Nutrition Support of Children with Chronic Liver Diseases :

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Introduction: Malnutrition is a known as well as a common complication of childhood chronic liver diseases (CLD) including cholestatic and end-stage liver diseases. It is associated with increased morbidity and mortality of the patients with CLD. Identification of the nutritional deficiency is of utmost importance especially in children with end-stage liver disease requiring transplantation, as optimized pre-transplant nutrition may hasten post-transplant recovery while simultaneously decreasing complications.

Aims:

1. To summarizes the available literature on various aspects of nutrition in children with chronic liver diseases (CLD).
2. To discuss the challenges and approaches in the nutritional assessment of children with CLD
3. To summarize the pathophysiology of the malnutrition in the context of CLD and to treatment recommendations and future research focus

Pathophysiology of malnutrition in children with chronic liver disease:

There are various risk factors associated with development of malnutrition in children with cholestasis and end-stage liver disease and are summarized in figure 1. Children with cholestatic liver diseases suffer from maldigestion and malabsorption of nutrients from the very early stage of disease. Later on, with the progression to end-stage liver disease, the factors such as anorexia, nausea and vomiting, abnormal nutrient metabolism, increased energy expenditure and iatrogenic factors also come to the play making the process more complex.

Nutritional Status Assessment

- History: daily oral/enteral intake, medication history, socioeconomic factors, such as access to food and vitamins or supplements.
- Physical Examination: Anthropometry (weight, height, mid upper arm circumference (MUAC), triceps skin folds (TSF). Look for features of protein, essential fatty acid, and fat-soluble vitamin deficiencies,
- Frequency of assessment depends on the severity of malnutrition, ranging from every 2 weeks in severe to every 3 months in mild degree of malnutrion

Functional assessment of nutritional status

- Handgrip strength: It can be easily measured at the bedside and has been used in adults with liver disease. Normative data for pediatric handgrip strength exist for children 4 years of age and older but its use in children with liver disease needs further studies.
- Frailty: It reflects nutritional status. It is a measure of 5 components namely slowness, weakness, shrinkage, exhaustion and diminished activity and has been found to correlate with the morbidity and wait-list mortality in adults with ESLD. A modified version of frailty for pediatric use has been developed which includes 6 minute walk for slowness, TSF for shrinkage, handgrip strength for weakness, PedsQL questionnaire for exhaustion and a physical activity questionnaire to assess diminished activity

Imaging Approaches to Determine Nutritional Status

- Dual-energy X-ray Absorptiometry, Bioelectrical impedance and Air-displacement plethysmography: These modalities provide a measure of fat and fat-free mass. However, the accuracy is decreased in fluid overload state
- Sarcopenia: It is defined as severe muscle depletion and acts as a marker of poor nutritional status. It is determined on the basis of cross-sectional imaging of psoas muscle. Sarcopenia has been shown to be associated with waitlist as well as post liver transplant mortality in adults with end-stage liver disease.

Assessment and challenges in nutritional support of children with cholestasis and end-stage liver diseases

Energy Expenditure: The energy requirements of patients with liver disease depend on their resting energy expenditure (REE), their activity level, and the severity of their maldigestion/malabsorption and disease severity. Indirect calorimetry is ideal to measure the REE but when not available, World Health Organization/United Nations University equation, can be used.

Fat: The fat requirements depend on the nutritional status as well as the presence and severity of maldigestion/malabsorption. Requirement can be assessed with serial measurement of TSF and signs of essential fatty acid deficiency (dry, rough skin, poor growth, numbness, paresthesias, and vision impairment). Total fatty acid profiles in the red blood cells can be used to test for essential fatty acid deficiency.

Protein: Requirement is increased in view of protein loss, increased amino acid oxidation, and poor nutritional status. Assessment of protein status based on markers like albumin, prealbumin, transferrin, and retinol-binding protein may be inaccurate due to their decreased synthesis or increased losses (in stool, urine or the interstitial space). Similarly, blood urea nitrogen is affected by hydration status, and the capacity of the liver to make urea. Other parameters, such as measures of sarcopenia (discussed above), may be more useful indirect indicators of chronic protein depletion.

Carbohydrates:

Usually patients receive 50% to 65% of their total calories in the form of carbohydrates. Hyperglycemia and hypertriglyceridemia may suggest insulin resistance, but former may also indicate excess carbohydrate provision. Conversely, there is risk of hypoglycemia which may go unnoticed particularly in young infants.

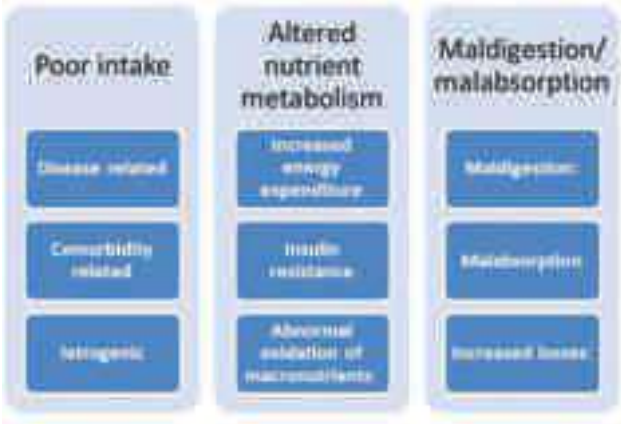

Figure 1: Pathophysiology of malnutrition in chronic liver disease

Vitamin A

Vitamin A status is usually assessed by measuring serum retinol and retinol binding protein levels but may be inaccurate with advanced liver disease. If serum retinol is <20 mg/dL, a modified relative dose response test can be used to confirm the result. Ophthalmologic assessments have poor sensitivity and specificity to detect vitamin A deficiency.

Vitamin E

Vitamin E deficiency manifests predominantly with neurologic symptoms, which may be irreversible. Screening should be done by measuring ratio of vitamin E to total lipids (triglycerides, phospholipids, and total cholesterol) in serum. The cut-off is 0.6 mg of serum vitamin E/g of total lipids in those 1 to 12 years of age and 0.8 mg/g in older children and adults.

Vitamin K:

International Normalized Ratio (INR) is used routinely in clinical practice to assess vitamin K status. However, it may be normal in cholestasis with vitamin K deficiency. Plasma PIVKA-II (protein induced in vitamin K absence) levels may assist in determining vitamin K deficiency in such patients followed by further work-up including measurement of serum parathyroid hormone, calcium, and phosphate levels.

Vitamin D

Vitamin D deficiency manifests as osteopenia and rickets. Both cholestasis and noncholestatic patients are also at risk for VDD, particularly in the context of advanced liver disease. Serum parathyroid hormone, calcium, and phosphate levels should be measured in children with suspected deficiency of vitamin D.

Zinc

Zinc deficiency manifests as skin rashes and diarrhea. In children with cirrhosis, serum zinc levels do not correlate with tissue zinc content and, as such, clinicians should have a high index of suspicion. A low alkaline phosphatase levels may be suggestive of zinc deficiency but need to be interpreted with caution in patients with cholestasis and/or bone disease, which cause elevations in this biomarker.

Recommendations of nutritional support in children with cholestasis: It should focus on providing increased total calories, lipids, and protein, while avoiding extended periods of fasting. Correction of fat-soluble vitamin deficiencies can be challenging in view of global shortage of supplements with enhanced absorption. Recommendations are summarized in table 1.

Table 1: Recommendations for nutritional support in children with cholestasis

Energy/Nutrient	Requirement	Comments
Energy	130% of requirement for age	• Account for losses associated with maldigestion/malabsorption • Monitor MUAC and TSF every 2-4 weeks • Use NG/NJ feeding if unable to meet energy goals for more than 2 weeks
Protein	~130-150% of requirements for age	•Account for losses associated with maldigestion/malabsorption
Carbohydrates	40-60% of total calories	• Hyperglycemia can occur due to insulin resistance • Hypoglycemia can also occur
Fat	• 30-50% of total calories • Start with MCT/LCT ratio of 30%/70% of total fat calories • Provide a minimum of 3% of total kcal from LA and 0.7-1% from αLA	• Increase MCT if suboptimal growth with LCT • MCT may be added in the form of both MCT oil, and MCT-containing formula. •Development of steatorrhea may suggest excessive MCT supplementation • Monitor for EFAD • Dietary sources of EFA include soy, canola, corn, walnut or fish oils, egg yolks
Vitamin A	• <10 kg – 5,000 IU/day • >10 kg – 10,000 IU/day	• Adjust based on results of monitoring labs
Vitamin D	• Cholecalciferol: 2,000-5,000 IU/day	• Larger weekly doses (e.g. 50,000 IU/once per week) are used in some centers; limited available data preclude formal recommendations re: weekly dosing • Calcitriol can be used in patients with rickets/osteoporosis in the context of cholestasis/cirrhosis; limited data in paediatrics.
Vitamin E	• TPGS: 15-25 IU/kg/day	• Adjust based on results of monitoring labs
Vitamin K	• 2-5 mg per day	• 1-10 mg IV may be required • May also be given IM
Iron	• Meet DRI for age	• Adjust based on results of laboratory investigations • Note that hepatotoxicity from iron overload can occur; clinicians should carefully consider the need for IV iron provision
Calcium	• Meet DRI for age	• Adjust based on results of laboratory investigations • Increase calcium and decrease oxalate intake in cholestatic patients with oxalate stones
Sodium	• 1-2 mEq/kg/day	• Restrict if fluid overloaded
Potassium	• 2 mEq/kg/day	• Adjust based on results of laboratory investigations

αLA= a-linolenic acid; DRI = dietary reference intake; EFA = essential fatty acids; EFAD= essential fatty acid deficiency; IM =intramuscular; IU= international units; IV= intravenous; kcal= kilocalories; LA= linoleic acid; LCT= long-chain triglycerides; MCT= medium chain triglycerides; MUAC = mid-upper arm circumference; NG = nasogastric; NJ =nasojejunal; REE = resting energy expenditure; TPGS= D-alpha-tocopheryl polyethylene glycol 1000 succinate; TSF = triceps skin folds.