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Feature Article

Medical Nutrition Therapy in Liver and Renal Failure: Conflicts and Commonalities

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Liver and renal failure occur together from a variety of circumstances. These may include primary renal disease with a liver disease co-morbidity (Hepatitis B or C glomerulonephritis), concurrent renal and liver disease (Polycystic disease), liver failure with renal dysfunction (Hepatic-Renal Syndrome (HRS) types 1 and 2), post-liver transplant renal failure due to calcineurin inhibitor toxicity, or other scenarios such as Hyperoxaluria (1). These can be categorized as occurring in an acute setting, such as HRS type 1 or Acute Tubular Necrosis. Or they may develop over a prolonged period of time, as in the case of chronic kidney disease or HRS Type 2 (1). The medical treatment and nutrition therapy are often similar for any of these situations, but the priorities between liver and renal disease may be different. This article will review the pathophysiology and medical nutrition therapy (MNT) to help decrease the burden on liver and renal systems, as well as slow the progression of the disease process, thereby reducing morbidity and mortality (2).

The metabolic changes in liver disease are numerous and often similar to changes that also occur in renal dysfunction:

- Changes in carbohydrate metabolism are notable. There is increased glucose intolerance and insulin resistance, decreased glycogen stores, and concurrent increases in gluconeogenesis. Ultimately, this puts the individual at risk for diabetes. In patients with diabetes or impaired fasting glucose metabolism, poor glycemic control also contributes to altered metabolism. This elicits depletion of fat and muscle stores due to gluconeogenesis (3). With the variability of liver function and potential hepatotoxicity of some glycemic agents, many diabetics with liver disease will ultimately require insulin therapy for best glycemic control. The same is true for those with renal failure.
- Fat metabolism is most commonly seen as an impaired synthesis of polyunsaturated fatty acids. There may also be malabsorption due to inadequate bile within the bowel. This is most commonly seen in those with a cholestatic liver disease profile.
- Protein metabolism alterations include increased protein catabolism, amino acid imbalances, and increased protein losses (3).
- Micronutrient abnormalities also occur and will be discussed further.

Nutritional assessment in liver and/or renal failure is complicated by the lack of reliable laboratory markers of nutritional status and by the inaccuracy of weight assessment due to fluid retention. Subjective global assessment includes a physical exam, laboratory values, nutritional intake history, and other parameters, and is the preferred method of assessment for this patient population (4,5). Pikul et al (5) has determined a 4-point scale for use in liver patients that is appropriate for the initial assessment. Care should be used with the interpretation of serum albumin and other proteins as they are affected by the liver synthetic function as well as nutritional intake (6). In addition, glomerular filtration rate (GFR) tends to overestimate renal function in patients with liver disease (7). Handgrip strength, skinfold thickness and arm muscle circumference can also be used in long-term patients to monitor nutritional stores (8).

Physiology

In situations of acute onset renal dysfunction or failure, medical treatment includes managing the initiating insult, such as acute liver failure, sepsis or gastrointestinal bleeding, as well as the renal failure. Type 1 HRS is characterized by a rapid decrease in GFR, an increase in blood urea nitrogen (BUN) and creatinine (Cr), oliguria, hyponatremia, and hyperkalemia. By definition, it is when the initial serum Cr doubles to > 2.5 mg/dL or when there is a 50% decrease in creatinine clearance (to < 20 mL/min) within 2 weeks (9). The development of HRS type 1 carries a poor prognosis with a median survival time of only 2 weeks after onset (10). While it is unclear if renal replacement therapy (RRT), either as hemodialysis (HD) or as continuous RRT, improves survival, it is often provided as the standard of care. This is often the case for patients who have potentially reversible disease or those awaiting liver transplantation (11). Dialysis allows for the removal of fluid, electrolytes, and toxins, including ammonia and urea which may help control or treat portosystemic encephalopathy (PSE). These patients will be critically ill with multisystem organ failure and may require nutrition support due to their inability to consume adequate oral intake. Nutrition therapy includes maintaining calorie and protein needs appropriate for the RRT chosen. Protein should be given in divided doses throughout the day. Limit sodium, potassium, and phosphorus intake as necessary. Oral supplementation with calorie-dense and lower electrolyte beverages can be a mainstay of intake. Use of branched chain amino acid supplements continues to be controversial in these circumstances, but may be used from the perspective of "doing every thing possible" or "might help and probably won't hurt." This is an area prime for research and development of best practices as evidence-based medicine.

In the chronic development of renal failure in liver disease, the changes in portal hypertension create arterial vasodilatation that eventually progresses to arterial hypotension and decreased perfusion of organs (9). The first change in renal function that occurs in cirrhosis is the decreased ability to excrete sodium and water (1). This is a subclinical finding until the excretion rate decreases below dietary intake, thereby causing the development of ascites. The decreased ability to excrete sodium contributes to dilutional hyponatremia, so Aldactone is prescribed to increase the rate of sodium excretion. Eventually, renal vasoconstriction decreases GFR (9). Monitoring renal function using serum Cr can be deceiving as levels can be falsely low or normal due to the impaired hepatic synthesis of Cr, increased tubular secretion of Cr, and/or the effect of hyperbilirubinemia (>10 mg/dL) on Cr measurement, as well as being low in patients with decreased muscle stores (9). Use of the most accurate GFR measurement technique is the best means to assess true renal function and dictates the treatment plan (11).

Alternately, type 2 HRS, which develops chronically over weeks and months, is characterized by a more gradual decrease in GFR with a more moderate increase in BUN and Cr. The chronicity leads to progressive renal impairment which may become permanent. Other aspects to consider in the diagnosis of HRS are ruling out preexisting renal disease or compromises in renal size and blood flow, sepsis effect, and fluid losses (1,9). The development of HRS in liver disease has a huge effect on the outcome and survival, both with and without transplantation. At any Model for End-Stage Liver Disease score, the equation used to stratify a patient's need for transplantation, those with HRS have significantly decreased 3 month survival (12). The score does include the serum Cr as one of the factors within the equation, which weighs the prognostic score and allocation of livers to those with worsening renal function. Primary nutrition therapy for type 2 HRS includes strict compliance to dietary sodium restriction (< 2000 mg per day), adequate calorie and protein intake, and fluid restriction if necessary.

In instances of true chronic renal failure with liver disease, the treatment plan and nutritional care can follow standard renal failure MNT guidelines. As with renal failure, a high priority would be to ensure adequate calorie intake and maintenance of nutritional status.

When to start RRT, and which mode, continues to be a complex medical and ethical dilemma. Determining when it provides benefit or is an element of futile care requires further study to clarify outcome data and set practice guidelines, as well as to determine the effect on morbidity and mortality (9-11).

Table 1
General Nutritional Recommendations for Liver and Renal Failure (2,11,13-17)

CALORIES	25 to 40 kcal/kg dry weight Encourage weight loss if BMI > 35
PROTEIN	Pre-HD with liver disease/failure: 0.75-1.0 g/kg HD with liver disease/failure: 1.0-1.2+ g/kg CRRT with liver failure: 1.2+ g/kg
SODIUM	< 2000 mg/day
POTASSIUM	< 2300 mg/day if necessary
PHOSPHORUS	< 1000 mg/day if necessary
FLUID	Limit as needed for renal failure, hydration and if hyponatremia < 128 mg/dL
CALCIUM	1500 mg/day
IRON	Careful supplementation
VITAMINS/MINERALS	General vs. renal-specific Fat-soluble replacement
ALCOHOL	Avoid intake
EXERCISE	Encourage regular activity to maintain strength, endurance and combat fatigue
MEAL PLAN	Encourage intake as 4 to 6 feedings per day Supplement products as needed

Medical Nutrition Therapy

The general nutrition concepts in patients with liver and/or renal dysfunction have some similarities. In both groups, restricting the diet only as much as necessary is the goal, with sodium and potassium restrictions being the most common. In addition, herbal, complementary or alternative medicine products should be used with extreme caution due to the untested and unknown side effects. In liver disease, fluid restrictions are usually only indicated for hyponatremia (serum sodium levels <128 mg/dL) or when ascites or edema becomes difficult to control despite maximal diuretic therapy.

The meal schedule/timing in liver disease is more important than in renal failure to prevent the onset of gluconeogenesis. This can occur after only 4 to 6 hours of fasting. Patients should be encouraged to eat or drink nutrient dense foods or beverages 4 to 6 times per day to enhance their ability to meet their needs, overcome fatigue, address anorexia, treat early satiety, as well as maintain their nutritional wellness.

Many, but not all, patients with liver and/or renal dysfunction have increased metabolic demands from their illness. Those who are hypermetabolic have calorie needs of 30-40 kcal/kg, while others will be able to maintain adequate nutritional stores at 25-30 kcal/kg. In liver disease, calories can be provided from a greater variety of protein sources as they do not need the same emphasis on high biological value or the limits on potassium and phosphorus. However, due to issues with obesity and liver disease, obese liver disease patients may need calorie restriction to promote weight loss in anticipation of transplant. Table 1 summarizes nutritional requirements and recommendations.

Obesity may be both a cause and effect of liver and renal disease. The incidence of obesity is increasing in both populations and can prevent or compromise candidacy for transplantation. Non-alcoholic fatty liver disease, the steatotic liver disease associated with obesity and metabolic syndrome, is becoming the most common liver disease. It may progress to hepatocellular cancer, cirrhosis, and/or liver failure (18). Weight criteria for liver and renal transplantation candidacy are often different, with stricter criteria often employed for liver transplant candidates. For liver transplantation, having a BMI >35 seems to be an important morbidity and mortality break point, implying decreased survival at 3 years, even when corrected for co-morbidities (19). A study of 58 obese patients listed for liver transplant showed that patients may safely lose weight through a structured diet and exercise program. Conversely, the "reverse epidemiology" concept of excess weight protecting HD patients' survival makes many providers hesitant to encourage significant planned weight loss for those with renal failure (20). However, BMI > 30 correlates with delayed graft function, increased renal graft loss, decreased patient and graft survival, as well as increased post-transplant complications. Despite this, transplant continued to provide an increased survival rate as compared to continuing on HD (21).

Protein intake is a key nutritional component in both liver and renal disease. Consuming protein in divided portions is very

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important in both situations, but for slightly different reasons. In liver disease, goals for intake are usually at least 1 gram per kg of "dry" weight, with less of a focus on the need for high biological value choices. Dairy protein sources are often well tolerated and encouraged since potassium and phosphorus don't usually need to be limited. Patients with end-stage liver disease can become protein intolerant, as demonstrated by alterations in mental status (PSE). This is best controlled by medical management and keeping protein portions to no more than 2-3 ounces per meal, while still maintaining an adequate protein intake over the course of the day. Conversely, while early renal failure patients need to limit their protein intake to ease renal solute workload, they are rarely physically protein intolerant. Although, both may have similar alterations in protein taste perceptions.

Uremic encephalopathy and PSE both can present with alterations in mental status and asterixis. HD can provide a transient benefit of filtering hepatotoxins and ammonia to help control the altered mental status. The altered mental status may affect the individual's ability to consume adequate intake by decreasing their ability to eat safely and to comply with diet restrictions. PSE is treated first by eliminating the underlying causes, which are most commonly GI bleeding, fluid and electrolyte abnormalities, dehydration, and infection. Lactulose, given in doses to promote 3 to 5 soft bowel movements per day, limits bacterial production of urea within the colon and may help decrease symptoms. However, there may also be nutritional losses from diarrhea if the dosage is not titrated correctly. Then, if needed, protein restriction may be used in the late, chronic stages. Additionally, patients who require placement of a transjugular intrahepatic portosystemic shunt (a stent placed between the portal vein and the hepatic vein to relieve portal hypertension thereby decompressing adjacent veins and varices) are also at increased risk for developing PSE due to the bypassed blood flow through the liver.

Vitamins and Minerals

Supplementation of vitamins and minerals is important in both liver and renal failure; however, the amounts and needs are different. In chronic liver disease, a product that provides 100% of the RDA for vitamins and minerals is the base of supplementation. For many, a product that is low in iron would be necessary due to alterations in iron metabolism and potential for deposition in the liver, as well as in other organs and tissues, such as the heart. A low iron product is also necessary for those with the liver disease hemochromatosis. Therefore, use of medications to stimulate erythropoiesis must be used with care in patients with liver disease (17,22).

Both folate and vitamin B12 levels are often low and require supplementation, especially with losses due to HD. When liver and renal failure occurs together in the short-term, patients may not need to be changed to a renal failure product. But if it continues for more than 4 weeks and/or they require chronic RRT, patients should be switched to a renal vitamin product (2).

Fat-soluble vitamin metabolism and storage is skewed in liver disease with patients often requiring supplementation of A, D and E. Serum vitamin A levels are usually the first to become abnormal with vitamin D levels next, and then vitamin E last. Patients with decreased serum levels of vitamin A may exhibit actual symptoms of night blindness. Vitamin A is especially bile dependant for absorption, as well as needing conversion within the liver. Because of this, traditional over-the-counter (OTC) or standard supplements (or the vitamin A precursor, beta-carotene) are usually not effective in improving serum level markers. Most patients will require supplementation with the prescription, water-miscible form (usual dose 25,000 IU three times per week). However, long-term use of vitamin A supplementation may be contraindicated due to potential for poor renal clearance and tissue accumulation. Vitamin D supplementation is often necessary in both liver and renal failure. In end stage renal failure patients, ergocalciferol cannot be hydroxylated at the 1st position due to the proximal tubular dysfunctions. Therefore, these patients require 1,25 (OH) vitamin D instead of the non activated vitamin D such as ergocalciferol. In severe cholestatic and hepatotoxic liver disease patients, they have compromised flow and synthesis of the bile acids, respectively. Therefore, they have compromised vitamin D absorption, but they may also have compromised ability to hydroxylate vitamin D at the 25th position. Thus, if there are mainly absorptive issues, high dose of ergocalciferol supplementation of 50,000 IU, three times per week, may be prescribed as an initial dosage regimen. Careful dosage monitoring is required. For those patients who are not able to hydroxylate the 25th position sufficiently, 25 or 1,25 pre-hydroxylated vitamin D preparations are required. Traditional vitamin E supplementation of 400 mg/day is usually adequate but not excessive (2,22,23).

Patients with liver disease also often have alterations in serum mineral levels including zinc, magnesium, selenium and copper. Zinc tends to be low, partially due to its albumin-bound nature, making serum zinc an invalid marker as liver failure progresses. An association has been found between patients with low serum zinc levels and increased PSE symptoms. Therefore, patients with PSE and low zinc levels can be started on 220 mg zinc sulfate (50 mg elemental zinc), 1-3 doses daily for 10-14 days, as tolerated. If PSE symptoms improve with supplementation, 15 mg zinc/day can be maintained indefinitely. However, zinc supplementation can be

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hard to tolerate due to altered taste perceptions (worsening metallic tastes) and some GI symptoms. Magnesium levels tend to be low in liver disease but elevated in renal failure, so levels need to be followed closely, especially if supplementation is begun. Selenium levels tend to be low in renal failure but are not well studied in liver disease, so any supplementation needs to be carefully monitored. Copper levels are elevated in several liver diseases, most notably Wilson's disease, as well as renal failure, so most patients should not take more than the standard amount within a multivitamin product. (2,22,23).

Nutrition Support

In the setting of liver and renal failure, the ability to consume adequate nutrition becomes very difficult due to multiple factors. These include anorexia, early satiety, nausea and vomiting, diarrhea, taste aversions, fatigue, and diet restrictions. Many patients will eventually become unable to eat enough on their own and need nutrition support. Enteral nutrition is the preferred mode of feedings and soft bore nasoenteric access may be an option, even in patients with esophageal varices. Because of a myriad of GI symptoms, small bowel feedings are generally better tolerated. Formula choices depend most on protein and fluid limitations. Parenteral nutrition is used only in situations with a non-functioning GI tract, or if safe passage of a feeding tube is not possible and nutrition support is indicated. As in enteral nutrition, protein and fluid requirements determine the exact formula, with lipid emulsions included with usual precautions (24).

Summary

MNT in combined liver and renal failure is complex. There are many commonalities but also some conflicts regarding nutritional goals and needs. The primary goal is to help the patient maintain their best possible nutritional status as they use food for both nutrition and treatment of their disease process. As always, this group of patients appreciates emphasis on what they can eat and minimizing dietary restrictions to only what is necessary. Goals and restrictions often change as symptoms and organ function evolve, so careful monitoring, reassessment and continuous patient education are key. ◆

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