J Hepatobiliary Pancreat Surg (2002) 9:459–468

Journal of HBP Surgery

Hepatobiliary nutrition: history and future

Stanley J. Dudrick and Stephen M. Kavic

Department of Surgery, Bridgeport Hospital, Yale-New Haven Health, 267 Grant Street, Bridgeport, CT 06610, USA

Abstract The liver is a master metabolic gland; consequently, liver disease commonly results in significant malnutrition. Complex metabolic derangements always accompany liver failure, often reflect the magnitude of hepatic insufficiency, and are characterized by accentuated catabolism. Nutritional assessment is problematic in these patients, because many of the usual indicators of nutritional status are altered directly by the hepatic pathophysiology rather than, or in addition to, preexisting or subsequent secondary malnutrition. The objective of nutritional support in patients with liver failure is to provide adequate nutrients to ensure the availability of specific substrates for energy and protein synthesis and for normal hepatocyte survival and function, without inducing or accentuating encephalopathy or otherwise compounding hepatic insufficiency. In the near future, guidelines must be developed for the specific nutritional support of patients with fulminant hepatic failure, cholestatic liver disease, steatosis, and cirrhosis. Currently, work is underway to develop an artificial liver for patients awaiting transplantation; to use genetic engineering technology to provide an alternative source of hepatic tissue; and to test the utility of various intermediary metabolites for hepatobiliary nutrition support. No ideal regimen for nutritional support of all forms of liver failure exists, and this also represents a significant challenge for future basic and clinical investigations. However, it is mandatory to attempt to maintain optimal nutrition in patients with severe liver failure if morbidity and mortality are to be reduced and survival is to be maximized.

Key words Nutrition · Liver · Cirrhosis

Introduction

The complexity of the biochemistry and physiology of the liver and its central role in the nutrition, metabolism, and homeostasis of the body cell mass can best be appreciated by the magnitude of the clinical problems encountered in managing a patient with compromised hepatic function. Among the many activities of this master metabolic organ are synthesis of blood proteins, including albumin, prealbumin, transferrin, and prothrombin; secretion and excretion of bile, required for the digestion and absorption of lipids; conjugation, degradation, and excretion of products of metabolism and of potentially toxic substances (ammonia, bilirubin, drugs, poisons, and environmental contaminants); and modulation of the flow of nutrient substrates among the cells and tissues of the body during fed and fasting states. The paramount importance of these functions is demonstrated by the fact that hepatic failure resulting in endstage liver disease ranks among the leading causes of death on surgical services throughout the world.

Liver disease can be categorized by duration (acute, chronic), extent (mild, moderate, severe), pathophysiology (hepatocellular, cholestatic) and etiology (viral, alcohol, toxin, autoimmune).[1] Chronic hepatic insufficiency usually occurs with endstage cirrhosis in which much of the liver has been replaced by scar tissue. The reserve capacity of the liver is so great that 80%–90% of liver cells must be injured before these functions are manifestly impaired.[2]

Malnutrition is common in liver diseases, especially in patients with severe hepatocellular dysfunction, and is manifested most commonly as protein-calorie malnutrition (PCM) and wasting.[3] The prevalence of malnutrition has been reported to be between 20% and 80% in patients with alcoholic liver disease admitted to tertiary care hospitals and as high as 100% in hospitalized patients with acute alcoholic hepatitis.[4,5] More recently, the incidence of malnutrition in patients with cirrhosis has been reported to range from 27% to 87%.[6] Most of the current information on nutrition in liver disease is derived from studies of patients with endstage cirrhosis of various etiologies. Some data are also available in patients with acute alcoholic hepatitis, and even less is

Offprint requests to: S.J. Dudrick

Received: February 19, 2002 / Accepted: March 8, 2002

known about nutrition in noncirrhotic chronic liver diseases such as chronic hepatitis, chronic cholestasis, or hepatic steatosis.[2]

The development of malnutrition in liver disease is subtle and complex, and often involves multiple processes.[1] Gastrointestinal symptoms which limit food intake occur commonly and include anorexia, nausea, vomiting, and dysgeusia due to zinc and/or magnesium deficiencies.[7] Ascites is responsible for increased protein loss, and may contribute to early satiety secondary to increased intra-abdominal pressure.[8]

Dietary intake may also be severely limited by protein-deficient and salt-restricted diets. Fat malabsorption secondary to decreased production of bile acids can occur in cholestatic liver disease or when pancreatic exocrine insufficiency occurs with alcoholic cirrhosis.[1] In its fulminant form, liver failure has a grave prognosis, adversely affecting hepatocellular function and structure, primarily as a result of increased nutrient requirements in the presence of hypermetabolism; anorexia with inadequate oral intake; and impaired digestion, absorption, and assimilation of nutrients. Malabsorption is present in as many as 50% of alcoholics, in 70% of nonalcoholic cirrhotic patients, and in all patients with severe obstructive liver disease.[9] The common regimen of dietary protein restriction and use of neomycin and lactulose as therapeutic modalities causes even more deterioration of the nutritional status of these patients.

Abnormal amino-acid metabolism is a hallmark of liver disease, characterized by low plasma levels of methionine and the branched-chain amino acids (BCAA), leucine, isoleucine, and valine. Patients with liver disease also have elevated plasma levels of the circulating aromatic amino acids (AAA), phenylalanine, tyrosine, and tryptophan.[1] Protein breakdown, indicated by endogenous leucine flux and oxidation, is increased in the postabsorptive state, and the whole body protein synthesis that ordinarily occurs in response to a meal is attenuated.[10]

The metabolism of carbohydrate and fat is also altered in liver failure and can be characterized as a more rapid transition of substrate utilization from the fed to the starved pattern.[1] After fasting overnight, patients with stable cirrhosis derive approximately 75% of total calories from fat compared with only 35% for healthy control subjects.[11] The primary mechanism believed to be responsible for this altered metabolic pattern is the marked insulin resistance which occurs with cirrhosis.[12]

In liver failure, increased nutritional requirements may occur acutely due to generation of ascites, spontaneous bacterial peritonitis, or variceal hemorrhage.[13] In a study of 123 stable patients with various stages and etiologies of liver disease, resting energy expenditure expressed per unit of lean body mass was increased, normal, or decreased in 18%, 51%, and 31% of the patients, respectively, compared with noncirrhotic controls.[11] The degree of increased energy requirements correlated with diminished body cell mass, but not with the etiology or the duration of liver disease. Neither plasma bilirubin nor albumin levels were predictive of hypercatabolism in this study. Based on Harris–Benedict equation calculations, estimates of the caloric needs of patients with cirrhosis are frequently inaccurate, tending to underestimate caloric needs by 15%–18% compared with figures derived using indirect calorimetry.[14]

Nutritional assessment

Nutritional assessment is difficult in patients with liver disease because many of the usual indicators of nutritional status, including plasma albumin, prothrombin time, and body weight, are altered independently of nutritional status.[1] Although adverse outcomes are associated with the presence of one or more indices of malnutrition, it is not possible to identify patients with cirrhosis consistently who are likely to experience poor outcomes based on any single nutritional index. Presently, a multivariate approach to nutritional assessment is recommended. The subjective global assessment (SGA) of nutritional status, modified for patients with cirrhosis, is a simple, reproducible, and validated method which includes the nutritional history, physical examination, and basic anthropometrics.[15] Additionally, because of the frequency of micronutrient deficiencies in cirrhotic patients, plasma levels of zinc; vitamins A, B, and E; and prothrombin time should be measured periodically.[1] Most commonly, the liver function tests show elevations only in alanine and aspartate aminotransferases, ALT and AST, respectively, indicating nonspecific inflammation of the liver. Some patients may also have cholestasis or failure to excrete bile, resulting in increased plasma levels of direct and total bilirubin and alkaline phosphatase.[2]

The predominant feature of advanced liver disease is protein malnutrition, characterized by low plasma albumin and transferrin levels, decreased creatinine/height index, reduced triceps skinfold thickness, and decreased total lymphocyte count. The most important prognostic nutritional index is a low plasma albumin level, which results from decreased synthesis, malnutrition secondary to malabsorption and poor oral intake, and third-space losses in ascites and the extravascular compartment. Indeed, decreased plasma albumin is the preeminent biochemical factor in Child's classification of patients with cirrhosis and is a good index of hepatic reserve capacity. A measurement of other plasma

proteins produced by the liver (fibrinogen, transferrin, prealbumin, and retinol-binding protein), with their shorter half-lives, can be useful in following acute changes in hepatic synthetic function in response to therapeutic nutritional measures. However, controversy exists regarding the use of traditional nutritional assessment techniques in cirrhotic patients, because the plasma levels of visceral proteins and the usual clinical measures of immunologic indices appear to be abnormal in patients with cirrhosis, independent of the nutritional status.[16] On the one hand, functional alterations and histologic abnormalities are known consequences of protein malnutrition, and protein levels correlate best with the degree of liver damage. Moreover, protein malnutrition profoundly depletes liver protein stores and adversely affects the breakdown and conversion of polysomes to free ribosomes.[17] On the other hand, markers of lean body mass and stores, such as creatinine/height index, triceps skinfold thickness, and midarm circumference, are not true indicators of structural liver damage. More recently available nutritional assessment techniques such as bioelectrical impedance have not been shown to be reliable in cirrhotic patients with ascites or edema.[18] However, SGA has been shown to be somewhat useful in the nutritional assessment of cirrhotic patients.[15] Measurement of nitrogen balance in cirrhotic patients also has its limitations, because it is difficult to differentiate impaired hepatic protein synthesis from accelerated breakdown of circulating protein.[4] Isotopic dilution is the most accurate method to measure body cell mass, but this technique is not readily available to clinicians, except for investigational purposes. However, such methodologies have documented that body cell mass is decreased even in early stages of cirrhosis, and clinical application of this useful technology is likely to occur in the near future.[19]

Another interesting experimental technology is the hepatic mitochondrial redox potential, which represents the ratio of acetoacetate to beta-hydroxybutyrate and can be expressed as the arterial blood ketone-body ratio (KBR). Although the arterial KBR is not a specific measurement of liver insufficiency, it does allow grading of the severity of the liver damage characterized by hepatic mitochondrial accumulation of nicotinamide adenine dinucleotide, reduced (NADH), which subsequently inhibits transport through the respiratory chain and markedly depresses the enzymes of the tricarboxylic acid cycle and other metabolic pathways. When the KBR decreases to less than 0.4, the mortality rate increases dramatically, reflecting significant metabolic derangements of the entire body.[20]

Although the current indices used to evaluate nutritional status are not ideal for application to the patient with liver failure, they have value when applied judiciously by the clinician and should be used discriminately when planning and evaluating nutritional support until more specific and efficacious techniques for nutritional assessment of cirrhotic patients become available.[21]

Pathophysiology of chronic liver failure[21]

The portal vein carries nutrients absorbed by the intestinal tract and accounts for as much as 75% of the total blood supply to the liver. The hepatic artery carries peripheral toxins, is rich in oxygen, and accounts for the remaining 25% of the hepatic blood supply. The liver may be viewed either histologically, as lobules surrounding a central vein, or functionally, as acini surrounding a portal triad. The portal and arterial blood is mixed in the hepatic sinusoids and percolates outward to the central veins, whereas the excreted bile moves inward toward the biliary canaliculi.

Toxic injury, which includes that induced by alcohol, causes periportal inflammation and fibrosis that impinge on the canaliculi, resulting in biliary stasis and cholestatic jaundice. Circulatory problems, exemplified by hypotension and hypoxia, result in injury to hepatocytes near the central vein and can cause centrilobular fibrosis. Viral hepatitis and other infectious processes may cause diffuse hepatocyte injury and necrosis. Acute and chronic forms of all three of these patterns of liver disease (toxic, circulatory, and infectious) exist. Acute fulminant hepatocellular injury with liver failure is seldom reversible and has an extremely poor prognosis, with a 50%–90% mortality rate. Chronic liver disease is more common and insidious, often requiring meticulous metabolic management to prevent complications and progression of the disease to an irreversible state.

The liver is a privileged organ because of its ability to regenerate after injury. However, recurrent insults and hepatocyte death followed by regeneration and repair can induce architectural distortion with fibrosis and scar formation resulting in altered lobular perfusion. Unfortunately, attempts by many investigators to suppress or reverse the collagen deposition which leads to this pathologic scarring have not been successful to date. This represents a fertile field for future investigative efforts in the pathogenesis and treatment of cirrhotic liver disease.

As a result of fibrosis and anatomical distortion, portal hypertension develops to maintain optimal perfusion to compensate for the increased vascular resistance in the altered hepatic lobule. Once portal venous pressure exceeds systemic venous pressure, portal-systemic shunting is inevitable, and variceal changes in the esophagogastric and hemorrhoidal plexuses result as a physiological consequence of this process. Spontaneous portal-systemic shunting allows nutrient substrates,

Table 1. Metabolic effects of chronic liver disease[21]

Alteration	Mechanism
Increased plasma glucagons	Portal-systemic shunting Impaired hepatic degradation Hyperammonemia Increased plasma aromatic amino acids (AAA)
Increased plasma cortisol and epinephrine	Impaired hepatic degradation
Accelerated gluconeogenesis (hepatic, renal, and intestinal)	Hyperglucagonemia
Hyperglycemia (fasting and postprandial)	Portal-systemic shunting Increased glucose production Decreased insulin-dependent glucose uptake Decreased insulin-hepatic glycolysis
Hyperinsulinemia	Increased peripheral insulin resistance Impaired hepatic degradation Decreased effective insulin-glucagon ratio
Decreased liver and muscle carbohydrate stores	Accelerated glycogenolysis Impaired glycogenesis
Hyperammonemia	Deamination Accelerated gluconeogenesis Colonic bacterial degradation of protein
Increased plasma AAA (phenylalanine, tyrosine, and free tryptophan)	Decreased hepatic clearance Increased release into circulation Hypoalbuminemia, hyperbilirubinemia Decreased incorporation of AAA into proteins
Increased plasma branched-chain amino acids (leucine, isoleucine, and valine)	Hyperinsulinemia Increased uptake (muscle, heart, and brain) Increased utilization as energy source

toxins, and microorganisms to bypass the liver cell mass, which accounts for many of the complications of liver failure. Accordingly, amino-acid precursors flood the central and peripheral aminergic nervous system.[22] Furthermore, impaired hepatic deactivation of circulating hormones is partly responsible for the hypercatabolic state of patients with severe liver disease.

Deterioration of liver function is not manifested by clinical testing as long as 25%–30% of the hepatocytes are viable. The severity and duration of the etiologic factors determine the clinical presentation of the acute or chronic form of liver failure, although acute exacerbations can be superimposed on chronic liver disease. Viral hepatitis B and C or severe chemical insults are typical causes of acute fulminant liver failure, characterized by diffuse massive hepatocellular necrosis, diffuse hyperaminoacidemia (with the exception of low serum levels of BCAA), and hepatic encephalopathy. Conversely, chronic liver failure that evolves as a result of repeated insults and injury is characterized by inexorably progressive cirrhosis, manifested by debilitating hepatic insufficiency.

Fulminant hepatic failure is associated with up to a fourfold increase in the rate of protein catabolism, concomitant with a decrease in capacity for ammonia removal.[23] Additionally, glucose metabolism is greatly disrupted, characterized by diminished insulin sensitivity, high blood levels of insulin and glucagon, and a strong tendency to develop hypoglycemia.[24] To date, a uniformly effective method of preventing hypoglycemia and glucopenic brain injury has not been established.[1]

Complex metabolic derangements accompany liver failure and reflect the magnitude of the problems associated with insufficiency or total failure of the liver (Table 1). Accentuated catabolism characterizes the metabolism of chronic liver failure. The key abnormality of carbohydrate metabolism in chronic liver failure is glucose intolerance. Reduced insulin activity, on the other hand, may be a consequence of depletion of insulin receptors on target cells. As a result of decreased insulin activity, increased amounts of free fatty acids are released into the circulation. Impaired degradation, portal-systemic shunting, and increased plasma concentrations of ammonia and AAA are responsible for elevated plasma levels of glucagon (Table 1). The effective insulin-to-glucagon ratio, together with lipoprotein lipase activity, is also decreased in chronic liver failure. The hepatic clearance of exogenous triglycerides is reduced, and the patient may be intolerant of large amounts of fat. Impaired glucose and fat utilization is

responsible in large part for the increased catabolism of protein and is the limiting factor in meeting the caloric needs of patients with advanced liver disease.

A most important metabolic change in chronic liver failure is alteration of plasma amino-acid levels. Liver insufficiency and increased muscle breakdown induce increases in the levels of AAA and reductions in the plasma levels of the BCAA. This consistent abnormality in the plasma amino-acid profile in the patient with chronic liver failure strongly suggests a role of these amino acids in the pathogenesis of hepatic encephalopathy and most likely explains protein intolerance. Decreased clearance of AAA by the liver is a significant cause of elevations of their concentrations in the plasma and brain, but decreased plasma BCAA contribute to the accumulation of AAA in the brain as well. Together with methionine, asparagine, glutamine, and histidine, AAA ordinarily undergo 80%–100% first-pass clearance by the normal liver. Portal-systemic shunting with bypass of the liver significantly affects the normal metabolism of these amino acids.

The characteristic profile of amino-acid disturbances in the blood and brain of patients with cirrhosis formed the basis for the initial formulation of nutrient regimens enriched in BCAA as potentially effective nutritional therapeutic modalities for the treatment of chronic liver failure and hepatic encephalopathy.

The progression and severity of symptoms of hepatic encephalopathy vary from insidious depression of mental processes with impaired judgment and execution of motor skills to obvious progressive cerebral dysfunction and coma, depending upon the acuity or chronicity and magnitude of the liver insult.[21] In fulminant hepatic failure, the course of encephalopathy is characterized by a short prodrome and rapid onset, often advancing to coma within hours.[25] In chronic liver disease, on the other hand, encephalopathy is characterized by intermittent acute exacerbations which may be precipitated by identifiable and reversible factors, for example, azotemia, gastrointestinal bleeding, protein intoxication, sedation, tranquilizers, hypokalemia, or alkalosis. Although ammonia is thought to be a direct cerebral toxin and one of the most important etiologic elements in hepatic encephalopathy, it is not the only factor, and at least three other compounds that accumulate during liver failure (mercaptans, phenols, and short-chain fatty acids) appear to have synergistic actions in the genesis of encephalopathy.[21] Furthermore, various endogenous metabolic derangements accompanying liver failure, including hypoxia, hypovolemia, hypotension, hypoglycemia, hypoalbuminemia, hyponatremia, hypokalemia, and hypomagnesemia all may contribute directly or indirectly to abnormal mental status.[26]

The ammonia concentration in portal venous blood is five to ten times that in mixed venous blood because the ammonia that originates from the large and small intestine is absorbed and transported through the portal venous blood to the liver, where it is metabolized to urea.[27] Compromised liver function interferes with this natural detoxification process and shifts ammonia metabolism to skeletal muscle, where it is used in the conversion of glutamate to glutamine. However, muscle wasting in cirrhotic patients further reduces the capacity of the body to detoxify systemic ammonia.[26] The brain cannot synthesize urea from ammonia because it lacks the requisite urea cycle enzymes, but it can metabolize urea by reductive ammonation of alpha-ketoglutarate to form glutamate, and by generating glutamine from glutamate in ATP-dependent amidation reactions.[28]

In patients with hepatic coma, the cerebrospinal fluid (CSF) concentration of alpha-ketoglutamate can be increased 10- to 50-fold, and is a more specific indicator of the severity of hepatic encephalopathy than are the CSF levels of ammonia and glutamine alone.[29] Although the correlation between the spinal fluid glutamine level and the severity of encephalopathy is good, it is not perfect.[30] Increased plasma concentrations of methionine and AAA (phenylalanine, tyrosine, tryptophan), concomitantly with decreased concentrations of BCAA (leucine, isoleucine, valine), are prominent features of chronic liver failure and hepatic encephalopathy. Because the increased levels of AAA compete at the blood-brain barrier for the carrier-mediated transport system used by the BCAA, the cerebral uptake of BCAA is limited by the high concentrations of AAA.[31] As indicated previously, the correction of this imbalance was the rationale behind formulating the nutritional regimen high in BCAA and low in AAA for treating patients with hepatic encephalopathy (Table 2).[21]

Table 2. Rationale for use of branched-chain amino acids (BCAA) in hepatic encephalopathy

BCAA may provide as much as 30% of energy requirements for skeletal muscle, heart, and brain when gluconeogenesis and ketogenesis are depressed.
BCAA may regulate the flux of other amino acids across the myocyte membranes.
With adequate glucose for energy, BCAA increase hepatic protein synthesis and decrease the plasma concentration of aromatic amino acids.
BCAA compete with aromatic amino acids for transport across the blood-brain barrier.

Nutritional and metabolic therapy

The objective of nutritional support in patients with liver failure is to provide adequate calories, protein, and

Table 3. Principles of treatment of hepatic encephalopathy

General
Identify, treat, or exclude concomitant medical conditions.
Monitor and adjust protein balance (nitrogen balance) meticulously.
Monitor hemodynamic status closely.
Monitor arterial blood gases regularly.
Avoid
Abrupt volume shifts through extensive paracentesis or dialysis
Vigorous diuretic administration
Acetazolamide
Antidepressants and hypnotics, except for severe mania
Lumbar puncture
Strong cathartics
Overhydration
Correct hyponatremia cautiously and slowly.
Supplement vitamins.
Specific
Stop protein administration in acutely deteriorating condition.
Infuse branched-chain amino acids (BCAA) up to 125 g/day.
Hypertonic dextrose and lipids for balance of required energy.
Lactulose (70–100 g/day, PO or per rectum).
Neomycin (2 g/day, PO or per rectum).
Insulin intravenously as required.
Correct electrolyte anomalies.

Table 4. Nutritional support for fulminant hepatic failure

Initially infuse 10% dextrose solution to prevent hypoglycemia.
Introduce standard total parenteral nutrition (TPN) with amino acids (0.6 g/kg per day).
If nitrogen balance is negative with standard amino acids, increase protein to 0.9 g/kg per day or switch to branched-chain amino acids (BCAA) (0.6–0.8 g/kg per day) and increase as tolerated.
Restrict water and sodium as required to avoid or relieve intracranial hypertension.
Resume normal protein intake when encephalopathy improves.

other nutrients to ensure the availability of synthetic and energy substrates to the hepatocytes without inducing or accentuating hepatic encephalopathy (Table 3).[21] Nutritional support for hepatic failure is a great challenge and continues to be controversial, but it is important to maintain optimal hepatocyte fucntion, recovery, and regeneration. Although considerable overlap exists in the nutritional support in patients with hepatic insufficiency secondary to various liver disorders, nutritional support can be divided arbitrarily into three fundamental nutritional management regimens for the support of fulminant, acute, or chronic hepatic failure.

Fulminant hepatic failure results from an acute, severe liver insult to the vast majority of hepatocytes and is a rare, but life-threatening, condition whose etiology includes severe viral hepatitis, medications, toxins, and idiopathic causes. Although the patients are hypercatabolic secondary, in part, to increased catecholamines and cortisol, the severe restriction of hepatic function greatly limits protein tolerance. Despite elevated protein and calorie requirements, nutritional support must be initiated cautiously and advanced slowly. Moreover, the presence of cerebral edema mandates fluid restriction and limits the ability to administer nutrients. To modulate the rampant catabolism and to prevent hypoglycemia, hypertonic dextrose should be provided initially by intravenous infusion. If the gastrointestinal tract is functioning, the patient can be fed by nasogastric or nasoenteric tubes. If this is not possible or advisable, then total parenteral nutrition (TPN) is indicated to provide sufficient calories primarily in the form of carbohydrates, while limiting lipid and protein administration in the presence of encephalopathy.

Caloric requirements, estimated at 30–35 kcal/kg per day, should be provided primarily by carbohydrates initially. Lipids can be added cautiously to augment the caloric ration, and protein support should be instituted with amino acids at 0.6 g/kg per day. In the presence of severe encephalopathy, or if standard amino-acid solutions aggravate existing encephalopathy, BCAA should be used either as the primary amino-acid source or to supplement standard amino-acid formulations. If the liver failure improves, the nutrient regimen may be normalized to standard parenteral or enteral nutrition as tolerated. In the most severe forms of fulminant liver failure, the patient may require liver transplantation followed by postoperative standard TPN, or may succumb to the massive insult (Table 4).[2]

Acute liver failure can be caused by alcohol toxicity; steatosis (fatty liver); acute hepatitis caused by viruses such as Epstein-Barr and Hepatitis A, B, or C; medications; poisons; Wilson's disease; shock or sepsis; or exacerbation of cirrhosis. In acute alcoholic hepatitis, cytokine-mediated metabolic abnormalities occur that are similar to those of cirrhosis or other catabolic states.[32] Oral intake of nutrients is limited by severe anorexia, nausea, vomiting, and, in some patients, acute pancreatitis. Because all of these patients are catabolic and most are anorectic, a high-calorie (30–35 kcal/kg per day) and normal protein (1–1.2 g/kg per day) diet should be administered enterally if possible. If the patient manifests encephalopathy initially or develops encephalopathy on the nutrition regimen, it may be necessary to restrict protein or to initiate TPN enriched with BCAA. Wernicke's encephalopathy (thiamine deficiency) must be differentiated from hepatic encephalopathy and treated accordingly (Table 5).[2] If the patient fails to improve with adequate nutritional support, the prognosis for survival has been shown to be grave.[33] No disease-

Table 5. Nutritional support for acute alcoholic hepatic failure

High-calorie oral diet or enteral formula (30–35 kcal/kg per day)
Without encephalopathy, standard protein (1.0–1.2 g/kg per day)
With encephalopathy, protein restriction (0–0.6 g/kg per day)
With ascites and/or edema, restrict sodium
Parenteral thiamine, vitamin K, and folic acid supplementation

Table 6. Causes of malnutrition in liver failure with cirrhosis

1. Decreased oral intake
Anorexia, nausea, vomiting, early satiety, taste abnormalities, alcohol abuse, medications, iatrogenic due to partially or totally restrictive oral intake
2. Maldigestion and malabsorption
Fat malabsorption due to cholestasis and/or chronic pancreatitis
Water-soluble vitamin malabsorption due to excessive alcohol intake
Calcium and lipid-soluble vitamin malabsorption due to cholestasis
3. Metabolic abnormalities
Glucose intolerance and increased protein and lipid catabolism, as in sepsis, trauma, and other catabolic states

specific recommendations are uniformly accepted for the nutritional management of acute nonalcoholic hepatitis secondary to the etiologies indicated previously. Supplemental fat-soluble vitamins (A, D, E, K) are strongly recommended with prolonged or profound cholestasis.

Chronic liver failure, manifested by cirrhosis, represents the endstage of most chronic liver diseases which may be caused by alcohol, viral hepatitis, medications, poisons, morbid obesity, heavy metals, hemochromatosis, or autoimmune liver injury. The malnutrition in cirrhosis has many etiologies, which can be classified into three groups: those that limit oral intake, those that decrease the digestion and absorption of nutrients, and those that interfere with the metabolism of nutrients (Table 6).[2] Poor nutritional status is associated with a poor survival prognosis regardless of the etiology of the cirrhosis.

Cirrhosis without accompanying ascites or encephalopathy is defined as compensated cirrhosis. Such patients usually have a plasma albumin concentration above 3.5 g/dl and a total bilirubin level less than 1.5 mg/dl, and protein restriction is not indicated. A nutritional regimen providing 30–35 kcal/kg per day and a protein ration of 1.2 g/kg per day can usually be tolerated (Table 7).[2] Oral supplementation with liquid diets is often unsuccessful in these patients because of anorexia and other gastrointestinal symptoms, and longterm enteral nutrition is contraindicated in cirrhotic patients with ascites.[2] Indeed, the cooperative multicenter Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) trial produced data supporting the conclusion that enteral tube feeding was associated with decreased survival in patients with cirrhosis.[34]

Table 7. Nutritional support for liver failure with cirrhosis

Cirrhosis without encephalopathy
No protein restriction (1.0–1.2 g/kg per day)
High complex carbohydrate, high-calorie diet (30–35 kcal/kg per day)
Frequent small meals and bedtime snack
Water restriction only with hyponatremia
Sodium restriction only with ascites or edema
Supplemental multivitamins, calcium, zinc, and magnesium
Cirrhosis with acute encephalopathy
Temporary protein restriction (0.6–0.8 g/kg per day) until encephalopathy is ameliorated or resolved
Substitute or supplement with BCAA for refractory encephalopathy or negative nitrogen balance
Normal protein intake (1.0–1.2 g/kg per day) as encephalopathy resolves
High-calorie diet (30–35 kcal/kg per day) enterally or with TPN
Water restriction with hyponatremia
Sodium restriction with ascites or edema
Cirrhosis with chronic encephalopathy
Restrict standard protein (0.6–0.8 g/kg per day)
Initiate vegetarian diet or high-fiber diet with low animal protein
Frequent carbohydrate-rich meals and a bedtime snack
Sodium restriction with severe ascites or edema
Water restriction only with severe hyponatremia
Supplemental vitamins and minerals as needed

Cirrhosis with accompanying ascites or encephalopathy is defined as decompensated cirrhosis, and is characterized by a plasma albumin level less than 3 g/dl and total bilirubin level greater than 2.5 mg/dl. The protein requirement in cirrhotic patients is recognized to be 1–1.2 g/kg per day. Most patients tolerate this amount of protein well, and only cirrhotic patients with chronic intractable encephalopathy require protein restriction to 0.6–0.8 g/kg per day (Table 7).[2] Indeed, during acute episodes of severe encephalopathy, protein should be restricted, but restored to normal intake soon after the encephalopathy has been successfully treated. In noncritically ill cirrhotic patients with chronic or recurrent encephalopathy, dietary manipulation or supplementation with high-fiber or vegetarian diets may be useful[2,35] (Table 7).

The nutritional therapy of patients with endstage liver failure requiring liver transplantation is beyond the

scope of this review. Few nutritional studies exist in this field, and the majority of these focus on nutrition in the postoperative period. Many potential post-transplant complications are related to nutritional status and support, and include rejection, preservation injury, delayed graft function, infection, surgical complications, hyperglycemia, hypertension, and electrolyte imbalances.[36] Many transplantation centers do not have a formal preoperative nutrition regimen despite the known importance of adequate nutrition in this population.[37]

Another group of patients with hepatobiliary disorders in whom perioperative nutritional support should be used are those undergoing liver resection for hepatocellular carcinoma associated with cirrhosis.[1] A large, randomized, controlled study has demonstrated significantly decreased morbidity in those patients receiving 14 days of perioperative intravenous nutritional support compared with the control group (34% versus 55%).[38] Additionally, the requirement for diuretic agents to control ascites was reduced, and patients had less weight loss and less deterioration of liver function when perioperative nutritional support was provided.

Future horizons in hepatobiliary nutrition

Future efforts in the vital area of the nutritional support of patients with liver failure must emphasize morbidity, mortality, quality of life, length of hospital stay, and resource utilization as additional outcomes in evaluating therapeutic efficacy.[2] Further guidelines must be developed, as no uniform standards are available currently for the specific nutritional support of patients with cholestatic liver disease secondary to primary biliary cirrhosis or primary sclerosing cholangitis. Present nutritional recommendations consist only of supplementation of calcium, the lipid-soluble vitamins (A, D, E, and K), and, in patients with weight loss, the addition of medium-chain triglycerides to enhance absorption of fat moieties.

Another area that bears further study is the hepatic steatosis and cholestasis which have been associated with the use of TPN. It is intriguing that some patients receiving long-term TPN for decades have never developed cholestasis or steatosis, whereas other patients manifest these complications within days of the initiation of nutritional support with TPN. The precise explanation for this phenomenon remains obscure and perplexing. It has been suggested that steatosis is related to essential fatty acid deficiency, carnitine deficiency, and increased hepatic lipid synthesis due to continuous glucose infusion and/or excessive calorie rations that stimulate hyperinsulinemia.[39] Multiple other factors which may be implicated include preexisting hepatic injury, nutrient deficiencies, and the potential hepatotoxicity of nutrient formulations. Providing an optimal calorie-to-nitrogen ratio of TPN (100:1) and supplementing the regimen with lipids has been shown to decrease the incidence of hepatic steatosis.[2] Intrahepatic cholestasis is not often a significant clinical problem in adult patients, and can be treated by various measures, including administration of cholecystokinin[39] or ursodeoxycholic acid,[40] cycling TPN, restricting carbohydrate, avoiding overfeeding, and transitioning from TPN to enteral nutrition as soon as possible to stimulate hepatic bile flow and gallbladder contraction. Additional investigation is indicated in this important area to determine indigenous specific factors to account for the differences in the incidence and extent of the expression of cholestasis in individual patients receiving current TPN formulations.

From a clinical standpoint, great interest exists in some of the general biochemical activities of the liver, including protein synthesis, especially of albumin, globulins, and other specialized proteins; enzyme synthesis and function in the various metabolic pathways; energy metabolism; cholesterol synthesis, breakdown, and excretion; bile composition, secretion, and stasis; and gallstone formation. Current work is underway to develop an artificial liver for the temporary support of patients awaiting liver transplantation or until the liver can be returned to normal or adequate levels of function. Maintaining effective donor liver perfusion for long-term preservation prior to transplantation is another major challenge having a nutritional component. Genetic engineering and cloning may provide an alternative source of hepatic tissue suitable for transplantation in patients with irreversible liver failure. Moreover, nutritional strategies for optimal growth and maturation of engineered tissue must be developed, such as in the in vitro and in vivo support of cultured hepatocytes for the expanding field of cellular transplantation.

It is anticipated that specially formulated nutrient mixtures, consisting of intermediary metabolites, will eventually be developed in order to achieve better therapeutic results and outcome than are now possible with the currently available substrates. Intermediary metabolites, theoretically, would be more readily and more effectively utilized by the hepatic cell mass specifically in various forms of liver failure than are the current formulations of amino acid, fatty acid, glucose, and other micronutritent substrates. Finally, it might some day be possible to prevent, modulate, or reverse the collagen deposition, contraction, and scar formation which so adversely alter the anatomy, physiology, and cellular function of the liver, resulting in cirrhosis and hepatic failure. It is exciting to speculate that the judicious manipulation of nutrients might obviate, attenuate, or otherwise influence the biochemical and physicochemical processes of collagen synthesis and

maturation in a manner which would ameliorate their role in the pathogenesis of cirrhotic liver failure.

In conclusion, it is apparent that no ideal regimen for the nutritional support of all forms of liver failure exists currently, and this represents a significant challenge for future basic and clinical investigations. However, it is mandatory to attempt to maintain optimal nutrition, and to correct obvious metabolic alterations in patients with severe liver failure. This goal must remain a high priority as an adjunct to other supportive measures pending the development of more specific therapies for liver failure and its associated nutritionally related lethal sequelae.[21]

References

1. American Society for Parenteral and Enteral Nutrition (2002) Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. J Parenter Enteral Nutr 26:65SA–68SA
2. Teran JC, McCullough AJ (2001) Nutrition in liver diseases. In: Gottschlich MM (ed) The science and practice of nutrition support. A case-based core curriculum. Kendall/Hunt, Dubuque, IA, pp 539–552
3. Bashir S, Lipman TO (2001) Nutrition in gastroenterology and hepatology. Prim Care 28:629–645
4. McCullough AJ, Mullen KD, Smanik EJ, Tabbaa M, Szauter K (1989) Nutritional therapy and liver disease. Gastroenterol Clin N Am 18:619–643
5. Morgan MY (1982) Alcohol and nutrition. Br Med Bull 38:21–29
6. McCullough AJ, Bugianesi E (1997) Protein-calorie malnutrition and the etiology of cirrhosis. Am J Gastroenterol 92:734–738
7. Gloria L, Cravo M, Camilo ME, Resende M, Cardoso JN, Oliveira AG, Leitao CN, Mira FC (1997) Nutritional deficiencies in chronic alcoholics: relation to dietary intake and alcohol consumption. Am J Gastroenterol 92:485–489
8. Cabre E, Gassull MA (1998) Nutrition in chronic liver disease and liver transplantation. Curr Opin Clin Nutr Metabol Care 1:423–430
9. Reilly JJ Jr, Gerhardt AL (1985) Modern surgical nutrition. Curr Probl Surg 22:49–52
10. McCullough AJ, Mullen KD, Tavill AS, Kalhan SC (1992) In vivo differences between the turnover rates of leucine and leucine's ketoacid in stable cirrhosis. Gastroenterology 103:571–578
11. Muller MJ, Lautz HU, Plogman B, Burger M, Korber J, Schmidt FW (1992) Energy expenditure and substrate oxidation in patients with cirrhosis: the impact of cause, clinical staging and nutritional state. Hepatology 15:782–794
12. Petrides AS, Groop LC, Riely CA, DeFronzo RA (1991) Effect of physiologic hyperinsulinemia on glucose and lipid metabolism in cirrhosis. J Clin Invest 88:561–570
13. Charlton MR (1998) Energy and protein metabolism in alcoholic liver disease. Clin Liver Dis 2:781–798
14. Shanbhogue RLK, Bistrian BR, Jenkins RL, Jones C, Benotti P, Blackburn GL (1987) Resting energy expenditure in patients with end-stage liver disease and in normal population. J Parenter Enteral Nutr 11:305–308
15. Hasse J, Strong S, Gorman MA, Liera G (1993) Subjective global assessment: alternative nutrition assessment technique for liver transplant candidates. Nutrition 9:339–343
16. Shenkin A (1979) Assessment of nutritional status: the biochemical approach and its problems in liver disease. J Hum Nutr 33:341–349
17. Sidransky H (1972) Regulatory effect of amino acids on polyribosomes and protein synthesis of liver. In: Popper H, Schaffner F (eds) Progress in liver disease. Grune and Stratton, New York, Volume 4, p 31
18. Zillikens MC, vandenBerg JW, Wilson JHP, Rietveld T, Swart GR (1992) The validity of bioelectrical impedance analysis in estimating total body water in patients with cirrhosis. J Hepatol 16:59–65
19. McCullough AJ, Mullen KD, Kalhan SC (1991) Measurement of total body and extracellular water in cirrhotic patients with and without ascites. Hepatology 14:1102–1111
20. Shimahara Y, Kiuchi T, Yamamoto Y (1990) Hepatic mitochondrial redox potential and nutritional support in liver insufficiency. In: Tanaka T, Okada A (eds) Nutritional support in organ failure. Elsevier Science (Biomedical Division), Amsterdam, pp 295–308
21. Latifi R, Killam RW, Dudrick SJ (1991) Nutritional support in liver failure. Surg Clin N Am 71:567–578
22. Fischer JE, Baldessarini RJ (1971) False neurotransmitters and hepatic failure. Lancet. II:75–79
23. O'Keefe SJD, Abraham RR, Davis M, Williams R (1981) Protein turnover in acute and chronic liver disease. Acta Chir Scand 507 (Suppl):91–101
24. Vilstrup H, Iversen J, Tygstrup N (1986) Glucoregulation in acute liver failure. Eur J Clin Invest 16:193–197
25. Hiyama DT, Fischer JE (1988) Nutritional support in hepatic failure. Nutr Clin Pract 3:96–105
26. Munro HN (1982) Interaction of liver and muscle in the regulation of metabolism in response to nutritional and other factors. In: Arias I, Popper H, Schacter D (eds) The liver: biology and pathobiology. Raven, New York
27. Lockwood AH, McDonald JM, Reiman RE, Gelbard AS, Laughlin JS, Duffy TE, Plum F (1979) The dynamics of ammonia metabolism in man. J Clin Invest 63:449–460
28. Weil-Malherbe H (1962) Ammonia metabolism in the brain. In: Elliott KAC, Page IH, Quastel JH (eds) Neurochemistry, 2nd edn. Charles C Thomas, Springfield, MA, p 321
29. Duffy ET, Plum F (1982) Hepatic encephalopathy. In: Arias I, Popper H, Schacter D (eds) The liver: biology and pathobiology. Raven, New York
30. Nespoli A, Bevilacqua G, Staudacker C, Rossi N, Salerno F, Castelli MR (1981) Pathogenesis of hepatic encephalopathy and hyperdynamic syndrome in cirrhosis; role of false neurotransmitters. Arch Surg 116:1129–1138
31. Oldendorf WH (1971) Brain uptake of radiolabeled amino acids, amines, and hexoses after arterial injection. Am J Physiol 221:1629–1639
32. McClain CJ, Cohen DA (1989) Increased tumor necrosis factor production by monocytes in alcoholic hepatitis. Hepatology 9:349–351
33. Mendenhall CL, Tosch T, Weesner RE, Garcia-Pont P, Golberg SJ, Kiernan T, Seef f LB, Sorrell M, Tamburro C, Zetterman R (1986) Veterans Administration cooperative study on alcoholic hepatitis II. Prognostic significance of protein calorie malnutrition. Am J Clin Nutr 43:213–218
34. Borum ML, Lynn J, Zhong Z, Roth K, Connors AF Jr, Desbiens NA, Phillips RS, Dawson RV (2000) The effect of nutritional supplementation on survival in seriously ill hospitalized adults: an evaluation of the SUPPORT data. J Am Geriatr Soc 48:S33–S38
35. Weber FL, Minco D, Fresard KM, Banwell JG (1985) Effect of vegetable diets on nitrogen metabolism in cirrhotic subjects. Gastroenterology 89:538–544
36. Hasse JM, Weseman RA (2001) Solid organ transplantation. In: Gottschlich MM (ed) The science and practice of nutrition support. A case-based core curriculum. Kendall/Hunt, Dubuque, IA, pp 601–618
37. Weimann A, Kuse ER, Bechstein WO, Neuberger JM, Plauth M, Pichlmayr R (1998) Perioperative parenteral and enteral nutrition

for patients undergoing orthotopic liver transplantation. Results of a questionnaire from 16 European transplant units. Transpl Int 11 (Suppl 1): S289–S201
38. Fan ST, Lo CM, Lai EC, Chu KM, Liu CL, Wong J (1994) Perioperative nutrition support in patients undergoing hepatectomy for hepatocellular carcinoma. N Engl J Med 331:1547–1552
39. Quigley EMM, Marsh MN, Shaffer JL, Markin RS (1993) Hepatobiliary complications of total parenteral nutrition. Gastroentrology 104:286–301
40. Beau P, Labat-Labourdette J, Ingrand P, Beauchant M (1994) Is ursodeoxycholic acid an effective therapy for total parenteral nutrition-related liver disease? J Hepatol 20:240–244