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Role of Nutrition in Pediatric Chronic Liver Disease

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The liver plays a central role in energy and nutrient metabolism. Malnutrition is highly prevalent among patients with chronic liver disease and leads to increased morbidity and mortality rates. This review addresses the causes of malnutrition, methods used to assess nutrition status, and appropriate treatment strategies in pediatric patients with chronic liver disease. *(Nutr Clin Pract*. 2011;26:401-408)

Keywords: liver diseases; end-stage liver disease; nutrition assessment; child; vitamins

Malnutrition is increasingly recognized as a complication of chronic liver disease (CLD). In children, CLD is most commonly associated with cholestatic conditions, including biliary atresia, α-1-antitrypsin deficiency, and Alagille syndrome. Malnourished patients with cirrhosis have an increased rate of complications, including delayed neurocognitive development,[1] and an overall increase in mortality.[2,3] In this article, we review the pathophysiology of malnutrition in pediatric CLD, means of assessing nutrition status, and the role of nutrition therapy in the various stages of CLD.

Pathophysiology of Malnutrition in Children With Liver Disease

Malnutrition in children with CLD is complex and involves several mechanisms, including decreased dietary intake, increased intestinal losses, malabsorption, increased energy expenditure, and disordered metabolism of various substrates.

Decreased Dietary Intake

Inadequate food intake is one of the primary causes of malnutrition and appears to be multifactorial in nature.[4] Anorexia, altered taste perception, early satiety, nausea, and vomiting are all common complaints in children with CLD and contribute to insufficient protein and calorie intake. Anorexia results, in part, from increased circulating levels of tumor necrosis factor and leptin.[5] Altered amino acid metabolism causing elevated plasma tryptophan levels and increased brain serotonergic activity also has been documented to contribute to anorexia.[6] A distortion or decrease in taste sensation associated with various mineral deficiencies is likely to contribute to poor oral intake and, subsequently, malnutrition.[7] Meanwhile, nausea and early satiety in CLD are thought to be related to a variety of causes, including gastroparesis, ascites, small bowel dysmotility, bacterial overgrowth, and adverse effects of medical therapies.[8,9]

Impaired Absorption and Digestion

Malabsorption is an important factor in the development of malnutrition. Although a number of mechanisms contribute to malabsorption, a primary problem in patients with advanced liver disease is a reduction in the bile salt pool, thus leading to decreased bile excretion and consequently fat malabsorption.[10,11] This is most significant for infants with CLD because infants derive a larger proportion of their total energy intake from fat than do adults. In addition, bile salt deconjugation from bacterial overgrowth, which frequently occurs in patients with blind small bowel loops (eg, Roux-en-Y loop in infants who have biliary atresia), can result in additional fat malabsorption by reducing the amount of conjugated bile acids available to facilitate the intestinal micellar uptake of fat and fat-soluble vitamins. As liver disease progresses, patients can develop portal hypertension resulting in

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enteropathy with vascular congestion, which contributes to nutrient malabsorption.[12]

Increased Energy Expenditure

Hypermetabolism is found in as many as one-third of patients with stable cirrhosis, with energy requirements documented in some studies to be as much as 140% of predicted needs.[13] Although the precise cause of hypermetabolism in CLD remains unclear, certain predisposing factors have been identified. One such factor is ascites. Ascites increases energy expenditure, however, this tends to be reversed with the removal of the ascitic fluid.[14] Another predisposing factor is infection. Unfortunately, individuals with CLD are at increased risk of infection because of decreased γ-globulin and complement factor production, which are vital in protecting the body from both viral and bacterial infections. Portal hypertension contributes to an increase in energy expenditure as evident by the fact that treatment of portal hypertension decreases hypermetabolism.[15]

Altered Metabolism

Patients with advanced liver disease have an altered pattern of metabolism such that there is a more rapid transition from the use of carbohydrates as the primary source of energy to the use of fat stores for energy.[16] As hepatic function decreases, there is a reduction in hepatic and muscle glycogen storage, which also leads to early recruitment of fat and increased reliance on amino acids as an alternative fuel.[16] The result is muscle wasting, hyperammonemia, hypoproteinemia, hypoglycemia, and reduced circulating triglycerides secondary to increased fat oxidation.

Nutrition Deficiencies in CLD

Carbohydrates

Children with CLD have disordered carbohydrate metabolism related to a decrease in hepatocyte function and loss of hepatocytes. Consequently, there is a decrease in gluconeogenesis and a reduction in capacity for glycogen storage. Accordingly, infants and small children with CLD are at increased risk for fasting hypoglycemia, whereas older children have a greater reliance on recruitment of fat and amino acids as alternative fuel sources.

Protein

In CLD, all plasma protein synthesis is decreased secondary to altered hepatocyte function and/or hepatocyte loss. This results in hypoalbuminemia as well as a decrease in synthesis of insulin-like growth factor (IGF-1). The decrease in IGF-1 causes growth hormone resistance, which is likely a contributing factor to the poor growth seen in children with CLD.[17] In addition, patients with chronic cholestasis and cirrhosis have abnormal plasma amino acid profiles with low levels of branched-chain amino acids (BCAAs) and an elevated ratio of aromatic amino acids (AAAs) to BCAAs.[18] BCAAs are predominantly metabolized in skeletal muscle, whereas AAAs are metabolized by the liver. An abnormal AAA–BCAA ratio has been implicated in the pathogenesis of hepatic encephalopathy. Finally, infants and children with biliary atresia have a persistent negative nitrogen balance resulting from a decreased capacity for glycogen storage and gluconeogenesis from carbohydrates and an increased use of amino acids for fuel.

Fat

A child with CLD will frequently have biochemical evidence of chronic cholestasis with elevations in serum levels of conjugated bilirubin, alkaline phosphatase, γ-glutamyl transferase, and bile acids. This results in poor absorption of long-chain fatty acids (LCFAs) attributable to diminished bile. As a result, digestion and absorption of long-chain triglycerides (LCTs) are impaired in comparison with medium-chain triglycerides (MCTs), which are more water-soluble and are readily absorbed by enterocytes in the absence of micelles. Because fat is a main source of calories (9 kcal/g from LCTs and 8 kcal/g from MCT oil), the addition of MCT oil–based products (ie, formula, powders, and oils) helps children achieve the necessary energy intake for continued growth and/or weight maintenance.

Children with CLD are at risk for essential fatty acid (EFA) deficiency (linoleic and linolenic acids), resulting from a combination of malabsorption and decreased intake of these EFAs. Deficiency of EFAs results in growth impairment, a dry scaly rash, thrombocytopenia, and impaired immune function.[19] Accordingly, linoleic acid levels and plasma triene–tetraene ratio should be measured in a cholestatic child with poor growth to evaluate for EFA deficiency and subsequently the need for supplementation.

Fat-Soluble Vitamins

The intestinal absorption of vitamins A, D, E, and K is strongly dependent on adequate hepatic secretion of bile acids into the intestinal lumen. Malabsorption of fat-soluble vitamins is common when intraluminal bile acid concentrations are below the critical micellar concentration of 1.5-2 mmol/L.

Vitamin A. Vitamin A refers to retinol and its derivatives. The recommended daily allowance (RDA) for vitamin A is

375 mcg retinol equivalents (REs) for 0-1 year of age and 700-1,000 mcg REs for older children and adults. Chronic vitamin A deficiency can result in night blindness and irreversible damage to the cornea in the form of xerophthalmia and/or keratomalacia. Vitamin A utilization can also be impaired in liver disease, because the liver synthesizes retinol-binding protein (RBP), which transports the vitamin to peripheral tissues. The evaluation of vitamin A status in cholestasis is complicated by poor correlation between serum and hepatic vitamin A concentrations. Because of the inaccuracies in using serum retinol, other potential indices have been proposed for the evaluation of vitamin A status during cholestasis, including the relative dose response (RDR). The RDR is based on the observation that serum retinol levels increase sharply after an oral or parenteral dose of vitamin A in patients who are vitamin A deficient.[20,21] The retinol–RBP ratio, ophthalmologic slit-lamp examination, and rapid dark-field adaptation test are helpful in evaluating vitamin A status.[22,23]

Vitamin D. The 2 major forms of vitamin D are vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Vitamin D must be activated by 2 stages of hydroxylation: first in the liver to form 25-hydroxy vitamin D (25-OH-D) and second in the kidney to form 1-25-dihydroxy vitamin D. Vitamin D_3 is synthesized in the skin from 7-dehydrocholesterol upon exposure to sunlight. The American Academy of Pediatrics recommends that all infants and children, including adolescents, have a minimum daily intake of 400 international units (IU) of vitamin D beginning soon after birth.[24] The absorption of vitamin D_2 is dependent on micellar solubilization; thus, vitamin D_2 malabsorption has been observed in cholestasis. Around 25% of children with CLD have low serum 25-OH-D levels, 17% have radiologic evidence of rickets, and 11% will experience fractures. In children with chronic cholestasis, bone mineral densitometry is often >3 standard deviations less than the mean.[25] A recent adult study showed that at least one-third of patients with CLD suffer from severe vitamin D deficiency.[26] The likely causes of vitamin D deficiency are multifactorial but include dietary insufficiency, malabsorption, and reduced exposure to UV light. In addition, medication occasionally used to treat cholestasis can actually contribute to vitamin D deficiencies. For instance, phenobarbital therapy has been shown to alter vitamin D metabolism, resulting in rickets.[27]

Measuring serum 25-OH-D blood levels is performed initially to evaluate vitamin D status in cholestatic children. However, precisely defining vitamin D deficiency or insufficiency on the basis of 25-OH-D values is a matter of debate. A recent report from the Institute of Medicine defined insufficiency as serum 25-OH-D levels <30 ng/mL and deficiency as <20 ng/mL.[28,29] Serum calcium, phosphorus, alkaline phosphatase, and parathyroid hormone levels, as well as bone radiography, should be monitored routinely in children with cholestasis secondary to CLD to identify osteopenia or rickets.

Vitamin E. Vitamin E refers to a group of 8 compounds called tocopherols and tocotrienols. The RDA in children is 4-15 mg/d of d-α-tocopherol depending on age.[30] The major function of vitamin E is its role as an antioxidant protecting the cell membrane from oxidative stress. Vitamin E deficiency during childhood leads to sequential development of neurologic symptoms, including ataxia, depressed vibratory and position sensation, peripheral neuropathy, proximal muscle weakness, ophthalmoplegia, and retinal dysfunction. Deficiency of vitamin E also has been associated with hemolytic anemia in premature infants. Plasma tocopherol or the tocopherol–cholesterol ratio should be used to screen for vitamin E deficiency and to monitor response to therapy. Absorption of oral vitamin E in cholestatic patients can be improved by using the form d-α-tocopherol polyethylene glycol 1,000 succinate (TPGS), which can form micelles without the need for bile salts.[31] Elevated serum lipid levels during cholestasis draw vitamin E out from cellular membranes and can increase the serum vitamin E concentration into the normal range.[32] Accordingly, vitamin E status in children with cholestasis should be determined by the ratio of the serum vitamin E concentration to total serum lipid concentration.[32] Vitamin E deficiency is indicated by a ratio of <0.6 mg/g in children under 1 year of age and <0.8 mg/g in older children.[16]

Vitamin K. Vitamin K_1 (phylloquinone) is the main dietary source of vitamin K in humans. Small amounts of vitamin K_2 (the menaquinones) are derived from bacterial metabolism within the gut. Menadione (vitamin K_3) is not a natural form, but is synthesized chemically and has better water solubility than the 2 natural forms.[20] Vitamin K is necessary for the posttranslational carboxylation of glutamic acid residues of the vitamin K–dependent coagulation factors (factors II, VII, IX, and X; protein C; and protein S).[33] Another protein requiring vitamin K–dependent carboxylation is osteocalcin, suggesting a possible link between vitamin K deficiency and bone disease.[34] The body has limited storage capacity for vitamin K, so it is one of the earliest fat-soluble vitamins to become deficient in individuals with CLD and cholestasis.

Clinically, vitamin K status is evaluated by measuring the prothrombin time and international normalized ratio. A decrease in prothrombin time secondary to parenteral administration of vitamin K is the most accurate means of diagnosing deficiency. Although not widely available, a

more sensitive measure of vitamin K status is the plasma level of protein-induced vitamin K absence or antagonist II (PIVKA-II). This protein is induced in the absence of vitamin K.

Water-Soluble Vitamins and Trace Elements

Deficiencies in multiple water-soluble vitamins are well described in adults and are commonly associated with alcoholic cirrhosis. Although decreased intake and malabsorption secondary to enteropathy can be risk factors for deficiencies in children with CLD, the prevalence of these vitamin deficiencies is not known.[35] Decreased levels of trace elements such as zinc, magnesium, sodium, and phosphorus are more common than deficiencies of other elements.[36] Calcium and magnesium metabolism is closely related to vitamin D status. In addition, fat malabsorption during cholestasis decreases the intestinal absorption of calcium and phosphate, resulting in the formation of insoluble soaps. This, in turn, results in mineral deficiency and can contribute to bone disease that is unresponsive to normalization of vitamin D status. Low plasma zinc levels are commonly found in infants with chronic cholestasis. In a series of 27 children awaiting liver transplantation, 42% were reported to have low plasma zinc concentrations.[37] Unfortunately, plasma zinc concentrations do not correlate well with total body zinc status. Therefore, identifying children with chronic zinc deficiency can be difficult. In contrast, copper and manganese accumulate in the liver during all forms of cholestasis because their major excretory pathway is through the biliary system.[38] Consequently, cholestatic patients receiving parenteral nutrition (PN) are at higher risk for manganese toxicity, which can cause neurological complications from deposition in the basal ganglia.[39]

Nutrition Assessment

Although a thorough nutrition assessment should be performed on every patient with CLD at the first visit and should be used to monitor effects of nutrition rehabilitation, this is not easily accomplished. Many of the markers commonly used as measures of malnutrition are not useful parameters for predicting malnutrition in this patient population. For example, weight gain can result from hepatosplenomegaly and/or ascites.[40] Thus, weight-for-age and weight-for-height measurements can indicate better nutrition status (Table 1). In addition, syndromes that influence growth independent of nutrition status (Alagille syndrome) can reduce the utility of serial height-for-age plots.[41]

Serial triceps skinfold thickness and midarm circumference measurements compared with age- and height-matched norms are useful to estimate body fat and muscle bulk, respectively. The upper limb measurements are less likely to be influenced by edema and thus can provide an accurate picture of the patient's overall nutrition status. However, this method is not without its problems. Anthropometric measurements require experienced personnel to achieve reliable and consistent results.[42] Another method of nutrition assessment is the subjective global assessment (SGA). This technique combines multiple elements of nutrition assessment to classify the severity of malnutrition, including weight loss during the previous 6 months, changes in dietary intake, gastrointestinal symptoms, functional capacity, metabolic demands, signs of muscle wasting, and the presence of presacral or pedal edema.[43] The SGA has been shown to be useful in predicting outcome following liver transplantation.[44] Measurement of serum proteins (albumin, prealbumin, RBP, and transferrin) can be helpful, however, liver synthetic failure and vitamin A deficiency can confound interpretation of these tests. Retinol-binding protein and prealbumin have half-lives of 12 hours and 2 days, respectively, and thus can be useful to follow during nutrition rehabilitation.

Nutrition Therapy

Energy

The goal of nutrition therapy should be to compensate for anorexia, increased energy requirements, malabsorption, and abnormal liver metabolism. The goal for caloric intake in the presence of steatorrhea and increased energy expenditure is approximately 130%-180% of the RDA based on dry weight.[13] To meet the increased energy needs, infant formula can be concentrated to an increased caloric density or fortified with additional supplements such as glucose polymers or fats (mainly MCTs) for cholestatic infants. With increasing anorexia secondary to progressive liver disease, supplemental nasogastric feeding can be required to meet caloric and fluid requirements. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines support the use of nasogastric feeding tubes when necessary in patients with CLD.[45] Complications from portal hypertensive gastropathy with development of gastric varices and bleeding from the stoma site make gastrostomy tubes difficult to manage. Behavioral problems and feeding difficulties can be present secondary to delayed oral–motor skills, unpalatable diets, taste changes, individual preferences, long-term tube feedings, and medications. It is essential that normal feeding development is initiated before transplant.[46]

Carbohydrates

Close monitoring of blood glucose should be instituted in all young children with CLD because they are at high risk for hypoglycemia, particularly when fasting (eg, for procedures) or during intercurrent illnesses.

Protein

Protein restriction is not necessary except perhaps in extreme cases of severe or intractable encephalopathy or emergent fulminant hepatic failure and coma. Adequate protein intake (2-3 g/kg/d) is essential given the increased protein demands for growth. In a study by Charlton et al,[47] 10 children with advanced cirrhosis and malnutrition were fed for 8 weeks with a nasogastric feeding of whey protein, fat (as 34% MCTs and 66% LCTs), and glucose polymer. The researchers showed that nutrition rehabilitation using 130% of recommended caloric intake with 4 g/kg/d protein in children with CLD awaiting liver transplant improved nutrition status without hyperammonemia.[47] A double-blind, randomized controlled trial (RCT) of cirrhotic adults showed that oral BCAA supplementation decreased mortality, progression of liver disease, hospital admissions, and improved quality of life.[48] In children with CLD, a small, crossover, RCT using BCAA-fortified formula compared with semi-elemental formulas with the same caloric density showed significant increases in total body potassium, mid–upper arm circumference, and subscapular skinfold thickness with the BCAA supplements, whereas no significant changes occurred during the standard formula period. Significantly fewer albumin infusions were required during BCAA supplementation.[49] Although critical objections regarding the effects of BCAAs can be raised, there are strong arguments for BCAA supplementation as a standard nutrition approach in treating patients with hepatic disease: the rationale of BCAA administration in chronic hepatic illness; the favorable effect of BCAAs on nutrition state, repair, and regeneration of hepatic tissue; and the safety of their administration.[50] Despite the above findings, a recent Cochrane review of the beneficial and harmful effects of BCAA for patients with hepatic encephalopathy did not find any convincing evidence that BCAA had a significant beneficial effect on patients with hepatic encephalopathy.[51] Accordingly, the use of BCAA as a supplement in pediatric patients with CLD remains experimental.

Fat

The majority of infant formulas contain insufficient quantities of MCT oil (which provides a good energy balance in cholestatic infants). About 30%-60% of total fat should be provided as MCT oil, with at least 40% from LCFAs. Formulas predominantly containing MCT oil are frequently used in cholestasis, like Pregestimil (Mead Johnson, Evansville, IN; 55% of total fat as MCT oil) and Alimentum (Abbott Laboratories, Ross Labs Division, Columbus, OH; 33% of total fat as MCT oil). In addition, MCT oil can be supplemented separately in a total daily dose of 1-2 ml/kg/d divided in 2-4 doses. Although MCT oil supplementation is important in the nutrition management of children with cholestatic CLD, MCT oil is not a viable source of EFA. Therefore, it is important to ensure intake of sufficient LCFAs to prevent EFA deficiency.

Correcting Specific Nutrient Deficiencies

Vitamin A

The recommended oral supplementation of vitamin A ranges from 5,000 to 25,000 IU of water-miscible preparations of vitamin A per day (eg, Aquasol A, Aquasol Corporation, North Tonawanda, NY).[20] Careful monitoring during vitamin A repletion and supplementation is mandatory because hypervitaminosis A can result in hepatotoxicity. Vitamin A toxicity is manifested by increased intracranial pressure and painful bone lesions.[52]

Vitamin D

Vitamin D supplementation in children with CLD and low 25-OH-D levels, osteopenia, or pathologic fractures is recommended. Ergocalciferol (vitamin D_2) can be administered daily in a dosage 3-10 times the RDA for a child of that age. Depending on vitamin D level, cholecalciferol (vitamin D_3) can be given in a dose between 50 and 100 units/kg/d. Close monitoring of vitamin D toxicity is required in either case. Cosupplementation with a micellar vitamin E formulation (TPGS) has been shown to improve vitamin D absorption in children with cholestatic liver disease.[53] If patients fail to respond, have significant bony changes, or have severe cholestasis, supplementation with 1-25-dihydroxy vitamin D at a dosage of 0.05-0.20 mcg/kg/d should be administered. Optimizing a patient's vitamin D status before liver transplant is important because early posttransplant bone loss can aggravate preexisting bone disease.

Vitamin E

Routine supplementation with vitamin E is indicated for all infants and young children with chronic cholestasis. A dose of 25-50 IU/kg/d of vitamin E (α-tocopherol, α-tocopherol acetate, α-tocopherol succinate, or α-tocopherol nicotinate) or 15-25 IU/kg/d of the liquid preparation of the water-soluble ester of vitamin E (TPGS) should be given as a single morning dose with breakfast when the bile flow is maximal. High doses of vitamin E increase the vitamin K requirement and therefore can cause coagulopathy in patients who are deficient in vitamin K.[54]

Vitamin K

Vitamin K deficiency should be routinely prevented. Oral forms of vitamin K in supplements of 2.5-5.0 mg, 2-7 times a week, should be given to all children with

Table 1. Nutrition Assessment Tools and Treatment Options in Pediatric Chronic Liver Disease

Nutrition Element	Assessment Tools	Treatment Options
Energy/calorie intake	Anthropometric measurements Triceps skinfold thickness	Caloric goal of 130%-180% of RDA based on weight for height at 50th percentile MCT oil: 1-2 mL/kg/d in 2-4 doses Add glucose polymers and supplemental nighttime nasogastric drip feedings
Essential fatty acid deficiency	Triene–tetraene ratio >0.3 Decreased linoleic acid	Oral vegetable oil or intravenous fat emulsions
Vitamin A deficiency	Retinol–RBP molar ratio <0.8 or serum retinol <20 mcg/dL Xerosis Bitot spots	Vitamin A: 5000-25,000 units/d orally of water-miscible preparation
Vitamin D deficiency	Serum vitamin D level (25-OH-D) <30 ng/mL	Ergocalciferol: 3-10 times RDA Cholecalciferol based on weight and vitamin D levels: Weight >40 kg <10 ng/mL: 5000 units/d 11-19 ng/mL: 4000 units/d 20-29 ng/mL: 3000 units/d Weight <40 kg <10 ng/mL: 100 units/kg/d 11-19 ng/mL: 75 units/kg/d 0-29 ng/mL: 50 units/kg/d
Vitamin E deficiency	Vitamin E level Vitamin E–total lipid ratio: <0.6 mg/g (age <1 y) <0.8 mg/g (age >1 y)	α-Tocopherol (acetate): 25-200 IU/kg/d TPGS: 15-25 IU/kg/d
Vitamin K deficiency	Prolonged prothrombin time Elevated PIVKA-II	Vitamin K: 2.5-5 mg, 2-7 times/wk Intravenous vitamin K might be required
Water-soluble vitamin deficiency	Serum vitamin levels	Multivitamin preparation providing at least 100% of the RDA
Trace element deficiency	Plasma zinc <60 mcg/dL	Elemental zinc: 1 mg/kg/d
Iron deficiency	Decreased iron level and increased total iron-binding capacity	Elemental iron: 5-6 mg/kg/d

IU, international units; MCT, medium-chain triglyceride; PIVKA-II, protein-induced vitamin K absence or antagonist II; RBP, retinol-binding protein; RDA, recommended daily allowance; TPGS, tocopherol polyethylene glycol 1000 succinate.

chronic cholestasis. Parenteral supplementation may be necessary because of poor absorption of oral vitamin K.

In lieu of several individual fat-soluble vitamins, a commercially available multivitamin supplement that is rich in fat-soluble vitamins (AquADEKs, Axcan Pharma, Birmingham, AL) is frequently used.

Water-Soluble Vitamins

In adults with CLD, deficiencies of vitamins B_1, B_6, and C, as well as folic acid have been described,[55] but no similar data have been identified in pediatric patients with CLD. Therefore, it is prudent to supplement the vitamins normally present in the diet with an additional 1-2 times the RDA of water-soluble vitamins. Many children would benefit from a complete pediatric multivitamin to ensure adequate intake of water-soluble vitamins. However, because many complete multivitamins contain fat-soluble vitamins, it is important to monitor for toxicity.

Trace Elements

Identifying infants and children with chronic zinc deficiency can be difficult. If infants are not growing with

adequate oral intake or if plasma zinc concentration is low (<60 mcg/dL), supplementation with 1 mg/kg/d elemental zinc as a zinc sulfate solution for 2-3 months is recommended as a therapeutic trial.[56] Iron deficiency is also common in children with biliary atresia. This deficiency is readily corrected with oral iron supplements. Vitamin E deficiency should be corrected prior to administration of iron therapy to prevent precipitation of hemolysis, because iron, by producing an oxidant load, damages red cell membrane. Supplementation with magnesium in the face of low serum magnesium levels can improve bone status in children with cholestasis.[57] Both copper and manganese are excreted primarily in bile and accumulate in the liver in children with chronic cholestasis. It is recommended that copper and manganese supplements be withheld from PN solutions administered to infants and children with cholestasis of CLD. However, a case series described 4 pediatric patients with cholestasis who developed copper deficiency while on copper-free PN. A high index of suspicion is required for diagnosis when the patient develops clinical features of copper deficiency (anemia, neutropenia, and hypopigmentation).[58]

Nutrition and Hepatic Encephalopathy

Few data are available regarding appropriate nutrition for children with hepatic encephalopathy. However, hypoglycemia is a frequent metabolic disturbance and merits particular attention and therapy, and glucose level should be closely monitored.

In 1997, ESPEN recommended increased protein intakes for patients with CLD.[59] In clinical intervention trials, protein or amino acids were given in amounts of 0.6-1.2 g/kg/d in patients with cirrhosis and severe encephalopathy. An RCT in adults that compared high protein intake (1.2 g/kg/d) with low protein intake (0.5 g/kg/d) in patients with hepatic encephalopathy showed that a low-protein diet increased protein catabolism and that restricting protein intake during encephalopathy had no beneficial effect.[60] Updated ESPEN guidelines for nutrition in liver disease, published in 2006, recommend that patients with acute liver failure receive enteral nutrition via nasoduodenal tube, but no recommendation concerning a disease-specific composition of enteral formulas was given.[45]

Summary

Malnutrition is a well-known complication of advanced liver disease and is associated with detrimental consequences if left untreated. Infants with CLD are at higher risk for severe malnutrition than are older children because infants have a lower reserve for nutrients. The first step in nutrition support for children with liver disease is increased macronutrient intake followed by generous supplementation with oral fat-soluble vitamins. Nutrition support via tube feeding can be necessary if appetite decreases; however, it is still important to continue to feed infants by mouth to retain feeding skill and to feed older children by mouth as a psychological benefit.

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