Carol Rees Parrish, R.D., M.S., Series Editor

Nutrition Concerns of the Patient with Primary Biliary Cirrhosis or Primary Sclerosing Cholangitis

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Cholestatic liver diseases are characterized by impairment of the bile flow. The main nutritional consequences of cholestasis are related to malabsorption caused by lack of sufficient bile acids in the intestinal lumen. Many digestive enzymatic reactions are affected by impaired bile flow into the small bowel. The decrease in biliary excretion of cholesterol and other lipids in cholestasis often lead to hyperlipidemia. This review provides an overview of the nutritional assessment, diagnosis and management of patients with chronic cholestatic liver disorders, in particular, primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune cholangiopathy.

INTRODUCTION

Malnutrition is often observed in patients with chronic cholestatic liver diseases, namely primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and autoimmune cholangiopathy. In one study, malnutrition was found in 40% of patients with PBC, and this problem did not appear related to poor dietary intake (1). Patients who develop severe weight loss often have steatorrhea, but others become malnourished without overt symptoms of malabsorption. Nutritional compromise in patients with chronic cholestasis may be expressed as loss of muscle mass, fatigue, metabolic bone disease, or sequelae related to deficiency of fat-soluble vitamins.

Although protein-energy malnutrition is prevalent in cirrhosis, it is less common in chronic liver disease without cirrhosis. In contrast, deficiencies of vitamins and minerals may develop in the absence of fully developed cirrhosis in patients with cholestatic liver disease, especially when significant cholestasis (serum bilirubin greater than 5 mg/dL) is present. Several mechanisms account for the nutritional complications of chronic liver diseases in general, and cholestasis in particular (Table 1). A major factor specific to PBC and PSC is the

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Table 1
Mechanisms of Malnutrition in Cholestatic Liver Disease*

- Decreased intake secondary to anorexia, nausea, vomiting, and disease associated depression
- Impaired nutrient digestion and absorption secondary to luminal bile salt deficiency and pancreatic insufficiency
- Increased energy requirements from hypermetabolism and stresses caused by infection
- Accelerated protein breakdown and inefficient protein synthesis
- Enteropathy from portal hypertension

*Modified from Munoz S. Nutritional Therapies in Liver Disease. *Sem Liver Dis,* 1991;11(4):278.

failure of bile components to reach the intestinal lumen in sufficient amounts to form micelles for fat absorption.

NUTRITIONAL ASSESSMENT

The evaluation of the nutritional status of patients with chronic cholestatic liver disease is an important part of their overall medical care. Table 2 outlines indices used to assess various nutritional components (2). Nutritional assessment begins with a detailed medical and nutritional history, time course and extent of weight loss, and a careful physical examination. Anthropometric measures such as triceps skinfold thickness to assess subcutaneous fat and mid-arm circumference to measure skeletal muscle mass may have limited usefulness since chronic liver disease is often associated with some degree of water retention. The creatinine-height index is generally a good indicator of the lean body mass in patients with hepatic failure, provided that there is no associated renal dysfunction. Immune function testing has been used as a nutritional indicator (lymphocyte count, delayed hypersensitivity skin test, serum immunoglobulins, and complement level) but it can also be depressed by non-nutritional factors, including the presence of advanced liver disease, and the abnormal immunologic reactivity of primary biliary cirrhosis (3).

Table 2
Nutritional Assessment in Chronic Liver Disease*

Nutrient	*Parameter*
Energy	Body weight, triceps skin fold thickness
Protein	Mid arm muscle circumference
Fat	Total serum cholesterol, linoleic acid level
Vitamin D	Serum 25 OH cholecalciferol
Vitamin E	Vitamin E (alpha tocopherol) to total serum lipids ratio
Vitamin K	Prothrombin time
Vitamin A	Serum retinol level, retinol-binding protein
Calcium	Serum calcium, 24 hour urinary calcium excretion
Phosphorus	Serum phosphorus
Magnesium	Serum magnesium level
Iron	Serum iron, TIBC, iron saturation, ferritin

*Modified from Bavdekar A, Pandit A. Nutrition Management in Chronic Liver Disease. *Indian J Pediatr,* 2002;69(5):427.

In patients with established cirrhosis, nutritional assessment is more difficult than in the pre-cirrhotic state. Circulating levels of serum albumin, prealbumin, retinol-binding protein as well as immunologic parameters may be abnormal in cirrhotic patients for a variety of reasons. Despite the limitations imposed by edema and ascites, estimation of fat and muscle protein compartment by anthropometry of the upper extremities is still used by clinicians to determine the prevalence of protein-calorie malnutrition (PCM) (4). More accurate methods, such as bioelectrical impedance or body cell mass determinations, remain cumbersome, are unreliable in cirrhosis, or are investigational at this point. A useful clinical assessment is the subjective global assessment (SGA), which categorizes patients as mildly, moderately, and severely malnourished depending on the answers to specific questions (Table 3) (5). SGA evaluates historical, symptomatic, and physical examination parameters. This approach defines malnourished patients as those at increased risk for medical complications that would presumably benefit from some form of nutritional therapy.

PROTEIN-CALORIE MALNUTRITION

Severe protein-calorie malnutrition is uncommon in cholestatic liver disease before the stage of established cirrhosis. It is more often seen in advanced and progressive PBC/PSC, typically in patients who have had the disease for more than one or two decades. Patients with chronic cholestasis may experience

anorexia and nausea, which limit food intake. No formal specific nutritional recommendations on protein and calorie intake have been formulated for patients with non-cirrhotic, chronic cholestatic liver disease. A diet containing 1.0–1.5 g of protein/kg/day and 25–35 kcal/kg/day, as recommended for healthy individuals, is a reasonable approach. Neither protein nor sodium restriction is necessary in the early stages of PBC and PSC (4).

On the other hand, PCM is highly prevalent in the presence of cirrhosis. The reported prevalence of PCM in patients with nonalcoholic cirrhosis ranges from 27% to 87% (6). Furthermore, most studies suggest that poor nutritional status, as assessed by anthropometric parameters, correlates with a negative prognosis. Studies on carbohydrate metabolism in cirrhosis have shown a high prevalence of glucose intolerance and insulin resistance (7). In patients with clinically stable cirrhosis, energy requirements for maintaining body composition is 25–30 kcal/kg/day from non-protein sources (3). In malnourished patients and those with decompensated liver disease, the non-protein energy intake should amount to 35–40 kcal/kg/day (3). A diet including 1.0 to 1.5 g of protein/kg/day is desirable, however, during acute episodes of severe hepatic encephalopathy (stage III or IV), we have found that temporary protein restriction may be beneficial to expedite recovery from the encephalopathy (there are no randomized studies that validate the benefit of protein restriction in this setting).

In patients with tense ascites, and/or tendency to hypoglycemia, frequent small meals including bedtime snack is recommended. Sodium and water restriction is necessary only when ascites or edema develops (8).

FAT MALABSORPTION

Patients with PBC and PSC are clearly at risk for development of fat malabsorption and consequent fat-soluble vitamin deficiency. Symptoms of this type of malabsorption include fatigue, tiredness, weakness, diarrhea, foul smelling stools, weight loss and flatulence. Subsequently, patients may develop ascites, bone pain, spontaneous fractures, easy bruisability, edema, follicular hyperkeratosis, xerophthalmia and night blindness (9). The enterohepatic circulation of bile salts is disrupted in cholestatic liver disorders leading to steatorrhea, but the presence of massive steatorrhea suggests a component of pancreatic failure. Patients with PSC or PBC occasionally have an associated chronic pancreatitis, either of autoimmune origin, or related to chronic excessive alcohol consumption. Nutrient losses associated with steatorrhea results in variable weight loss, which can be estimated in part by subscapular or triceps skinfold thickness measurement. Given the deficiency of bile salts in the intestine, dietary fat may also be poorly tolerated. Cholestyramine therapy used for cholestatic pruritus may worsen the steatorrhea. In patients with PBC receiving about 70 gm of dietary fat a day, fecal fat loss approximates 10g/24 hr (normal: less than 9 gm/72 hr) (10). Since disturbances of micelle formation can occur in the presence of minimal or no steatorrhea, patients with PBC and PSC should be screened at least once for fat-soluble vitamin deficiency.

Restricting dietary fats may be necessary in patients with severe steatorrhea, however, at the cost of decreased caloric intake, unless the patient is given specific recommendations to meet caloric requirements with alternative calorie sources. Patients may require restriction of dietary fat to about 30–40 g/day, but patients not infrequently have inadequate compliance with this level of fat restriction (10). Additional fat may be supplied in the form of medium-chain triglycerides (MCT). MCT oil supplementation may be added to the diet to increase the patient's energy intake, especially in severely malnourished and malabsorbing patients. MCT of chain lengths C5 or C10 prepared from coconut oil are easily hydrolyzed in the absence of bile salts, and mainly absorbed into the portal vein as free fatty acids. MCT rate of absorption in patients with cirrhosis and

Table 3
Subjective Global Assessment (SGA)

- History and physical findings: Weight change in last 2 weeks and 6 months, muscle wasting, subcutaneous fat, edema, cutaneous and hair changes (texture; loss)
- Estimate of oral intake in term of type and duration
- Gastrointestinal symptoms that persist for >2 weeks: anorexia, nausea, vomiting, and diarrhea
- Estimate of functional capacity: bedridden, suboptimal active, or full capacity
- Estimate of metabolic demand (stress): fever, infection, inflammation, trauma

steatorrhea is similar to that of normal subjects (11). MCT at doses of 15 mL, three or four times daily may add 350–450 kcals to the patient's diet. Some patients may complain about poor palatability, while others may develop abdominal discomfort or worsening of the diarrhea. Patients should be started generally on small amounts of MCT (1 teaspoon/meal), and gradually increase the dose. The use of MCT oil in cooking or by adding to beverages may help with patient compliance.

Since part of the problem in cholestasis is related to decreased intraluminal bile acid supply, supplementation of oral bile salts seems reasonable. Ursodeoxycholic acid (UDCA; ursodiol) is a naturally occurring dihydroxy bile acid with choleretic properties, which improves the liver biochemical profile and may slow down the progression of PBC. Patients with mild or moderate disease appear to derive greater benefit from therapy than those with advanced disease. Thus, UDCA is used even in asymptomatic patients with mild hepatic histologic abnormalities (12). Recommended doses of ursodiol in PBC are 13 to 15 mg/kg per day. Doses less than 10 mg/kg per day are probably suboptimal (13).

The association between celiac disease and primary biliary cirrhosis (PBC) has been well described (14). The prevalence of this association seems to be in the 8%–12% range (15). Screening for celiac disease in PBC patients who exhibit significant weight loss, malabsorption or unexplained iron deficiency is important; both PBC and celiac disease impact negatively upon bone mineralization and are risk factors for osteoporosis.

Pancreatic insufficiency should be suspected in patients with severe steatorrhea and modest or little cholestasis. A trial of pancreatic enzyme supplementation and histamine H_2-receptor blockers, or proton pump inhibitors, may prove beneficial.

HYPERLIPIDEMIA

Patients with chronic cholestasis are likely to have elevated serum triglycerides and total cholesterol. Blood lipid levels may be in the 300–500 mg/dL range. Hyperlipidemic patients may exhibit skin xanthomas or xanthelasmas, which are likely to occur when the total serum lipids exceed 1,000 mg/dL (11). Xanthomatous neuropathy due to the deposition of excess lipids in peripheral nerves is a more rare complication, usually presenting as pain in the fingers and hands on gripping hard objects.

Two studies have suggested the hyperlipidemia in patients with PBC may not be associated with excess mortality from cardiovascular atherosclerotic disease. Pharmacological therapy of hyperlipidemia is, therefore, suggested only in patients who have multiple risk factors for coronary artery disease, such as premature atherosclerotic cardiovascular disease in the family, severe obesity and diabetes mellitus (16).

FAT SOLUBLE VITAMINS DEFICIENCY

Vitamin D

Causes of vitamin D deficiency in chronic cholestasis include decreased dietary intake, fat malabsorption, lack of photoisomerization (insufficient sunlight exposure in certain geographic locations), and impaired hepatic hydroxylation to produce 25-OH vitamin D. Since there could be significant retention of 1, 25-dihydroxy vitamin D due to decreased biliary excretion in PBC, the clinician must interpret serum levels of vitamin D cautiously, as a normal value could still be seen in the setting of deficiency. In the deficient state, plasma calcium is usually normal, phosphorus is low, parathormone (PTH) level may be high, 25-OH vitamin D level is low, and 1,25-dihydroxy vitamin D may be normal (17). Bone changes can complicate chronic cholestasis, sometimes prior to the onset of hepatobiliary symptoms. This may be more common in patients with PBC, in whom osteoporosis could be detected even at presentation. Fat malabsorption is usually associated with decreased dietary calcium absorption and increased oxalate absorption. This is due to the increase in luminal free fatty acids and preferential binding to calcium in the digestive tract, making it unavailable for absorption. In addition, vitamin D deficiency further impairs gastrointestinal calcium absorption.

Hepatic osteodystrophy consisting of osteoporosis and osteomalacia may be associated with secondary hyperparathyroidism. Patients with osteomalacia may have bone pain, low levels of serum 25-OH vitamin D, but serum calcium may be normal or low. Osteoporosis is common and patients with advanced disease frequently experience painful pathological fractures.

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Table 4
Consequences of Fat-soluble Vitamins Deficiency in Cholestatic Liver Disease

Vitamin	*Complication*
Vitamin D	Osteomalacia, osteoporosis Rickets, Tetany in children
Vitamin E	Ataxia Progressive neuromuscular disorder
Vitamin K	Hypoprothrombinemia Possible impaired osteoblast function
Vitamin A	Impaired dark adaption Xeropthalmia

Hence, dual energy X-ray absorptiometry (DEXA scan) should be part of the screening process of patients with PBC, and is useful in assessing the extent of osteopenia or osteoporosis. Osteoporosis and osteomalacia must be differentiated as the etiology and the treatment of each differ; yet they often coexist in a given patient. Patients with chronic cholestasis should have serum 25 (OH) vitamin D and 1,25 dihydroxy vitamin D blood levels measured at periodic intervals, perhaps every two to three years, depending on the clinical severity of the PBC/PSC.

Vitamin D requirements vary according to age, gender, and physiologic state. Since many patients with cholestatic liver disease are elderly, the need for vitamin D and calcium may be increased. Adequate sunlight exposure and an increased intake of good sources of calcium and phosphorus should be encouraged. If vitamin D deficiency is found, supplementation with 400–800 IU/day of vitamin D may be helpful. Intestinal absorption of these supplements can be improved by the co-administration of oral TPGS-vitamin E as a solubilizing agent (Liquid E™, Twinlabs) (18). If vitamin D deficiency is not corrected by these measures, oral calcitriol at doses of 25 to 50 µg once or twice a week should be considered. Monitoring for vitamin D toxicity is important when using this potent synthetic vitamin D analogue. Urinary calcium:creatinine ratios, serum calcium and phosphorus levels, levels of 25-(OH) vitamin D and 1,25-(OH) vitamin D should be closely monitored. Supplementation with large doses of oral vitamin D without monitoring vitamin D levels may be hazardous (19). In general, calcium should be supplemented in patients with chronic cholestatic liver disease in conjunction with vitamin D supplement.

In patients with steatorrhea, fat in the gut may form insoluble soaps with calcium, preventing further calcium absorption (20). Medium-chain triglycerides may be of value in improving calcium absorption (21). Some studies emphasize the importance of keeping dietary triglycerides low, supplementing with medium-chain triglycerides, and giving calcium supplements between meals. Calcium usually binds oxalates in the intestine, so fatty acid malabsorption results in increased absorption of free oxalates, predisposing to kidney stones. Cholestatic patients with severe PBC and PSC may be advised on a low oxalate diet. Bisphosphonates may also be used, provided the patient is previously evaluated for portal hypertension. The presence of large varices and/or severe portal gastropathy constitutes a relative contraindication to the use of bisphosphonates.

Vitamin E

Vitamin E deficiency is common in patients with prolonged cholestasis especially in the setting of steatorrhea. Vitamin E is transported in plasma bound to lipoproteins. Normal or elevated levels of vitamin E can be found due to the hyperlipidemia associated with cholestatic liver disease. Under these circumstances, vitamin E levels must be corrected (see below) for total serum lipids to obtain a better assessment of circulating vitamin E (22). In one study, vitamin E deficiency was present in 17% patients with PBC and appeared to be caused by gastrointestinal malabsorption (23).

The significance of vitamin E deficiency in adults with chronic cholestasis is uncertain. A progressive neurologic syndrome including peripheral neuropathy has been observed in children with chronic cholestatic disorders and vitamin E deficiency (24). Vitamin E deficiency has been thought to be associated with psychomotor dysfunction in PBC (25). Other possible manifestations include ataxia, ophthalmoplegia, myopathy, and pigmented retinopathy. Adults with persistent cholestasis (longer than 1–2 years), who have a serum bilirubin level above 3.5 mg/dL, steatorrhea, or advanced stage PBC, should be screened for

Table 5
Summary Guidelines

Nutrient	*Dosing*	*Monitoring*	*Suggested Frequency*
Vitamin D (1,2)	400–800 IU/day	25 OH and 1,25 vit D levels	Every 6–12 mo if initially low
Vitamin K (3)	10 mg IM or SQ	Prothrombin time	Every 6–12 mo
Vitamin A (2)	See text	See text	See text
Vitamin E (2,4)	400–800 IU/day	Vit E/lipids ratio	Every 1–2 years
Calcium (2)	800–1,200 mg/d	DEXA scan	Every 1–2 years

1. May need replacement with calcitriol in refractory cases
2. Frequency of monitoring depends on the severity of the cholestasis
3. Only in the presence of severe coagulopathy due to vitamin K deficiency
4. Intestinal absorption of these supplements can be improved by the co-administration of oral TPGS-vitamin E as a solubilizing agent (Liquid E™, Twinlabs)

vitamin E deficiency. The ratio of serum vitamin E to total serum lipids (vitamin E/lipids) should be calculated, with vitamin E deficiency generally defined as a ratio below 0.8 mg/gm. The value of vitamin E supplementation in adults with cholestatic liver disease has not been established. Even though toxicity associated with vitamin E administration is rare, recent information suggest excess of vitamin E may have detrimental effects in terms of cardiovascular disease (26). Patients with symptomatic vitamin E deficiency may be treated with 800 units daily of alpha-tocopherol.

Vitamin K

Vitamin K is required for the hepatic synthesis of factors VII, IX, X and prothrombin. In one study, 23% of patients with PBC had decreased plasma vitamin K levels (27). As a result, a prolonged prothrombin time is commonly seen in cholestasis. However, impaired hepatic synthetic function may also compromise the synthesis of clotting factors in the absence of true vitamin K deficiency. Patients with prolonged prothrombin time may benefit from test doses of vitamin K supplementation. Daily vitamin K injections of 10 mg SQ, or IM, given initially for three days, and then followed by oral supplements, may be of some value. The initial therapy for 3 days helps to differentiate between vitamin K deficiency, and failure of the liver to synthesize coagulation factors. Abnormal prothrombin time corrects in the former setting, but not in the later. Monthly intramuscular injections of vitamin K (2–5 mg) may be needed in patients with severe, chronic cholestasis (28).

Vitamin A

Absorption of vitamin A also requires intact enterohepatic circulation of bile acids and micelle formation. Serum retinol levels in patients with cholestatic liver disease are frequently low. Impairment of hepatic synthesis of retinol-binding protein due to liver disease may result in low vitamin A serum levels in the absence of a deficient state. From a clinical standpoint, vitamin A deficiency is not common in adult patients with chronic cholestasis. Nevertheless, failure of dark adaptation (night blindness) does occasionally develop in patients with severe PBC or PSC who have never received vitamin A supplementation. Other potential manifestations include dermatologic disorders, and impaired humoral and cell-mediated immunity.

Screening for vitamin A deficiency includes determining serum retinol level, darkfield adaptation testing and slit-lamp examination of the cornea. The diet of the nonalcoholic patient with cirrhosis is generally supplemented with 5,000–15,000 IU daily of vitamin A. This may be useful in patients with prolonged cholestasis, if they have evidence of steatorrhea. However, caution must be exercised given the potential of vitamin A for hepatotoxicity. It has been suggested that concomitant use of oral vitamin A supplement at

the above doses and water soluble vitamin E-TPGS may enhance vitamin A absorption (29).

In non-liver patients with visual symptoms secondary to vitamin A deficiency, oral supplementation with 50,000 IU (15 mg) per day for one month or 25,000 to 50,000 IU three times a week for six months has been recommended (30). These can be followed by maintenance doses determined according to serum retinol levels (31). However, whether these amounts of vitamin A are necessary and safe in patients with liver disease is unknown. If vitamin A levels are found to be low in patients with PBC/PSC, cautious replacements with lower doses (5,000–10,000 units once or twice a week) and periodic determination of serum vitamin A levels, may be a prudent approach. Vitamin A hepatotoxicity is a concern in persons with underlying liver disease.

Signs of vitamin A toxicity include ataxia, alopecia, hyperlipidemia, bone and muscle pain, and visual impairment. Hepatotoxicity may hasten the progression of the underlying liver disease to cirrhosis and has also been associated with veno-occlusive disease. Several factors may increase the toxicity of vitamin A, including underlying liver and kidney disease, alcoholism, and the use of certain drugs such as tetracyclines.

SUMMARY

Patients with primary biliary cirrhosis or primary sclerosing cholangitis may experience significant nutritional complications, primarily caused by cholestasis-related impaired absorption of certain nutrients. Compromised hepatic synthetic capacity adds additional insult in the advanced stages of the disease with the onset of cirrhosis. Sodium and water retention and other factors may interfere with an accurate nutritional evaluation. Nevertheless, the nutritional complications of severe and progressive cholestasis should be addressed and treated in a systematic fashion in these patients. Prophylaxis of nutrient deficiencies can be accomplished by using suggested guidelines. ■

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