning, but more importantly, will increase lean muscle mass.

Rationale: An important component of the dietary management of the patient with advanced liver disease is to minimize periods without food intake because patients rapidly enter into starvation mode, with decreased glucose oxidation and increased protein and fat catabolism.[90] To prevent this, the diet should, optimally, be divided into three meals (the first of which should be early in the morning), three snacks, plus one bedtime supplement. The early breakfast improves cognitive function in patients with subclinical (minimal) hepatic encephalopathy and the bedtime supplement improves body protein stores.[91] Importantly, an improvement in muscle mass with nighttime supplements was demonstrated by Plank et al.,[62] who randomized 103 cirrhotic patients to receive two cans of Ensure Plus (710 kcal with 26 g of protein) or two cans of Diabetic Resource (500 kcal with 30 g of protein) either during the day or at bedtime, for a total of 12 months. Patients who received supplements at bedtime gained lean muscle mass (2 kg) over 12 months,[9] demonstrating the importance of late night snacking in maintaining muscle mass in patients with cirrhosis.

Patients with Decompensated Liver Disease

Patients with decompensated liver disease can be very challenging to manage because of the presence of ascites, encephalopathy, and the increased frequency of diminished renal function. Decompensated cirrhosis is defined as cirrhosis with ascites and/or encephalopathy. Liver chemistries usually show albumin < 3 g per deciliter and total bilirubin > 2.5 mg per deciliter. Patients with PSE may present with behavioral changes, reversal of sleep pattern, slurred speech, disorientation, or coma. The nutritional requirements mentioned earlier in this chapter do still apply to the decompensated patient, and it is more difficult to provide proper nutrition to patients with decompensated liver disease. It is recommended that if patients fail to achieve the recommended 35 to 40 kcal per kilogram and 1.0 to 1.5 g per kilogram of protein on their own, supplemental enteral nutrition in the form of nasogastric or orogastric tube feeds should be considered.[94,95] Enteral nutrition is preferred over parenteral nutrition because of cost, the risk of sepsis of the parenteral nutrition line, the preservation of the integrity of the gut mucosa, and the prevention of bacterial translocation and multiple organ failure. Moreover, total parenteral nutrition can, in some instances, cause liver disease as one of its complications. If enteral nutrition is not possible, parenteral nutrition can be used with the knowledge that it is important to return to the enteral route as soon as the small bowel shows evidence of recovered function. Parenteral nutrition can be started with a standard amino acid formula in amounts that are increased until nitrogen needs are met. If the patient develops PSE, then standard therapy with FDA-approved medications should be given. If the patient is still unable to tolerate the amount of amino acids needed to satisfy nitrogen requirements, then the standard amino acids can be replaced by a BCAA-enriched solution specifically designed for liver disease.[96,97] It is unusual to require either parenteral nutrition or BCAA formulas, and the primary goal is always aggressive enteral support (Practice Scenario 27-3).

TABLE 27-5 Nutritional Therapy in Cirrhosis

- Early assessment of nutritional status along with regular follow-up.
- Total energy can be estimated by the following formula: 1.2–1.4 × resting energy expenditure.
- Protein requirement: 1.0–1.5 g/kg/day.
- Fat requirement: 30%–40% of nonprotein calories.
- Replace vitamins and minerals as needed (eg, zinc, vitamin D, avoid excess iron and copper intake).
- Use enteral supplementation (ie, tube feeds) to complement other enteral intake (may use parenteral nutrition for shortest time possible if necessary).

Practice Scenario 27-3

Question: What are the appropriate nutritional interventions to institute in a malnourished inpatient with liver disease?

Scenario: A 60-year-old male with hepatitis C cirrhosis is admitted with portal systemic encephalopathy. In addition to his encephalopathy, a physical exam reveals ascites as well as bitemporal wasting and muscle atrophy. The patient is admitted and a nasoenteric tube is placed for enteral access and the administration of lactulose and rifaximin. An interview of the patient's wife reveals that the patient has had poor appetite for several years, but particularly in the last 3 to 4 weeks. He is currently on lactulose and rifaximin at home, but does not take any additional nutritional supplements, including no vitamin or mineral supplements.

Intervention: This patient shows characteristic signs of malnutrition (bitemporal wasting and muscle atrophy). In addition, his ascites and encephalopathy reveal that he has decompensated disease. As such, the patient is started on enteral tube feeding with additional protein modules to provide 1.2 g per kilogram of protein per day. The patient is also given nutritional supplements, including zinc.

Answer: Patients with malnutrition as a result of their liver disease require the early institution of nutritional supplementation. Patients with liver disease are likely to have protein calorie malnutrition. Adequate calories, specifically protein calories, must be given as soon as possible. In addition, patients with liver disease are known to be deficient in a variety of vitamins and minerals. Supplementation of these vitamins and minerals should also be a priority.

Rationale: It is recommended that, in patients unable to achieve the recommended 35 to 40 kcal per kilogram and 1.0 to 1.2 g per kilogram of protein on their own, supplemental enteral nutrition in the form of nasogastric or orogastric tube feeds should be considered.[95] Zinc is an essential trace element that participates in cellular function through hundreds of zinc proteins, including zinc metalloenzymes and critical zinc transcription factors. Zinc may be a helpful adjunctive therapy in hepatic encephalopathy.[121]

Complementary and Alternative Medicine Agents and Selected Micronutrients

A recent major change in therapy for liver disease has been supplementation with individual nutrients, or the use of CAM. A detailed discussion of CAM is necessary because estimates indicate that > 40% of the U.S. population uses CAM, and patients with chronic disease processes such as cirrhosis are frequent users of CAM. Moreover, CAM use is frequently not reported to physicians. A variety of forms of CAM have been used effectively to treat or prevent liver injury in animal models, and preliminary data with some agents suggest efficacy in human liver disease. It is the responsibility of healthcare workers to be aware of the potential benefits and toxicities of these agents and to demand well-designed randomized human trials on such products. The specific CAM agents that will be reviewed in relation to liver disease include vitamin E, glutathione (GSH) prodrugs and antioxidant cocktails, SAM and betaine, silymarin (milk thistle), and herbals. Selected other miscellaneous vitamin and mineral deficiencies frequently complicating chronic liver disease are also discussed.

Vitamin E

Vitamin E is a potent antioxidant that is widely used as a nutritional supplement. In patients with alcoholic liver disease and in experimental models of liver disease, depressed serum and hepatic levels of vitamin E have been documented. Vitamin E has been used extensively to protect against experimental models of liver injury, such as that induced by carbon tetrachloride via the inhibition of nuclear factor kappa B (NF-κB) activation.[98] Hill et al.[99] treated human peripheral blood monocytes and rat Kupffer cells in vitro with vitamin E, inhibiting both NF-κB activation and TNF production.[99] Vitamin E also inhibits the activation of hepatic stellate cells and collagen production in vitro.

Vitamin E was initially reported to have beneficial effects in some but not all studies of patients with fatty liver (NASH).[100–102] A pilot study in children showed improvement in liver enzymes, and a study from Japan showed that vitamin E not only improved liver enzymes but also decreased serum levels of the profibrotic cytokine, transforming growth factor beta (TGF-β).[100,101] Notably, a study in patients with alcoholic hepatitis showed improvement in hyaluronic acid, a marker of fibrosis. That same study did not demonstrate improvement in mortality, however.[103] The most important and compelling vitamin E data are from a large multicenter National Institutes of Health (NIH)-funded trial, which assigned 247 adults with NASH (without diabetes) to receive pioglitazone at a dose of 30 mg daily (80 subjects), vitamin E at a dose of 800 IU daily (84 subjects), or placebo (83 subjects) for 96 weeks.[102] Vitamin E therapy, as compared with placebo, was associated with a significantly higher rate of improvement in NASH (43% versus 19%, $p = .001$). Serum alanine and aspartate aminotransferase levels were reduced with vitamin E and with pioglitazone, as compared to placebo ($p < .001$ for both comparisons). No treatment demonstrated an improvement in fibrosis. Subjects who received pioglitazone gained more weight than did those who received vitamin E or placebo. In conclusion, vitamin E improved liver histology and liver enzymes, was not associated with the weight gain seen with pioglitazone, and at this time, 800 IU of vitamin E is the preferred "drug" therapy for NASH at some centers.

Glutathione Prodrugs and Combined Antioxidants

GSH is a tripeptide synthesized from glutamate, cysteine, and glycine. GSH, in its reduced form, is the main nonprotein thiol in cells and has an important role in the detoxification of electrophiles and in protection against reactive oxygen toxicity. This includes protection against intracellular free radicals, reactive oxygen intermediates, and several endogenous and exogenous toxins.[104] GSH also protects against toxicity from certain drugs (eg, acetaminophen). GSH cannot be taken up by hepatocytes, but a number of pharmacologic agents have been devised to enhance intracellular pools (eg, N-acetylcysteine, 2-oxothiazolidine-4-carboxylic acid). There are two distinct intercellular GSH pools: cytosolic (approximately 80%) and mitochondrial (approximately 20%). Mitochondrial GSH detoxifies hydrogen peroxide and other organic peroxides produced in mitochondria. Chronic alcohol consumption has been reported to deplete GSH levels.[104] Moreover, alcohol causes a marked depletion of GSH in the mitochondrial pool, with at least part of that depletion attributed to its impaired transport from the cytosolic pool. This depletion renders hepatocytes more vulnerable to oxidative stress. The molecular basis for the impaired GSH transport into mitochondria is unclear, but it has been reported that exogenous SAM, but not N-acetylcysteine (NAC) or other pro-GSH molecules, restores mitochondrial function, enhances mitochondrial transport, and corrects mitochondrial GSH deficiency.

GSH precursors also can regulate the production of proinflammatory cytokines, such as TNF and IL-8, by Kupffer cells and monocytes, with increased GSH levels decreasing cytokine production.[105] This occurs, at least in part, through the inhibition of the oxidative-stress–sensitive transcription factor NF-κB, which plays a central role in lipopolysaccharide-stimulated TNF production.

The glutathione precursor NAC has been used clinically for decades to treat acute acetaminophen overdose with good results if administered early (optimally within 12 hours of acetaminophen ingestion). A recent study evaluated the effects of an IV NAC on transplant-free survival in patients with nonacetaminophen-related acute liver failure.[106] The 173 patients received either NAC or a placebo. In patients with early stage nonacetaminophen-related acute liver failure, NAC improved transplant-free survival. This important study supports the use of IV NAC in patients with acute liver failure. Unfortunately, combined trials of antioxidants that not only increase GSH but

also provide other antioxidant effects have not shown efficacy in patients with chronic alcoholic liver disease. In contrast to administering exogenous antioxidants, an alternative approach uses CAM agents to stimulate the endogenous production of antioxidants. This approach (broccoli extracts) has been evaluated in preliminary hepatocellular carcinoma chemoprevention studies in Asian patients exposed to aflatoxins.[46] Thus, there is a scientific rationale for an antioxidant approach, but defining appropriate clinical populations and doses appear to be major challenges.

S-Adenosylmethionine/Betaine

Elevated methionine and decreased methionine clearance represent possible therapeutic targets for liver disease, especially ALD. In animal models of liver injury, decreased levels of SAM and elevated levels of S-adenosylhomocysteine are regularly observed. In human studies of alcoholic hepatitis and cirrhosis, abnormal hepatic gene expression occurs and contributes to decreased hepatic SAM, cysteine, and glutathione levels. Rodent and primate studies demonstrate that SAM depletion occurred in early stages of fatty liver infiltration in alcoholic liver disease, and decreased SAM concentration, liver injury, and mitochondrial damage could be reversed with SAM supplementation.[107] SAM attenuated oxidative stress and hepatic stellate cell activation in an ethanol-LPS–induced fibrotic rat model.[108] Most importantly, a randomized double-blind trial was performed in 123 patients with alcoholic cirrhosis treated with SAM (1200 mg per day, orally) or placebo for 2 years.[109] When Child class C cirrhotics were excluded from the analysis, the overall mortality/liver transplantation rate was significantly greater in the placebo group than in the SAM group (20% versus 12%), and differences between the 2-year survival curves of the two groups (defined as the time to death or liver transplantation) were also statistically significant. A subsequent Cochrane review of SAM and ALD could not find evidence supporting or refuting the use of SAM for patients with alcoholic liver diseases.[110] Further studies and long-term, high-quality randomized trials are clearly needed.

Betaine (trimethylglycine) is a key nutrient in humans and is obtained from a variety of foods and nutritional supplements. In the liver, betaine can transfer one methyl group to homocysteine to form methionine. This process removes toxic metabolites (homocysteine and S-adenosylhomocysteine), restores SAM levels, reverses steatosis, prevents apoptosis, and reduces both damaged protein accumulation and oxidative stress. Betaine also appears to attenuate alcoholic steatosis by restoring phosphatidylcholine generation via the phosphatidylethanolamine methyltransferase pathway.[111] Unfortunately, the most definitive human trial thus far (in NASH patients) showed no benefit.[112]

Zinc

Zinc is an essential trace element that participates in cellular function through hundreds of zinc proteins, including zinc metalloenzymes and critical zinc transcription factors. Zinc deficiency has also been well examined in liver disease.[113–115] Zinc deficiency can present as angular (perioral) cheilosis, muscle cramps, and neurosensory defects.[116] An altered zinc metabolism with zinc deficiency and decreased serum zinc is noted in most forms of clinical liver disease, especially ALD. Stress/inflammation caused by a variety of factors, including lipopolysaccharide/tumor necrosis factor (LPS/TNF), also causes an internal redistribution of zinc, with loss of zinc from some tissues (deficiency) and redirection to other tissues or organs such as the liver (redistribution). Importantly, zinc deficiency was recently shown to be induced by oxidative stress, in which thiol oxidation of zinc-finger transcription factors resulted in zinc loss, leading to a loss of DNA-binding activity.[117–119]

Recent studies from Kang and Zhou[114] provide major new insights into the molecular mechanisms of altered zinc metabolism in the development and progression of experimental ALD, with important potential therapeutic implications for ALD and other forms of chronic liver disease. In both acute and chronic alcohol-induced hepatotoxicity, alcohol intake and oxidative stress disrupt tight junctions in the intestine, leading to the translocation of bacterial products such as endotoxin.[113,117] Endotoxin activates Toll-like receptor 4 (TLR-4) and TNF production, with subsequent oxidative stress and liver injury. Endotoxin and TNF also play critical roles in liver fibrosis. The disruption of tight-junction proteins occurs not only in the intestine but also in the lung and likely at the blood–brain barrier, thus potentially predisposing the patient to lung injury and hepatic encephalopathy.[113] Zinc treatment in experimental animals with ALD attenuated the increased gut permeability, endotoxemia, TNF production, oxidative stress, and liver injury, while improving the activity of key zinc transcription factors.[113,114,117,118] Thus, zinc supplementation targets most postulated mechanisms for the development of ALD and certain other forms of chronic liver disease such as NAFLD.

A recent human pilot trial also suggests that zinc may stabilize or cause the regression of hepatic fibrosis.[120] Polaprezinc, a synthetic zinc-containing compound with 34 mg of elemental zinc, was administered daily for 24 weeks to patients with chronic hepatitis or cirrhosis, and zinc-supplemented patients significantly improved their serum zinc levels and markers of fibrosis. Zinc may also be effective in the treatment of hepatic encephalopathy.[121] There are no strict parameters for zinc replacement. Zinc can be replaced in patients with liver disease as 50 mg elemental zinc by mouth.[116] If higher doses are used, copper deficiency with cytopenias may ensue.

Silymarin

Silymarin, the active ingredient extracted from *Silybum marianum* (also known as milk thistle), was shown in experimental animals to protect against multiple types of liver injury, including that induced by carbon tetrachloride, acetaminophen, and iron overload, and, very importantly, mushroom poisoning.[122] Silymarin is probably the most widely used form of CAM in the treatment of liver disease. Clinically, it has been suggested to have hepatoprotective effects in various forms of toxic hepatitis, fatty liver, cirrhosis, ischemic injury, and viral-induced liver disease.[122] It has antioxidant activities, protects against lipid peroxidation, has anti-inflammatory effects, and

has antifibrotic effects. Large controlled trials performed in Europe of silymarin have had variable results.[123,124] Silymarin has become one of the most popular forms of CAM therapy for liver disease because it has a good safety profile, has been extensively investigated in multiple forms of experimental liver injury in animals, and some positive results have been reported in humans. However, the results of a Cochrane analysis questioned the beneficial effects of milk thistle for patients with alcoholic and/or hepatitis B or C virus liver diseases and highlighted the lack of high quality evidence to support this intervention.[125] A recently reported, high quality, randomized clinical trial of highly purified milk thistle found no beneficial effects on chronic HCV.[49]

Branched-Chain Amino Acids

An additional consideration in the management of individuals with cirrhosis is the addition of oral BCAAs. In addition to hepatic encephalopathy, the effects of BCAA supplementation have been studied on survival and hepatocellular carcinoma (HCC). In one study,[126] high doses of oral BCAA (12 g per day) were given to individuals with cirrhosis, but without a history of HCC. After 6 months of therapy, the patients receiving BCAAs had a lower incidence of HCC, as well as fewer medical complications related to their cirrhosis.[126] Additional support for BCAA supplementation was demonstrated in a study involving the administration of an identical dose of BCAA for 2 years. Patients given high-dose BCAAs were found to have an improved quality of life, increased event-free survivals, and improved serum albumin concentrations.[127] Benefits were also seen in patients undergoing a partial hepatectomy for HCC. In one study,[128] patients were given 14 days of IV nutritional therapy that consisted of 35% BCAAs. When compared to a control group undergoing the same procedure, the group receiving BCAAs had decreased postoperative morbidity, including less weight loss, less ascites, and fewer infectious complications.[128] Based on this evidence, BCAAs should be a consideration in the management of patients with cirrhosis.

Miscellaneous Vitamin and Mineral Deficiencies Complicating Cirrhosis

A substantial number of patients with liver disease, regardless of etiology, are known to be deficient in vitamin D.[129,130] This should prompt an assessment of vitamin D status in the form of a serum 25-OH vitamin D level. Although guidelines for the replacement of vitamin D in liver disease have not been completely delineated, replacement to achieve a 25-OH vitamin D level > 32 ng per milliliter has been suggested.[131] Importantly, vitamin D supplementation increases sustained virologic response (cure) rates in patients on HCV therapy with pegylated IFN and ribavirin.[50] Patients with cholestatic liver diseases may be at particularly high risk for vitamin D deficiency.

Thiamine deficiency may complicate chronic alcoholism and bariatric surgery.[132] This increases the risk of serious neurologic consequences, specifically Wernicke encephalopathy (WE), and should be treated aggressively. Likewise, alcoholics and bariatric surgery patients may also be at risk for refeeding syndrome.[133] Iron deficiency anemia may occur in some patients with chronic gastrointestinal blood loss due to portal hypertensive gastropathy or gastric antral vascular ectasia; iron should be replaced in these patients.[134]

Monitoring and Treating Complications

Many of the complications of liver disease can be effectively managed as long as there is an appropriate monitoring of signs and symptoms. This can begin with simple physical exam findings. Patients with decompensated liver disease often have ascites that are easily assessed by increased abdominal girth. There are simple nutritional interventions that can decrease the occurrence of ascites. Institution of a 2 g per day sodium diet is an important step in preventing the recurrence of ascites.[135] Hypervolemic hyponatremia is common in cirrhotic patients, but fluid restriction is not necessary in treating most patients because severe hypernatremia (< 125 mmol per liter) is relatively rare.[135] Practice guidelines indicate that fluid restriction for serum sodium < 125 mmol per liter is reasonable.[135] However, our practice is to institute a 1.5 to 2 L fluid restriction in patients with serum sodium concentrations < 130 mmol per liter, particularly if they are candidates for liver transplantation to avoid potential complications from intraoperative fluid shifts. Two calorie per microliter formulas may be used in cirrhotic patients with hyponatremia who are receiving enteral nutrition.

Furthermore, patients with decompensated cirrhosis present several unique challenges to the delivery of enteral nutrition. Patients in a hepatic coma will likely require nasoenteric tube placement for the delivery of medications as well as nutrition. Thrombocytopenia and coagulopathy typically accompany decompensated liver disease, and in this setting, epistaxis may complicate nasoenteric tube placement. Epistaxis in a patient with compromised airway protection due to hepatic encephalopathy can result in aspiration. Likewise, inadvertent tube displacement is not uncommon in patients with hepatic encephalopathy. Although we could find no published guidelines on these issues, our practice is to carefully place soft-tipped, fine-bore nasogastric tubes often accompanied by commercially available magnetic string-type bridles in these patients. Unless patients have a history of epistaxis and/or significant thrombocytopenia or coagulopathy, we do not routinely transfuse platelets or fresh frozen plasma prior to a nasoenteric tube placement. Anecdotally, we have administered topical vasoconstrictor sprays intranasally (such as oxymetazoline) prior to tube placement in an effort to reduce the likelihood of epistaxis. Although we could find no published data to support this practice, oxymetazoline did prevent epistaxis prior to nasotracheal intubation.[136]

A second potential problem confounding nasoenteric tube placement is esophageal varices. The risk that the placement of a soft-tipped, fine-bore nasally or orally placed feeding tube will precipitate varicocele hemorrhage (in nonbleeding varices) is low and should typically not preclude tube placement.[137] One important exception occurs during (or immediately following the treatment of) bleeding gastroesophageal varices. Bleeding esophageal varies are typically managed by an endoscopic band ligation. A tube could, theoretically, prematurely

dislodge the band from the varices and precipitate rebleeding. There is also a theoretical risk that enteral nutrition could increase intestinal blood flow and portal pressures. Although one small study found an increased risk of rebleeding when enteral nutrition was initiated within 72 hours of varicocele hemorrhage,[138] other authors advise holding enteral nutrition for the first 48 hours.[137] There is high mortality with percutaneous gastrostomy tube placement (PEG) in patients with cirrhosis, and especially those with ascites.[139] Therefore, PEG is contraindicated in patients with ascites. Patients with liver disease may also be intolerant of intragastric feeding due to nausea, vomiting, or increased gastric residuals. Although this may necessitate alteration in the delivery of nutritional supplementation, it should not lead to cessation. This issue can be addressed with use of postpyloric tube feeds.

Summary

Liver disease encompasses a heterogeneous group of disorders with diverse clinical outcomes ranging from acute hepatitis, acute liver failure, asymptomatic chronic elevation of liver enzymes, compensated cirrhosis, and end-stage liver disease. In many cases, poor nutrition has been linked to the pathogenesis and progression of liver disease. Likewise, data indicate that nutrition therapy my favorably impact the course of many liver disease cases. Therefore, nutrition support providers have a unique opportunity to positively affect the lives of these patients.

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