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Review Article

Evaluation and Management of Nutrition in Chronic Liver Disease

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Abstract

The majority of patients with chronic liver disease (CLD) experience malnutrition. There are multiple complex mechanism by which chronic liver disease leads to malnutrition, including anorexia and malabsorption. Assessing malnutrition in CLD is also difficult at this time as there are no standardized methods for quantifying nutritional status in this group of patients. However, newer methods are being developed to help ensure better diagnosis and thus start treatment earlier. These novel methods such as hang grip strength (HGS) and bioelectrical impedance analysis (BIA) are safe and inexpensive. However, further studies are needed to fully validate their reliability and testing in special groups, such as children. The goals of treatment are to provide adequate nutrition, support growth, preserve lean body mass, and prevent micronutrient and vitamin deficiencies. In addition to improving body mass, new studies are also focused on reducing sarcopenia (clinically relevant muscle wasting). Novel studies are revealing that improving muscle mass results in better long-term outcomes rather than just improving weight alone. This review will examine the scope of malnutrition in patients with CLD, its implications, the mechanisms by which malnutrition occurs, the methods to assess nutritional status, specific nutritional deficits, and current treatment approaches.

Introduction

There is no standard definition of malnutrition. An often cited general definition for adults states "an acute, subacute or chronic state of nutrition in which varying degrees of overnutrition or undernutrition with or without inflammatory activity have led to a change in body composition and diminished function" [1]. Note that overnutrition is considered malnutrition, but most of the discussion in this review will refer to malnutrition as undernutrition [2]. Chronic liver disease (CLD) is an established cause of malnutrition. Protein-calorie malnutrition occurs in 65-90% of CLD patients by several different mechanisms [3]. The liver is essential to normal metabolic functioning. Thus, CLD is associated with multiple factors that contribute to impaired metabolism leading to malnutrition. This review will examine the scope of malnutrition in patients with CLD, its implications, the mechanisms by which malnutrition occurs, the methods to assess nutritional status, specific nutritional deficits, and current treatment approaches.

Clinical implications of malnutrition in CLD

The degree of malnutrition is generally related to the severity of liver disease [4]. It is also an independent predictor of mortality. Several studies indicate that early aggressive nutritional rehabilitation can actually improve prognosis. Early screening, when malnutrition is less severe, can lead to early treatment and decrease complications [5]. Liver disease may be the initial catalyst for malnutrition in CLD; however, a comprehensive treatment approach for nutrition in addition to the liver disease is necessary to improve clinical outcomes. In fact, pre-liver transplant patients who are malnourished have higher risk of infection (61% vs 37%) and surgical complications (46% vs 23%) associated with liver transplant [6]. Addressing malnutrition prior to transplant leads to better post-surgical outcomes [7]. Post liver transplant patients also require nutritional rehabilitation to improve their long-term outcomes. Dr. Deirdre Kelly noted that "The most important aspect in achieving normal quality of life (QOL) after liver transplantation is to return to normal nutrition" [6]. Unfortunately, improved nutrition will not reverse end stage liver disease (ESLD). Thus, overall prognosis for the majority of patients with CLD is improved, especially post-transplant outcomes. However, improved nutrition does not seem to resolve their medical necessity for transplant.

Factors responsible for malnutrition in patients with CLD

There are many factors involved in causing malnutrition in patients with CLD. Patients with CLD often have anorexia, so their

total caloric intake is decreased. This can be due to poor motility, small intestinal bacterial overgrowth (SIBO), ascites, organomegaly and/or gastroparesis [8]. Dysguesia due to Low levels of zinc or magnesium can cause dysguesia which affects appetite. Elevated circulating cytokines like TNF in the inflammatory state secondary to CLD also decreased appetite. The low calorie intake may also be iatrogenic if the provider emphasizes low protein diets, low sodium diets, unpalatable foods or formulas, or prescribes medications that affect appetite (metronidazole, cholestyramine). Some of these diets are required for medical treatment, such as sodium restriction in patients with ascites. Stress of the disease, multiple doctor visits, and testing may affect the normal eating habits. This is especially true for children. To compound the problem of poor calorie intake, some studies have shown higher energy requirements demonstrated by an elevated resting energy expenditure (REE) [9]. Liver disease such as cirrhosis and NAFLD have been associated with an altered microbiome, but the final answers on how the microbiome affects nutrition in patients with CLD are still unknown [10,11]. Malabsorption is especially common in patients with cholestasis (impaired bile flow). Bile is required for normal fat absorption. Thus, fat soluble vitamins (A, D, E, and K) are often deficient. Absorption may not be optimal even without overt cholestasis since SIBO is often present [8]. In addition, portal hypertension may affect intestinal mucosal integrity that may affect absorption. CLD also leads to impaired metabolism with increased insulin resistance and decreased liver and muscle glycogen. Increased gluconeogenesis may utilize amino acids, especially from muscle, and contribute to sarcopenia (clinically relevant muscle wasting). Sarcopenia is found in up to 60% of patients with CLD, including pediatric patients [12]. In patients with CLD, the primary fuel source may shift from carbohydrate to muscle amino acids, so small frequent meals are advised [6]. Malnutrition by itself may lead to pancreatic insufficiency which would lead to fat, protein, and carbohydrate malabsorption [13]. Thus, malabsorption in CLD is often multifactorial.

Clinical Assessment of Nutritional Status

Clinical assessment of an individual's nutritional status is challenging. There are currently no established or standardized methods for quantifying nutritional status. Mueller listed 12 different screening tools used by different authors to define malnutrition. These tools all included combinations of weight loss, BMI, poor intake, tricep skin fold (TSF), and mid-upper arm circumference (MUAC) [1]. Using these factors individually to define malnutrition is not appropriate. For example, CLD often leads to fluid imbalance (ascites and edema) which makes weight alone an unreliable measurement. Likewise, BMI is not useful since often there is decreased linear growth that may persist even after successful liver transplant [14]. Skin fold thickness may be one of the most reliable, cost effective methods of assessing nutritional status. TSF reflects fat mass, an indication of energy stores. MUAC measures fat mass, muscle mass, and bone. The values of MUAC are stable in children 6-59 months old. In this age range, values of MUAC below 12.5-13 cm are consistent with significant malnutrition and Z-scores may even be more reliable [15,16]. Equations can be used to calculate the arm muscle area and arm fat area [17]. However, the results can be skewed based on the skill of the operator. Furthermore, the majority of practitioners lack the skill or time to perform these tests. Thus, having a registered dietitian who has expertise in body composition as part of the multidisciplinary team is imperative. The Subjective Global Assessment (SGA) has been proposed as a novel method for clinical diagnosis of malnutrition. However, this test was designed to evaluate malnutrition generally, and not specifically for patients with liver disease. The SGA form includes diet history (for calorie intake), weight, symptoms, and functional capacity. The test also includes a detailed physical exam including assessment of subcutaneous fat, muscle wasting, and fluid retention. Unfortunately, there is a significant amount of subjectivity in this test and no numerical score is created. Since it relies on many parameters, it may provide a comprehensive clinical impression of nutritional status. However, current studies reveal that it is not reliable in CLD, especially compared to other novel tests such as hand-grip strength [18]. Thus, diagnosing malnutrition clinically should include a team based approach with the help of a registered dietitian (RD). The final diagnosis is often tailored to the individual patient and provider since comprehensive clinical algorithms are not currently available. Furthermore, typical indicators of nutritional status used in patients with other diseases (e.g. albumin, prealbumin) are unreliable in patients with CLD.

Novel methods for nutritional assessment

Hand Grip Strength (HGS): This can be measured by dynamometry. HGS is a reliable indicator of functional capacity and is especially useful for following the same patient over time [19]. However, it is not reliable in the pediatric population as age-adjusted norms are not available. Furthermore, the test itself is challenging for younger children to operate. Sharma et al. compared several nutritional parameters in adults with liver disease including SGA, MUAC, TST, and HGS. They compared these methods in healthy controls, patients with chronic hepatitis, and patients with cirrhosis. All methods revealed worse signs of malnutrition in patients with cirrhosis [20]. A sensitivity analysis was then performed which showed that HGS had the best positive and negative predictive values for diagnosing malnutrition. HGS is becoming a more commonly chosen clinical method for diagnosing malnutrition in adults with CLD.

Bioelectrical impedance Analysis (BIA): This is a non-invasive, safe, easy to perform and relatively inexpensive technology that measures total body fat. A mild current is sent through the body and the resistance to the current varies with different tissues. The current moves slower through bone and fat, but fastest through water, like blood. The test reflects total body water which can then be used to estimate fat-free mass. The difference between total weight and fat-free mass is body fat. The results are affected by fluid and electrolyte status, recent exercise, meals, growth, and overall body composition that changes with time [21,22]. Limitations are explained in detail by Kyle [23] who notes that body composition

changes significantly between children and adults, so the equations used for calculating fat mass are different in different populations. Thus, no study has proven better reliability for BIA in the CLD population compared to other methods.

Indirect calorimetry: This measures resting energy expenditure (REE) by measuring oxygen consumption and carbon dioxide production. If the REE is 10-20% above expected, this would indicate a hypermetabolic state and indicate that the patient needs more calories than typically expected. Surprisingly, studies have been inconclusive as to whether patients with CLD have significantly increased REE. Consequently indirect calorimetry has not been used as a dependable indicator of nutrition status in CLD.

Frailty: Frailty has become an area of recent interest and encompasses more than the nutritional state alone. It encompasses the overall function of the patient and includes malnutrition, strength, and endurance. The original testing involved geriatric patients and included 5 elements that produced a score that was reproducible [24]. The elements include weakness (often measured by HGS), slowness (distance from a 6-minute walk), shrinkage (indicates weight loss, often measured with TSF), exhaustion (measured by questionnaire) and decreased physical activity (also measured with a questionnaire).

Lai et al. [27] modified this concept to create a liver-specific frailty score that emphasized physical frailty and this included HGS, time to do 5 chair stands, and time to hold difference positions of balance [25,26]. They showed that adults with higher liver-specific frailty scores had a higher mortality rate while on the waiting list for liver transplant. They also showed that physician's clinical visual assessment for frailty was inaccurate compared to their scoring system. Physicians failed to diagnose frailty clinically and underestimated the severity of frailty in CLD patients. A recent expert opinion statement noted that providers should measure physical frailty (which is very important when surgery is contemplated) as well as frailty related to cognitive dysfunction. However, there are currently no accepted standards for assessing frailty secondary to cognitive dysfunction, nor how psychoactive medications may confound this relationship [25,28].

Lurz et al. [29]recently adapted this tool to demonstrate frailty in children age 5-17 years old using 5 parameters similar to the initial studies in geriatrics. They found that there was a higher incidence of frailty in pediatric patients with end-stage liver disease (16 of 35 patients) compared to those with CLD (mostly stable autoimmune hepatitis, only 1 of 36 patients). They also found that the most abnormal elements of the score were weakness and slowness, not shrinkage. They confirmed findings seen in adult patients with CLD that showed that the SGA was not accurate compared to this tool. Remarkably, the frailty score did not correlate well with PELD/MELD score. More studies are needed to understand how the frailty score in both children and adults impacts short- and long-term outcomes in CLD. No study has yet to confirm if the frailty assessment is more or less useful than other accepted assessments of nutritional status in CLD. Empirically, one would expect that improved nutrition and exercise would improve frailty. Novel studies are using frailty as a predictive marker for outcomes. We predict that frailty scores will soon become a routine part of the assessment for liver transplant candidates.

Sarcopenia - a new component of CLD assessment

Sarcopenia is the loss of clinically relevant skeletal muscle. It has been studied in other diseases like HIV, chronic heart failure, geriatrics. There are studies of adults with CLD showing that worse sarcopenia will result in lower survival rates, poor QOL, more complications of cirrhosis, and worse post-transplant outcomes. These outcomes appear to be reflective of worse frailty in CLD. Mechanisms for inducing these poor outcomes include weakened respiratory muscles and diaphragm, which increases the risk of pulmonary complications. There is also an increased risk of infections from a weakened immune system. Skeletal muscle loss is associated with reduced protein stores in the body. Amino acids, the building blocks of proteins are therefore also decreased. Amino acids are needed to produce cytokines and maintain normal immune function. Thus, a reduction in muscle mass impairs immune system and the body's ability to fight infection. Hyperammonemia, a sign of concern in any patient with CLD, is also more common in patients with sarcopenia. Elevated ammonia levels develop as muscle catabolism leads to increased ammonia release. There is then an increase in the number of receptors on muscle cells that take up ammonia. Ammonia stimulates production of myostatin, which inhibits muscle cell functions, worsening the sarcopenia [30]. Thus, a persistent cycle of sarcopenia leading to hyperammonemia develops. Hepatic encephalopathy is also more frequent from the increased ammonia release. High ammonia levels in muscle will also decrease alpha-ketoglutarate levels. This negatively affects the tricarboxylic acid (TCA) cycle. Thus, adenosine triphosphate (ATP) production, required for energy for many cellular mechanisms, is inhibited. Several mechanisms have been discovered whereby ammonia injures neural cells, and likely some of these mechanisms also injure muscle cells [30].

Lurz et al. [12] recently published a report on sarcopenia in pediatric patients with CLD. They compared 23 infants (age 0.5-3.6 years old) with end stage liver disease (ESLD) to 46 healthy controls. They used computed tomography (CT) scans to measure psoas muscle surface area at L3-L4 and L4-5. Psoas muscle surface area is considered an excellent parameter to evaluate sarcopenia because these muscles are relatively independent of activity and water retention. The psoas surface area can also be normalized to height. Their results showed differences between pediatric patients with stable CLD compared to those with ESLD. Similar to frailty, the psoas muscle surface area did not correlate with PELD scores. Likely, routine evaluation of sarcopenia will be another factor added to the assessment of liver transplant candidates in the future.

Treatment of Malnutrition

The goals of treatment are to provide adequate nutrition, support growth, preserve lean body mass, and prevent micronutrient and vitamin deficiencies. The help of dieticians is

essential in this process. Specific vitamin and nutrient deficiencies can be tested and treated. Patients often have multiple deficiencies at once. Poor calorie intake is very common as patients with CLD often experience general malaise and anorexia. Thus, providing nutritional intake alone can be a challenge.

Diets

In general, a higher calorie intake is necessary if there is malabsorption or if the REE is elevated. Some infants require 150% more energy intake compared to healthy controls [3,5]. Studies show that patients with CLD often have limited muscle and liver glycogen stores. Overnight fasting then leads to amplified fatty oxidation and protein catabolism. One study showed that the metabolic changes that occur in normal patients after a 72 hour fast can be found within hours of fasting in patients with CLD [31]. Therefore, late night snacks and multiple small meals are encouraged [32]. Nighttime NG feeds are often used for this reason in infants. For patients with hepatic encephalopathy, many clinicians think that protein should be restricted. However, studies show that normal protein diets may actually improve hepatic encephalopathy [33]. Many CLD patients are protein calorie deficient and in negative nitrogen balance, so there is increased muscle breakdown leading to increased ammonia production. Reversal of this negative balance with normal or increased dietary protein may actually improve encephalopathy [34]. Protein should be restricted only when encephalopathy is severe and only in the acute setting.

Branch chain amino acids

There has been a lot of discussion of branch chain amino acid (BCAA) supplementation for patients with CLD over the past decades. The 3 branched chain amino acids are leucine, isoleucine and valine. These are among the 9 essential amino acids. Many studies, including in pediatric patients, confirm that patients with CLD have decreased serum levels of BCAA [35]. Simultaneously, patients with CLD have an increase in aromatic amino acids (AAA), so there is a low ratio of BCAA/AAA. The ratio imbalance worsens as liver disease progresses. Some authors have shown that a declining ratio is often associated with worsening liver disease progression [36]. Studies show an inverse relationship of plasma ammonia and BCAA, so it has also been long postulated that BCAA supplementation will improve hepatic encephalopathy. Ammonia will decrease BCAA because BCAAs release an amino group in muscle and brain that binds to alpha-ketoglutarate and forms glutamate. Glutamate then binds to ammonia to form glutamine, a major mechanism for ammonia detoxification [37]. In a review, Tajiri summarized very positive results showing that correction of low BCAA in animal studies and humans improved mitochondrial biogenesis, delayed hepatocyte apoptosis, and improved insulin resistance and immune function. Several clinical studies have suggested that BCAA supplementation improves prognosis in cirrhosis, as well as QOL [36]. Fuskushima showed that late night BCAA supplementation improved protein synthesis in patients with cirrhosis (38). Holecek wrote a detailed review of BCAA metabolism and again noted theoretical advantages of BCAA supplementation. However, studies have found no clinical improvement in patients with CLD using BCAA supplementation [37]. Yao recently wrote that BCAA supplementation shows promise (even after decades of research) in reducing cirrhosis-related complications. However, this is limited by abdominal pain and poor palatability [39].

A more recent Cochrane review showed benefit of BCAA supplementation for hepatic encephalopathy [40]. However, the authors found no benefit for mortality, QOL or nutritional parameters. A recent EASL practice guideline states that BCAA supplementation should be considered in decompensated cirrhosis patients who have inadequate protein intake [41]. There are theoretical reasons why BCAA supplementation may not be beneficial overall. The production of glutamine in muscle cells will decrease serum ammonia levels. However increased amounts of glutamine in the intestinal epithelial cells and kidney actually produce more ammonia, counteracting the BCAA supplementation. In addition, when glutamate is formed, alpha-ketoglutarate is consumed. Alpha-ketoglutarate is an essential step in the Krebs cycle and its disruption can lower the amount of ATP generated. In short, BCAA supplementation has many hypothetical reasons to be helpful in patients with CLD. However, clinical studies are inconclusive. Thus, there are no current recommendations for supplementation.

Additional Nutritional Support

Despite attempts to correct specific deficiencies and weight with different formulas and calorie supplements, many patients with CLD remain malnourished. This is especially common in infants with biliary atresia (BA). Aggressive nutritional support has been recommended for these infants using enteral feeds that may improve and reverse malnutrition [42,43]. Usually this is done with nasogastric (NG) feeds with close monitoring of growth parameters. If NG feeds fail to improve nutrition, several studies have shown the safety and benefit of parenteral nutrition (PN) by demonstrating increased weight gain as well as improvement in TSF thickness and MUAC [12,44]. Central line infections are a major concern in this situation, especially since liver dysfunction has been related to poor immune function. A Cochrane review noted that there was no compelling evidence to justify routine use of parenteral nutrition, especially with the risk of central line infections versus the benefit of providing increase calories [45]. In adults daily protein recommendations of 1.2-1.8 gm/kg/day are suggested, but for children the requirements are higher at 2-4 gm/kg/day [15]. Carbohydrates are the major source of calories for infants with CLD, composing about 50-60% of calories. Dietary fats and lipids typically make up 40% of calories for pediatric patients. Medium chain triglyceride (MCT) oil is used since it is absorbed even in the presence of cholestasis. However, many children do not find it palatable. Naturally occurring MCT is found in coconut and safflower oil. Excess MCT, considered over 80-90% of total fat intake, can lead to essential fatty acid deficiency (EFAD), so at least 10% of the fat should be long-chain fatty acids. Levels of essential fatty acids should be monitored in patients using long

term MCT. Pregestimil contains 55% MCT, and Alimentum contains 33% of total fat as MCT. For older children, Pediasure Peptide and Peptamen Junior both provide 30 calories per ounce and contain about 50% of fat as MCT. Fluid restriction for severe ascites may be necessary but this often limits caloric intake. Higher concentrated formulas 30 calories per ounce for infant and 45 calories per ounce for older children) are thus often required to limit volume without limiting calories.

Fat soluble vitamins

In the presence of cholestasis, Vitamins A, D, E, and K are often malabsorbed leading to low serum levels. Specific replacement doses have been determined [46].

Vitamin A: Vitamin A is a fat soluble vitamin, and the term actually refers to several different retinols and their precursors [47]. Absorbed retinols travel from the gut to the liver where 80% of Vitamin A is stored, mostly in hepatic stellate cells. Deficiency results in night blindness, retinitis pigmentosa, and impairs the immune system. Vitamin A status would best be monitored by liver tissue levels, but this is not routinely done as liver biopsy would be required. Other methods for evaluating Vitamin A status include ophthalmologic exam, darkfield adaptation, Schirmer's test, and conjunctival impression cytology [48].

The most accurate form of testing is the relative dose response (RDR) test. When hepatic Vitamin A stores are normal, plasma retinol levels do not increase following administration of Vitamin A. However, when hepatic Vitamin A stores are low, then Vitamin A administration leads to a rise in retinol level, usually more than 20% above baseline. This would indicate a positive RDR test. The rise has been tested at 5-9 hours after Vitamin A administration. Because cholestatic patients may not absorb oral Vitamin A very well, the test may be more accurate if Vitamin A is given intramuscularly. The serum retinol to retinol binding protein (RBP) test is not as accurate as the IM-RDR test. However, it is used more routinely out of ease and convenience [48]. The retinol to RBP ratio was used to show Vitamin A deficiency in up to 36% of patients with BA. This most often occurred when total bilirubin was above 2 mg/dl [49]. Freund reviewed data of Vitamin A levels in BA, primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) [47]. Low Vitamin A levels were confirmed in a high proportion of BA patients. The results for PSC and PBC were less consistent, but the sickest patients with PSC and PBC all had low Vitamin A levels. This review also noted that when stellate cells become activated, Vitamin A content decreases dramatically. The authors summarized several animal models of liver disease including bile duct ligation and carbon tetrachloride injury that showed improvement with Vitamin A supplementation. These points all lead to the idea that Vitamin A supplementation is important in patients with CLD, especially those with cholestasis. However, Chaves cautioned that Vitamin A can be toxic and interpose between lipids in the cell membrane leading to cell lysis. They stated that it is reasonable to hypothesize that Vitamin A supplementation may trigger harmful effects in those with cirrhosis [50]. Despite this warning, the standard of care is to monitor Vitamin A levels using the retinol/RBP ratio and supplement if the level is low. Dosing is 5,000-25,000 units per day. Current guidelines recommend that levels should be checked every 3 months.

Vitamin D: Metabolic bone disease is common in patients with CLD and in children following liver transplant [51]. Relevant factors causing bone disease include immobilization, steroid use, lack of sun exposure, and vitamin D deficiency due to malabsorption and poor intake of dairy products. Calcium, magnesium and phosphorus deficiencies also play a role in metabolic bone disease. Vitamin D is monitored by serum 25 hydroxyvitamin D (25-OH) levels that should be above 30 ng/ml. Metabolic bone disease, osteopenia, osteoporosis and rickets are all known to occur from Vitamin D deficiency. Vitamin D is also important in immune function. Replacement doses depend on age and degree of deficiency. For example, a patient over 40 kg with a low level below 10 ng/ml may require 5,000 IU/day. However, a patient less than 40 kg with a level below 10 ng/ml could require 100 IU/Kg/day. For convenience, many providers opt to treat deficient patients with 50,000 IU weekly. The levels should be monitored every 3-6 months.

Vitamin E: Deficiency in vitamin E can cause neurologic problems including spinocerebellar ataxia, decreased proprioception, decreased deep tendon reflexes, and retinopathy. Deficiency can also cause increased RBC fragility and anemia. Cholestasis affects Vitamin E absorption more than Vitamin D [52] and replacement requires D-alpha-tocopherol with polyethylene glycol succinate (TPGS). The dose is 15-35 IU/kg/day and is available in ADEK vitamins, but the amounts are low. In the USA, Liqui-E (Twinlab) and Aqua-E (Yasoo) are available, but sometimes difficult to obtain. In Europe, a product called Vedrop was shown to be safe and effective for correction of Vitamin E deficiency [53]. Meaningful measurement of vitamin E requires the vitamin E to total lipid ratio. This ratio should be above 0.6 mg/gm for patients less than 1 year old, and above 0.8 mg/gm for older patients. Levels should be monitored every 6-12 months.

Vitamin K: Vitamin K is typically monitored by the prothrombin time (PT) or the international normalized ratio (INR). Unfortunately, this test may be abnormal due to severe liver dysfunction and not due to vitamin K deficiency. Specific measurement of protein induced by vitamin K absence-II (PIVKA-II) is an alternative method to monitor vitamin K levels. One study found it to be low in 50% of patients with CLD who had a normal INR [54]. However, currently there are no recommendations to test PIVKA-II routinely and most providers use a combination of the INR and other fat soluble vitamin levels to determine if extra vitamin K supplementation is necessary. Vitamin K replacement can be given orally with 2.5-5 mg daily. In cases of severe cholestasis where oral preparations may not be ideal, parenteral Vitamin K every 2-4 weeks is a very effective alternative.

Micronutrients

Patients with CLD may have a variety of micronutrient deficiencies. Zinc deficiency can contribute to dysgeusia and

other metabolic abnormalities in patients with CLD [55]. Zinc replacement dose is 1 mg/kg/day. It should be remembered that CLD may cause elevated levels of manganese and copper. Selenium is an antioxidant. Low selenium levels have been documented in some patients with CLD [56] and selenium was shown to prevent apoptosis of cultured hepatocytes exposed to excess free fatty acids [57]. However, one large study in Chinese males found elevated selenium levels in patients with non-alcoholic fatty liver disease (NAFLD) and noted that selenium can induce liver insulin resistance and increase liver triglyceride levels [58]. Selenium levels should be monitored and replaced with 1-2 ug/kg/day of selenium if necessary. If Vitamin D is being replaced, then calcium should be supplemented with 25-100 mg/kg/day. Without calcium replacement, correction of Vitamin D may lead to large amounts of calcium entering bone, leading to pathologic hypocalcemia (hungry bone syndrome). Essential fatty acid deficiency (EFAD) can occur, especially if the diet contains more than 80-90% MCT. EFAD is diagnosed by testing the triene to tetraene ratio. The ratio should be less than 0.2 [55]. An elevated ratio indicates that more mead acid is being produced compared to arachidonic acid, which indicates EFAD. EFAD can affect platelet count and cause a dry, scaly rash. EFAD can also cause hair loss, poor wound healing, and growth restriction.

Exercise

Especially in the wake of sarcopenia and frailty, the importance of exercise in addition to appropriate diet therapy for CLD patients has increased. Williams et al. evaluated how a home based exercise program would improve frailty in adults with ESLD. At the end of the 12-week home based program, they found that participants had significant improvement in shuttle walk testing, physical performance battery testing, and anxiety and depression scores. Thus, a home based exercise program improved aerobic muscle capacity, functional muscle capacity, and health related quality of life [59]. More testing, including randomized controlled trials, are needed in order to confirm the impact on reducing sarcopenia and how it impacts CLD and ESLD. Trials are also needed in the pediatric population. However, this study shows that simple maneuvers may have a large impact on multiple health factors in patients with CLD.

Obesity

Malnutrition could also indicate over-nutrition. Some patients with CLD are overweight before liver transplant. The United Network for Organ Sharing (UNOS) reported that approximately 15% of children undergoing liver transplant in the period 1987-2010 were obese. Recently, the percentage of adults undergoing liver transplant who are obese has risen much higher than 15% because of cirrhosis due to NAFLD. Following liver transplant, there may be an increase in weight gain because of lack of physical activity, steroids, and cyclosporine (seen less frequently with tacrolimus). Two recent studies showed that up to 50% of pediatric patients are overweight following liver transplant [60,61]. Weight prior to liver transplant was the best predictor of post-transplant obesity [3,62]. These patients may also develop diabetes due to steroids and tacrolimus. Thus, it is important to monitor weight gain closely in these patients post-transplant to ensure further complications do not occur.

Conclusion

This review reveals the wide scope of malnutrition in CLD. Assessing for malnutrition is complicated and difficult at this time. However, newer methods are being developed to help ensure better detection of malnutrition. It is also important to assess for muscle wasting (sarcopenia) in addition to poor weight gain. There are no laboratory levels that a clinician can use to diagnose malnutrition. However, EFAD, micronutrient deficiency, and fat soluble vitamin malabsorption should all be assessed routinely. Treatment should focus on providing appropriate calories, often 150% in excess of healthy individuals. A dietitian is recommended to help with routine monitoring and care for all patients with CLD. Overall, malnutrition in CLD is a common yet complex disorder that requires close monitoring and attention to detail. Novel methods to better recognize and treat malnutrition in CLD are on the horizon.

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Conflict of Interest

No conflict of interest.

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