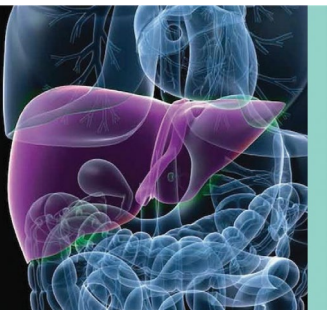

Nutritional Management of Cholestasis

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CHOLESTASIS

Cholestasis is defined as the impairment of bile production or an obstruction of bile flow. Bile is produced in the liver and stored in the gallbladder until needed for digestion of macronutrients.

When food is present in the enteric tract, bile travels from the gallbladder into the duodenum to aid in digestion of fats. In the setting of cholestasis, the flow of bile is halted between the liver and the duodenum. Clinical symptoms of cholestasis include jaundice, dark urine, and pruritis, as well as steatorrhea and fat and micronutrient malabsorption. One of the most sensitive indicators for cholestasis is an elevated total bilirubin concentration (>2 mg/dL); levels exceeding this value may require nutrition modifications.

NUTRITIONAL CONCERNS AND MANAGEMENT

Oral Intakes

Fat malabsorption. Due to insufficient bile release in patients with cholestasis, fat malabsorption is common. Fecal fat can be measured qualitatively, by either the presence or absence of fat, or quantitatively, by means of a 24- or 72-hour timed stool collection. Levels >7 g of fecal lipids per 24 hours are considered abnormal.[1] Symptoms of fat malabsorption can be the presence of greasy, frothy, foul-smelling, floating, or pale-colored stools. Temporarily following a fat-restricted diet can help manage these symptoms. Foods containing <3 g per serving are considered low fat, and fat restriction to <20 g/day is encouraged to manage symptoms of fat malabsorption.[2] Medium-chain triglycerides (MCTs) should be recommended when initiating a fat-restricted diet to prevent weight loss. MCTs, unlike long-chain fatty acids, are water soluble and shorter in carbon length (8-12 carbons). MCTs are absorbed by passive diffusion via the portal system, and therefore do not require formulation of micelles or bile salts for absorption.[1] MCTs are calorically dense and are available as commercial oils. Coconut and palm kernel oils contain a high concentration of MCTs (>50%), although these two oils still contain long-chain triglycerides, which can contribute to malabsorptive diarrhea.[3] MCT dosing guidelines are

Abbreviations: EFA, essential fatty acid; IM, intramuscularly; INR, international normalized ratio; IU, international units; IVLE, intravenous lipid emulsion; MBD, metabolic bone disease; MCT, medium-chain triglyceride; PBC, primary biliary cirrhosis; PN, parenteral nutrition.

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listed in Table 2. If a patient is required to follow a low-fat diet for greater than 1 to 3 weeks, they will require essential fatty acid (EFA) supplementation given MCTs do not provide EFAs. EFA needs can be met by providing 2% to 4% of total caloric intake from EFAs, which is equivalent to 2 to 3 tablespoons of oils containing linoleic acid (such as flaxseed, sunflower, and corn oils).[2]

Metabolic bone disease. Another nutritionally relevant complication of cholestasis is metabolic bone disease (MBD). Although the exact mechanism is unknown, it is thought that hyperbilirubinemia can lead to a reduction in osteoblast activity, as well as osteoclast dysfunction and activation, leading to reduced bone formation and increased bone resorption. Patients with chronic cholestasis should have baseline dual-energy x-ray absorptiometry scans and reassessment every 2 to 4 years. In addition, they should have close monitoring of serum calcium and vitamin D levels with supplementation as needed.[4] See Table 1 for dosing recommendations. Those at high risk for MBD should participate in adequate weight-bearing physical activity, smoking cessation, avoidance of alcohol, and a diet rich in calcium and vitamin D. Patients with chronic cholestasis are also at increased risk for kidney stones and calcium malabsorption given that increased intestinal fat binds calcium and subsequently increases oxalate absorption.[3]

Elevated serum lipids. Up to 80% of individuals with chronic cholestasis have elevated serum lipid concentrations. A study done by Longo et al.[5] demonstrated that patients with primary biliary cirrhosis (PBC)-induced hyperlipidemia do not have increased risk for mortality from cardiovascular disease. However, baseline lipid panels should be obtained, and familial or personal risk factors for cardiovascular disease should be identified. Individuals with cholestasis and elevated serum lipids may not require statin therapy. Those with hyperlipidemia in addition to familial or other risk factors may require pharmacological therapy or

TABLE 1. VITAMIN AND MINERAL DOSING GUIDELINES[7,12]

Vitamin	Serum Levels	Formulation Names	Repletion Dosage	Maintenance Dosage (Daily)†	Notes/Comments
Vitamin A*	Normal: 30-100 μg/dL	Vitamin A	100,000 IU (IM) daily × 3 days followed by	15,000 IU × 2 months	Use serum retinol for assessment of status
	Deficient: <10 μg/dL		50,000 IU (IM) daily × 2 weeks		Carried by a negative acute-phase protein, and therefore should be evaluated with other fat-soluble vitamins
					Repeat levels frequently to prevent oversupplementation
Vitamin D*	Normal: >30 ng/mL	Cholecalciferol (vitamin D3)	50,000 IU vitamin D3 (oral) weekly × 8-12 weeks	400-2000 IU vitamin D3	Use serum calcidiol (25-hydroxy-vitamin D) for assessment of status
	Deficient: ≤20 ng/mL	Ergocalciferol (vitamin D2)			Replete to achieve level >32 ng/mL
Vitamin K*	Normal: 0.15-1.0 μg/L	Vitamin K	2.5-10 mg (oral) twice weekly	5 mg	Use serum phylloquinone levels for assessment of status
	Deficient: <1.0 μg/L				Supplementation must be consistent in patients taking warfarin because this can impact INR
Vitamin E*	Normal: 0.5-2.0 mg/dL	Vitamin E (expressed in alpha-tocopherol equivalents)	200-2000 mg (oral) daily	15 mg	Use serum alpha-tocopherol for assessment of status
	Deficient: <0.5 mg/dL				Excessive supplementation (>1200 mg/day) interferes with vitamin K
Calcium	Normal: 8.6-10.2 mg/dL	Calcium carbonate	1200-2000 mg (oral)	1200-1500 mg	Supplementation should be divided into three to four 500-600 mg doses throughout the day for maximum absorption
	Deficient: <8.6 mg/dL	Calcium acetate			Iron and calcium should not be taken at the same time
		Calcium citrate			

*Water-miscible formulas are recommended for supplementation in the setting of fat malabsorption: Forvia, AquADEKs, and Celebrate Bariatric Vitamins Multi-ADEK.

†All maintenance dose recommendations are for oral supplementation.

management of risk factors through weight loss, physical activity, or diet management.

Micronutrient deficiencies. Chronic cholestasis can lead to malabsorption of vital micronutrients. Due to impaired fat digestion, deficiencies of fat-soluble vitamins (A, D, E, and K) are seen. Fat-soluble vitamin levels should be monitored yearly in patients with a bilirubin concentration persistently >2 mg/dL.[6] Patients with chronic cholestasis often present with suboptimal serum vitamin levels well before clinical signs of steatorrhea and fat malabsorption. The exact time frame for fat-soluble vitamin deficiencies to occur is unknown. In a study done in 2001 by Phillips et al.,[6] 180 individuals with PBC were examined for vitamin deficiencies. Vitamin A was the most prevalent fat-soluble vitamin deficiency (33.5%), followed by vitamin D (13.2%), vitamin K (7.8%), and vitamin E (1.9%). Notably, vitamin A is carried by retinol binding protein, which is a negative acute-phase protein, and levels can be decreased in the presence of inflammation. Due to this, all fat-soluble vitamin levels should be checked together.[4] In addition, excessive vitamin A supplementation can lead to hepatic toxicity and also the development of long-bone fractures, so levels should be tested prior to supplementation.[7] Patients with chronic cholestasis and diagnosed fat-soluble vitamin deficiencies are encouraged to supplement with water-miscible formulations of fat-soluble vitamins.[1] Supplementation guidelines are outlined in Table 2.

TABLE 2. RECOMMENDATIONS FOR NUTRITIONAL MANAGEMENT OF CHOLESTASIS[1,3,13,14]

Nutritional Complications	Recommendations
Fat malabsorption	Supplementation of vitamins A, D, E, and K* Low-fat diet with supplementation of MCT oils†
MBD	Supplementation of calcium Supplementation of vitamin D
Kidney stones	Supplementation of calcium Low-oxalate diet
Enteral nutrition dependency	Low-fat formula MCT-rich formula Vivonex, Portagen, Vital 1.5 Additional supplementation of vitamins and minerals as necessary

*Water-miscible formulas are recommended for supplementation in the setting of fat malabsorption. †The recommended daily dose is 60 to 70 g of MCT oil per day (4-5 tablespoons), based on tolerance. MCT oil should be gradually added into the diet (increased by 1 tablespoon/day) and dispersed among all meals throughout the day to minimize rise of gastrointestinal upset.

Enteral Nutrition

For patients who require enteral nutrition, modifications to formula selection may be necessary. Formulas with lower fat content should be considered. An MCT-rich formula is recommended for patients with fat malabsorption. Furthermore, patients may benefit from a peptide-based formula, because these are often higher in MCTs and are more readily absorbed.

Parenteral Nutrition

Parenteral nutrition (PN)-associated cholestasis (PNAC) occurs in more than 55% of patients who require prolonged PN.[9] Risk factors for PNAC include having less than 50 cm of remnant small bowel, as well as having frequent bacterial or fungal infections.[8,9]

Several nutrition strategies are commonly used to decrease the risk for development of PNAC (Table 3). First, high doses of commercial intravenous lipid emulsions (IVLEs) have been associated with cholestasis because of their proinflammatory components such as soybean oils and phytosterols.[10] Utilization of fish oil–based IVLE is of recent interest due to the anti-inflammatory properties and decreased phytosterol content.[11] Second, enteric stimulation through oral or enteral nutrition routes may promote the enterohepatic circulation of bile salts. Ursodeoxycholic acid can also be used as a pharmacological means for facilitating bile flow. Third, cycling PN (infusing over 12-18 hours) has been shown to prevent elevated conjugated bilirubin levels when compared with continuous PN infusions. In addition to these strategies, it

TABLE 3. RISK FACTORS AND MANAGEMENT OF PNAC[2,8,9]

Risk Factors	Recommendations
High-dose IVLEs	Provide <1 g/kg/day IVLEs Limit soybean oil–based IVLEs when able Withhold IVLEs altogether Consider use of fish oil–based IVLEs
Lack of enteral stimulation	Provide trickle enteral feeds when possible Consider allowance of oral pleasure feeds Use of ursodeoxycholic acid
Continuous parenteral infusion	Provide cyclic PN (infused over 12-18 hours)
Toxicity of hepatically stored trace elements	Copper and manganese should be held from PN solution with total bilirubin levels >5 mg/dL Add on trace elements individually (including zinc, selenium, chromium) Monitor trace elements every 90 days while patient is receiving PN

is recommended to hold specific PN components (copper and manganese) in the setting of PNAC given increased risk for toxicity when total bilirubin levels rise to more than 5 mg/dL.

SUMMARY

Patients with both acute and chronic cholestasis are at risk for several nutritionally relevant complications. These patients are at high risk for poor oral intakes, nutrient deficiencies due to malabsorption, MBD, and lipid derangements. Ongoing evaluation of a patient's nutrition status is crucial in the management of cholestasis. Patients with cholestasis should be referred to a registered dietitian to assist in nutrient optimization and to provide close monitoring of nutrition status.

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