Review Article

Malnutrition in Cirrhosis

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ABSTRACT

Malnutrition is very closely associated with cirrhosis. An important phenotype of malnutrition is loss of muscle mass or sarcopenia. Malnutrition can be defined as a state of nutritional imbalance either due to undernutrition leading to sarcopenia or overnutrition from excess caloric intake, as in NAFLD patients, leading to sarcopenic obesity. Major causes of malnutrition in cirrhosis are anorexia, altered taste and smell, nausea, vomiting, delayed gastric emptying, diarrhea, malabsorption, bacterial overgrowth, unpalatable diets, hormonal and cytokine disruption, and complications of cirrhosis. Each of these etiologies of malnutrition should be addressed and improved to the extent possible. In general a balanced oral diet should be achieved with 2 gm per day sodium restriction for patients with fluid retention. Protein intake is usually recommended at 1.2 - 1.5 gms/Kg body weight / day. Oral nutritional supplements should be used for patients who cannot consume the necessary amount of normal food. Frequent and small feedings are optimal. A bedtime snack with sufficient calories and protein is crucial to avoid nighttime starvation and muscle loss in outpatients as well as inpatients. Hospitalized patients should be carefully monitored to see if they are meeting their daily caloric and protein needs in the first 24-48 hrs after admission. Efforts should be made to provide >80% of estimated or calculated energy and protein goal within 48-72 hours to achieve the clinical benefit of enteral nutrition (EN). EN is favored over parenteral nutrition (PN) Cirrhotics with hepatic encephalopathy (HE) should receive the same amount of protein per day as those without HE. Each patient should have a nutritional plan and should undergo follow-up nutritional assessment to monitor progress.

Key-words : Cirrhosis, malnutrition, sarcopenia.

Introduction :

The liver is possibly the most complex organ in the body in terms of metabolic activity. The liver plays a vital role in protein, carbohydrate, and fat metabolism, as well as micronutrient metabolism. Due to that liver disease, especially advanced liver disease, frequently alters nutritional status. But apart from altered metabolism, in liver disease, malnutrition can result from undernutrition or overnutrition due to multiple factors. Examples include inadequate protein / calorie intake due to anorexia or nausea as well as large consumption of empty calories from alcohol. A widely recognized phenotype for malnutrition in liver disease is skeletal muscle loss (sarcopenia) with or without loss of fat mass.

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Nutrition support may have been the first carefully investigated form of therapy in cirrhosis. Indeed, the terms "nutritional cirrhosis" and "cirrhosis" were often used interchangeably in the first half of the 20th century. Interest in nutritional therapy in cirrhosis was initially stimulated when Patek, et al.[1] demonstrated that a nutritious diet (~3500 calories and 140 g protein) improved the 1 - and 5 - year outcome of patients with cirrhosis compared with historical control cirrhotic patients not offered the nutritious diet. Subjects were generally low-income patients with alcoholic cirrhosis.

Probably the most extensive longitudinal studies of nutritional status in patients with liver disease are in patients with alcoholic liver disease (usually cirrhosis with superimposed alcoholic hepatitis). The most detailed initial reports are two large studies from the United States Veterans Health Administration (VA) Cooperative Studies Program in patients with alcoholic hepatitis.[2-5] The first study demonstrated that virtually every patient with alcoholic hepatitis (AH) had some degree of malnutrition ***(Table 1)***[3]. Patients' mean alcohol

Table 1 : **Nutritional Status in Alcoholic Hepatitis**

Every Patient is malnourished			
Severity of Liver Disease			
Initial Laboratory	Mild	Moderate	Severe
Lymphocytes (1000 - 4000 / mm3)	2,067 + 148	1,598 + 90	1,366 + 83
Albumin (3.5-5.1 g/dl)	3.7 + 0.1	2.7 + 0.1	2.3 + 0.1
CHI - Creatinine - Height Index (% of standard)	75.7 + 2.84	62.9 + 3.3	64.0 + 4.65

The CHI ratio is the measured 24-hour urine creatinine excretion in the patient compared to expected excretion in a normal individual of the same sex and height : CHI > 80% indicates normal protein status : CHI 60 - < 80% indicates mild protein depletion; CHI 40 - < 60% indicates moderate protein depletion and CHI < 40% indicates severe protein depletion.[12,13]

consumption was an impressive 228 g/day (approximately 50% of energy intake was from alcohol). Thus, while calorie intake was generally adequate, there was often deficient intake of protein and important micronutrients. The severity of liver disease generally correlated with the severity of malnutrition in both studies.[6] The patients were given a balanced 2500-kcal hospital diet (monitored carefully by a dietitian) and encouraged to consume the diet. However, severe anorexia was common and was correlated with severity of liver disease. In the second study, patients in the therapy arm of the protocol also received an enteral nutritional support product high in branched-chain amino acids (BCAAs) as well as the anabolic steroid oxandrolone (80 mg/day). An anabolic steroid was used because patients with AH/cirrhosis frequently have low levels of anabolic hormones.[7-10] Patients were not fed by feeding tube even if voluntary oral intake was not adequate. Voluntary oral food intake measured over the month of hospitalization correlated in a stepwise fashion with 6-month mortality data. Thus, patients voluntarily consuming < 1000 kcal/day had > 80% 6-month mortality while those eating > 3000 kcal/day had virtually no mortality ***(Figure 1).*** Moreover, the degree of malnutrition correlated with the development of serious complications such as encephalopathy, ascites and hepatorenal syndrome, as well as mortality ***(FIgure 2).***[2]

Investigators attempted to address this important issue of inadequate food intake by administering nutritional supplements via nasogastric feeding

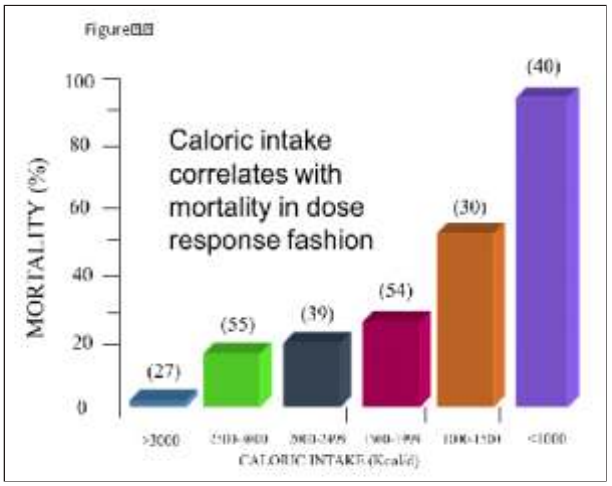

Figure 1 : **Data from VA Cooperative research indicates voluntary caloric intake over one month of hospitalization correlates in a dose response fashion with six months mortality**

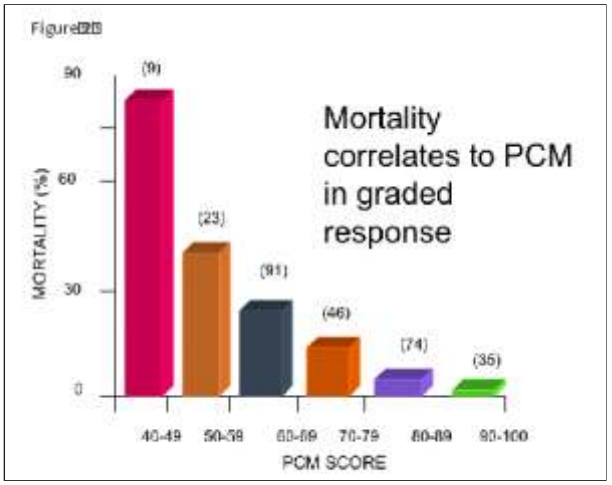

Figure 2 : **A protein / calorie malnutrition score demonstrates that protein/calorie malnutrition relates in a graded response with mortality (a perfect score is 100)**

tubes. Kearns, et al.[11] showed that patients hospitalized for alcoholic liver disease (ALD) and given an enteral nutritional supplement via feeding tube had significantly improved serum bilirubin levels and liver function as assessed by antipyrine clearance. Tube fed patients had improved caloric and protein intake compared to patients offered a nutritious diet alone, thus documenting the importance of tube feeding in many of these anorexic patients. A multicenter randomized study from Spain of enteral nutrition via feeding tube versus corticosteroids in patients with AH showed similar overall short-term mortality results (one month survival - primary endpoint).[12] Moreover, those receiving enteral nutrition (rich in BCAAs) had a better long-term outcome with fewer deaths from infections. In another multi-center trial of aggressive enteral nutrition in severe liver disease by Moreno et al., patients with biopsy-documented severe AH were treated with either intensive enteral nutrition via feeding tube for 14 days plus methylprednisolone or conventional nutrition plus methylprednisolone.[13] The primary end point was survival at six months. While the authors concluded in the title that intensive enteral nutrition was ineffective, the six-month mortality was numerically lower in the enteral group (44.4%) compared with the control group (52.1%), and this study was underpowered. More importantly, patients receiving < 21.5 kcal/kg/day had significantly lower survival rates, as did those receiving < 77.6 gm of protein per day. In summary, most cirrhotics have some evidence of malnutrition, with malnutrition correlating with severity of liver disease. Nutritional supplementation clearly improves nutritional status and, in some instances, improves hepatic function and other outcome indicators in cirrhosis.

These previously noted studies generally evaluated patients with an active inflammatory response (hepatitis) in acutely ill hospitalized patients. Thus, it was important to assess nutritional status in a population with stable cirrhosis without AH or other inflammation. One such study evaluated patients with stable cirrhosis followed in an ascites clinic who were not actively drinking, were free of AH, and had bilirubin levels < 3 mg/dl. These patients had indicators of malnutrition similar to those in patients with alcoholic hepatitis.[14] Thus, it appears that once advanced cirrhosis develops, malnutrition is frequently observed irrespective of acute inflammation. It is also possible that alcohol, rather than the underlying liver pathology, could be an important variable in malnutrition in liver disease. Several major studies compared patients having either ALD or nonalcoholic (especially viral) induced liver disease.[15-19] These reports from various countries present consistent findings that clinically important malnutrition occurred in alcoholic and non-alcohol-related causes of cirrhosis (although sometimes more severe when it was alcohol induced). For example, Sarin et al.[15] demonstrated that protein-energy malnutrition was equally severe in alcoholic and nonalcoholic liver disease and that dietary intake decreased equally in both diseases. Caregaro et al.[16] from Italy found that the prevalence, characteristics, and severity of protein energy malnutrition were comparable in alcoholic and viral-induced cirrhosis. Importantly, malnutrition correlated with the severity of the liver disease. Peng and co-workers performed a very sophisticated cross-sectional assessment of nutritional status in 268 patients with cirrhosis of multiple etiologies[20]. Total body protein was calculated by neutron activation analysis, grip strength by dynamometry, and respiratory muscle strength by using a pressure transducer. Dietary intakes of energy and protein were assessed. Significant protein depletion was noted in 51% of patients. The prevalence of protein depletion increased significantly with disease severity. Thus, multiple studies in different disease etiologies suggest that the severity of liver disease is critical in the development of malnutrition and muscle loss in cirrhosis.

CAUSES OF MALNUTRITION

Anorexia / Altered Taste / Smell

Anorexia is a major symptom associated with cirrhosis. VA Cooperative Studies indicated that over 60% of AH patients (most with cirrhosis) had anorexia, and greater severity of liver disease was

associated with more severe anorexia[2-6]. In an outpatient study of 200 liver patients from Eastern India, 100% of patients with alcoholic cirrhosis complained of anorexia[21]. Moreover, many patients with liver disease are older and anorexia is very common with aging. Furthermore, with both cirrhosis and aging, impairments in smell and taste can limit the desire to eat.

Nausea / Vomiting / Delayed Gastric Emptying

Nausea, vomiting, and abdominal bloating are important complaints frequently observed in cirrhotics. In VA alcoholic hepatitis studies, nearly 50% of subjects had nausea.[6] Similarly, in a large group of cirrhotics who were not eligible for transplantation, 58% had evidence of nausea.[22] Some of the abdominal pain, nausea and vomiting may be related to autonomic dysfunction and gastroparesis that is frequently observed in cirrhosis. These complaints may play an etiologic role in the malnutrition of chronic liver disease.

Diarrhea / Malabsorption / Bacterial Overgrowth

Diarrhea is a common clinical symptom in patients with advanced liver disease, with half of cirrhotic patients reporting diarrhea in VA Cooperative Studies.[6] Many times it is iatrogenic; secondary to the use of medicines like lactulose in the treatment and prevention of hepatic encephalopathy. Portal colopathy and generalized colonic edema due to hypoalbuminemia may also contribute to altered fecal consistency and increased stool output in patients with cirrhosis. Long standing malabsorption can also lead to continued diarrhea and malnutrition. The decline of hepatic synthetic function in cirrhosis causes hypoalbuminemia which predisposes to small intestinal bowel wall edema that can serve as a mechanical barrier to nutrient absorption. Furthermore, with severe portal hypertension portosystemic shunts can develop which can cause nutrients to bypass metabolism in the liver. All this, coupled with underling hepatic dysfunction and an increased catabolic state sets up a state of nutritional imbalance. Cholestatic liver diseases, such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) cause a dysfunction in bile acid metabolismand secretion which can result in malabsorption of fat and fat soluble vitamins. Small intestinal bacterial overgrowth (SIBO) has been frequently reported in patients with cirrhosis[23] due to delayed small intestinal transit time and an enhanced adrenergic state[24]. Due to this there is maldigestion that may predispose to the development of minimal hepatic encephalopathy[25]. Furthermore, SIBO can cause nausea and bloating which can reduce dietary intake.

Poor Food Availability / Quality / Unpalatable Diets (Na, Protein)

Patients with alcohol - or NASH-related cirrhosis frequently have unbalanced diets and may have high intake of empty calories through alcoholic or sugar-laden beverages. Cirrhosis patients are prescribed low sodium diets that may be unpalatable. Certain nutritional supplements also have palatability issues due, in part, to the taste of certain amino acid components. Unfortunately, some patients with cirrhosis are still incorrectly recommended a low-protein diet. These cumulative effects can cause an overall decrease in energy consumption and / or food quality, and possibly more importantly, a decrease in necessary protein intake.

Hormones / Cytokine Effects

Altered levels of anabolic hormones likely play a role in sarcopenia and malnutrition in cirrhosis. Testosterone levels are generally decreased in men with cirrhosis, and levels decrease as the severity of liver disease progresses.[7] Testosterone has well documented anabolic effects on non-reproductive tissue such as muscle, and it induces a dose-response increase in muscle mass. A 12-month, double-blind, placebo-controlled trial of intramuscular testosterone undecanoate in 101 men with cirrhosis and low serum testosterone documented the beneficial effect of this anabolic hormone on lean muscle mass.[26] Fat mass also was decreased, hemoglobin A1C was improved, and there were mild improvements in some quality of life measures. Cirrhotics also have reductions in other important anabolic hormones such as insulin-like growth factor 1 (IGF-1) that mediate many of the effects of growth hormone, since IGF-1 is extensively

produced in the liver. Not only are low levels of IGF-1 regularly observed in patients with chronic liver disease, but levels tend to decrease as severity of liver disease and sarcopenia increases.[8] Inflammation also appears to cause a decrease in IGF-1, and there is a negative correlation between IL-6 (proinflammatory cytokine) and IGF-1 in liver disease. Low IGF-1 levels have been shown to be harbingers of poor prognosis in subjects with decompensated liver disease[10]. Proinflammatory cytokines are frequently elevated in chronic liver diseaseand mediate muscle wasting through increased protein degradation and decreased protein synthesis.[27] Catecholamines and sympathetic over-activity can play a role in the sarcopenia of cirrhosis. Also, subsets of patients with liver disease appear to be hypermetabolic, possibly due to increased pro-inflammatory cytokine / sympathetic activity.[20, 27-29]

Complications of Liver Disease (Hepatic encephalopathy, Ascites)

Patients with complications of cirrhosis, such as ascites or hepatic encephalopathy, more often also have sarcopenia and malnutrition. Encephalopathic patients, even those with minimal encephalopathy, may be distracted and not eat appropriately. Moreover, some dietitians and physicians still counsel patients with encephalopathy to consume a low-protein diet. Patients with ascites may have abdominal fullness, gastric compression, anorexia and nausea.

Fasting for Procedures / Interruption of Feeding

Patients with cirrhosis are not only at high risk for malnutrition prior to hospitalization, but this risk also frequently escalates with hospitalization. These patients often have feedings interrupted due to fasting for procedures, such as endoscopies or radiologic tests. Feeding goals for patients in the hospital (especially the ICU) are frequently not met as observed by Arabi et al. in their study of permissive under-feeding vs. standard enteral feeding in critically-ill adults[30]. The standard group achieved only 71% of daily caloric requirement despite being in a clinical trial. The situation is probably worse for patients in routine practice.

COMPONENTS OF MALNUTRITION AND THEIR SIGNIFICANCE

A. Macronutrient Malnutrition

i. Protein -

Sarcopenia is one of the most evident clinical manifestations of malnutrition in patients with cirrhosis. Indeed, patients with advanced cirrhosis frequently have muscle wasting that has been shown to impact multiple outcome variables ranging from factors such as quality of life and fibrosis all the way to survival.[31-36] Patients with obesity can also have sarcopenia, termed "sarcopenic obesity." In sarcopenic obesity there is not only loss of muscle mass but also infiltration of ectopic fat into muscle. Both impaired protein synthesis and increased muscle breakdown have been postulated to play a role in the sarcopenia of liver disease. Multiple factors appear to mediate this sarcopenia, and metabolic pathways for sarcopenia have been detailed by Dasarathy's group and others over the past decade.[37-42] Hyperammonemia is a regular feature of cirrhosis. Hyperammonemia in skeletal muscle enhances muscle autophagy and it can impair muscle function irrespective of muscle mass.[42] It also induces an upregulation of myostatin. Myostatin is a member of the TGF-beta superfamily, and it inhibits protein synthesis by impairing mTOR signaling. Major increases in both muscle and plasma myostatin levels have been reported in cirrhosis. Other factors, such as decreased anabolic hormones (e.g., testosterone or growth hormone) and endotoxemia with increased proinflammatory cytokines, have also been postulated to play roles in the sarcopenia and an altered liver-muscle axis in cirrhosis.

An imbalance in plasma amino acid levels, with increased aromatic amino acids (AAA--phenylalanine, tyrosine, and tryptophan) and decreased branched chain amino acids (BCAA isoleucine, leucine and valine) is observed in various types of liver disease, especially more decompensated liver disease, including hepatic encephalopathy. Cirrhosis is a catabolic state, and there are frequently decreased hepatic glycogen stores. Therefore, gluconeogenesis frequently relies

on proteolysis of muscle and uses amino acids as a non-carbohydrate fuel source. Increased muscle catabolism of BCAAs is associated with decreased plasma levels but not necessarily muscle concentration. On the other hand, AAAs are metabolized in the liver, and with hepatic dysfunction, plasma concentrations are frequently elevated. The altered BCAA / AAA ratio has been postulated to play a role in hepatic encephalopathy, a concept popularized by Fischer and colleagues over 40 years ago.[43] The increased levels of AAAs due to liver disease accompanied by an increased breakdown of BCAAs would give rise to a decrease in the BCAA / AAA ratio, which is thought to play a role in an influx of AAAs into the brain, causing hepatic encephalopathy. The increased AAA levels are thought to lead to imbalances in neurotransmitter synthesis and possible accumulation of false neurotransmitters, such as octopamine. Also of interest is the impact of leucine on muscle metabolism. In studies performed on stable alcoholic cirrhotics administered a single oral branched-chain amino acid solution enriched with leucine showed improved mTOR signaling and autophagy markers.[44]

The primary management strategy for sarcopenic patients should be adequate nutrition and potential nutritional supplement support. Several studies suggest that cirrhotics consume inadequate amounts of protein. For example, VA Cooperative studies suggested that 85 gm of protein per day or more were required to maintain nitrogen balance, yet AH patients (both inpatient and outpatient) were consuming less than this.[6] Importantly, provision of excess energy in the form of non-protein calories did not positively impact malnutrition.

Cirrhotics have "anabolic resistance," and this response can also occur in the elderly or in stressed / septic ICU patients. Cirrhotics also tend to be older and frequently have infections or other inflammatory conditions, and thus, there are multiple reasons for anabolic resistance in cirrhotics. Meals enriched with branched-chain amino acids, especially leucine, may act as a trigger for protein synthesis. Consuming a stimulus of 20-35 gm high-quality protein several times a day is likely the optimal way of inducing protein synthesis in healthy individuals. Whether this translates to enhanced protein synthesis in cirrhotics is unclear. Importantly, levels of protein intake may need to be increased in both obese patients and elderly patients.

ii. Fat

Dietary fat is an important cofactor in the development and progression of fatty liver disease, both nonalcoholic (NAFLD) and alcoholic (ALD) in origin and it is an area of intense preclinical and clinical research. There are three main types of dietary fat : saturated, monounsaturated, and polyunsaturated. The difference between saturated and unsaturated fats relates to the fatty acid (FA) carbon bond structure. Saturated fatty acids (SFAs) contain no double bonds. Monounsaturated fatty acids (MUFAs) have one double bond, and polyunsaturated fatty acids (PUFAs, including ω-3 PUFAs (e.g., alpha linolenic acid (ALA, [18:3ω-3]), eicosapentaenoic acid (EPA, [20:5ω-3]) and docosahexaenoic acid (DHA, [22:6ω-3]) and ω-6 PUFAs (e.g., linoleic acid [LA, 18:2ω-6]) have more than one. FAs in the diet are also divided into short, medium and long chain FAs as assessed by the carbon chain length. There is evidence in the literature suggesting distinctive roles for different types of dietary fat in NAFLD and ALD pathogenesis. In general, dietary saturated fat is believed to promote NAFLD[45] and to protect against ALD, whereas dietary unsaturated fat is beneficial in NAFLD and exacerbates ALD. Based on epidemiological evidence, dietary intake of saturated fat (SF) is associated with lower mortality rates, whereas dietary intake of unsaturated fat (USF) is associated with a higher mortality from alcoholic cirrhosis in humans[46]. However, it is important to recognize that different SFAs (e.g., medium vs long chain SFAs) or PUFAs (e.g., ω-3 vs ω-6 PUFAs) may exert different metabolic effects. Based on current understanding it appears that amongst the SFAs, medium chain fatty acids are the more beneficial fatty acids while amongst the PUFAs the ω-3 fatty acids are more beneficial than

the ù-6 fatty acids. In fact the consumption of a diet rich in linoleic acid (ω-6 PUFA) is harmful in ALD and possibly has a deleterious effect in NAFLD too.

iii. Carbohydrate

Similar to excess fat consumption, increased carbohydrate intake has been associated with the development of fatty liver. When consumed in excess, all carbohydrates can cause obesity and fatty liver, but fructose has received special interest. The increased fructose consumption in the United States parallels the increased prevalence of obesity and NAFLD. In the US, fructose is consumed mainly as added sugars, such as sucrose and high-fructose corn syrup (HFCS), which represented 45% and 41% of the total added sugars ingested, respectively, as of 2007[47].

High fructose intake can induce a whole range of metabolic changes, including NAFLD[48-51]. Increased fructose consumption is associated with greater fibrosis severity in adult NAFLD patients[52,53]. Collectively, dietary fructose may be an important risk factor for the pathogenesis and disease progression of NAFLD.

B. Selected Micronutrient Malnutrition *(Table 2)*

i. Vitamins

Vitamin A : The liver is the major storage site for Vitamin A (> 90%), with most found in the stellate cells. Vitamin A is secreted from the liver bound to retinol binding protein (RBP). In liver disease, there can be inadequate intake of Vitamin A, impaired absorption (especially in cholestatic liver disease), altered metabolism (in part related to zinc deficiency), and poor hepatic storage related, in part, to stellate cell activation[54]. Most studies indicate that over 60% of cirrhotics have low serum Vitamin A levels, and 40% in one study had impaired dark adaptation that was not recognized by the patient.[54,55] Importantly, because RBP, the carrier protein for Vitamin A, is made in the liver, its serum concentration is frequently low in liver disease and does not increase appropriately after Vitamin A intake. This low RBP level potentially increases the risk for Vitamin A liver toxicity with Vitamin A supplementation. Thus, supplementation in patients with liver disease / injury must be undertaken with care, and patients need to be monitored for toxicity.

Vitamin D : Vitamin D deficiency is frequently observed in end-stage liver disease. In one study, 81% of cirrhotics evaluated for liver transplantation were Vitamin D deficient, and this impacts bone health. Cirrhotics are at high risk for osteoporosis both before and after liver transplantation. Moreover, Vitamin D may have multiple metabolic effects beyond bone health in liver disease, ranging from innate immune system activation to modulation of gut barrier function.

Folate : Chronic alcoholics are often folate deficient due to reduced dietary folate intake, intestinal

Table 2 : **Micronutrient Deficiencies in Alcoholic Hepatitis**

Nutrient Deficiency	Possible Manifestations
Vitamin A	Night blindness, Dry skin
Vitamin D	Bone Disease, Altered Immune and gut barrier function
Vitamin E	Possible increased susceptibility to liver injury, Oxidative stress
Folate/B_{12}	Anemia, Possible increased susceptibility to ALD, Altered methionine metabolism
Niacin	Pellegra dermatitis, Neurologic alterations, Hallucinations
Thiamine	Neurologic problems, Wernike's encephalopathy
Zinc	Skin lesions, Anorexia, Depressed wound healing, Hypogonadism, Altered immune function, Impaired night vision, Depressed mental function, Diarrhea, Increased Susceptibility to liver injury
Magnesium	Muscle cramps, Glucose intolerance
Selenium	Myopathy, Cardiomyopathy, Oxidative stress
Copper	Anemia, neutropenia, neuropathy

malabsorption, reduced liver uptake and storage, and increased urinary folate excretion.[56] In one study, folate levels were inversely associated with evidence of liver damage and with development of HCC in patients with chronic hepatitis B virus infection.[57]

Thiamine : Thiamine is absorbed in the jejunum and ileum and is transported to the liver bound to albumin via the portal circulation. Patients with chronic alcohol abuse or cirrhosis have been found to be thiamine deficient. Thiamine deficiency is especially prevalent in patients with alcoholic cirrhosis due to inadequate dietary intake and through the direct effect of ethanol on thiamine uptake from the gastrointestinal tract.[58] Thiamine deficiency can cause peripheral neuropathy or cardiac disease (beriberi) or neurologic impairment characterized by nystagmus, ophthalmoplegia, ataxia, and confusion (Wernicke's encephalopathy). Korsakoff syndrome can also develop from thiamine deficiency and is a chronic neurologic condition, usually as a consequence of Wernicke's encephalopathy, and is characterized by impaired short-term memory and confabulation with otherwise grossly normal cognition. Wernicke's encephalopathy is an acute disorder and requires emergent treatment, usually with intravenous thiamine, to prevent death and long-term neurologic complications (Korsakoff syndrome).

ii. Minerals

Zinc : Zinc deficiency or altered zinc metabolism is frequently observed in liver disease, especially ALD, and may result from decreased dietary intake, impaired absorption and increased urinary excretion, abnormal activation of certain zinc transporters.[59] Zinc deficiency may manifest itself in many ways, ranging from raised, crusting skin lesions around the eyes, nose and mouth ***(Figure 3)*** to impaired wound healing or liver regeneration, to altered mental status or to altered immune function.[59] The dose of zinc used for treatment of liver disease is usually 50 mg of elemental zinc taken with a meal to decrease the potential side effect of nausea. Intake of greater than 50 mg of elemental zinc per day can cause dose-related side

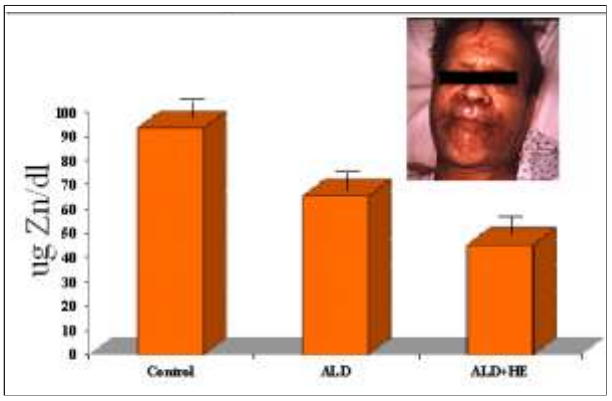

Figure 3 : **A large cohort of patients with alcoholic liver disease demonstrated that those without clinical decompensation had depressed serum zinc levels (ALD) compared with controls. Patients with decompensation and hepatic encephalopathy (HE) had the lowest serum zinc concentrations. The insert shows the classic crusting skin lesions (acrodermatitis) of severe zinc deficiency in a patient with ALD and recurrent vomiting.**

effects, such as copper deficiency, resulting from reduced copper absorption.

Magnesium : Magnesium deficiency can cause muscle cramps, a frequent complaint in patients with cirrhosis. Magnesium supplementation has been shown to reduce muscle cramps, with the dose of 400 mg of magnesium oxide frequently being used.

NUTRITIONAL RECOMMENDATIONS

a. In Patient / ICU

Patients with cirrhosis (and all stages of liver disease really) are at high risk for malnutrition during hospitalization. Multiple professional societies have established guidelines related to nutritional assessment and nutritional support for patients with liver disease. It is suggested that all liver patients admitted to the hospital, and not just to the ICU, be monitored for malnutrition because of their heightened baseline risk.

Initial assessment using simple measures such as anthropometry or Subjective Global Assessment (SGA) should be performed. Anthropometry refers to methods such as Body Mass Index (BMI) or change in body weight which are widely used to assess nutritional status. However, fluid retention

Table 3 : **Nutritional Recommendations for Patients with Liver Disease**

• Early evaluation of electrolyte disturbances
• Early nutrition assessment and regular follow-ups
• Total energy: 1.2-1.4 x resting energy expenditure or 35-40 kcal/kg BW/d
• Protein: 1.2-1.5 g/kg/d (upper level in hospital)
• Fat: 30-40% of non-protein energy
• Formulate water and electrolyte intake to individual needs, renal function, diuretic sensitivity
• Replace vitamins and minerals (avoid excessive iron, copper, and vitamin A supplementation)
• Complement daily requirements with enteral feedings (parental if enteral route otherwise contraindicated)
• Hypocaloric, high protein diet for obese subjects
• Nutrition education with dietician including nighttime snacks

with edema and / or ascites in cirrhotics can interfere with the accuracy of this method. Other anthropometric methods include the triceps skin fold (TSF) which is the width of a skin fold measured over the triceps muscle using skinfold calipers half way between the olecranon process of the ulna and acromion process of the scapula. The mid-upper arm circumference (MAC) is measured at that same midpoint using a non-stretchable measuring tape. The Mid Arm Muscle Circumference (MAMC) is derived from the TSF and MAC. The TSF reflects body fat and MAMC reflects muscle mass. Of note, these techniques also can be impacted by fluid retention[14, 60, 61].

Subjective global assessment (SGA) is a simple, bedside evaluation of nutritional status.[62] The SGA includes patient history regarding weight loss, usual dietary intake, functional capacity, gastrointestinal symptoms, and evidence of malnutrition on physical exam (loss of muscle or fat mass, or presence of edema).[63] Using this information, patients are classified as : 1) well nourished; 2) moderately malnourished; or 3) severely malnourished.

A defined approach to achieve appropriate nutritional support in patients with cirrhosis is needed as illustrated in ***Table 3.*** The use of oral nutrition supplements, including a night time snack is encouraged in patients able to consume projected energy requirements by the oral route. Protein intake is usually recommended at 1.2-1.5 g/kg BW/d. A caloric target of 35-40 kcal/kg BW/d is recommended in hospitalized non-obese patients[64].

It is important to monitor food intake because it is often underestimated. In patients with inadequate oral intake, early enteral nutrition (EN) support with a nasogastric feeding tube is especially important because it has the potential to reduce complications and length of stay, and to positively impact patient outcome. EN support should be initiated within 24-48 hours following hospitalization in patients unable to maintain oral nutritional intake. Efforts to provide > 80% of estimated or calculated goal energy and protein within 48-72 hours should be made to achieve the clinical benefit of EN.[65] A concentrated energy formula may be utilized in patients with ascites. When patients are started on EN support, they should be monitored daily for tolerance. Interrupting feeding for diagnostic tests and procedures should be minimized. Monitoring gastric residual volumes is not documented to be useful as a measure of feeding tolerance.[65] If nasogastric feeds are not tolerated, a nasojejunal tube can be placed to continue enteral nutrition.

Enteral nutrition is favored over parenteral nutrition (PN) because of cost, risk of line sepsis with parenteral nutrition and maintenance of the gut barrier function. Moreover, PN can, in some instances, cause liver disease as one of its complications. If EN is not possible, then PN can be used with the knowledge that it is important to return to the enteral route as soon as the small bowel shows evidence of recovered function. Parenteral nutrition can be started with a standard amino acid formula in amounts that are increased until nitrogen needs are met.

If patients develop hepatic encephalopathy (HE), then standard therapy with lactulose, neomycin, or rifaximin must be given. If the patient is still unable to tolerate the amount of amino acids needed to satisfy nitrogen requirements, then the standard amino acids can be replaced by a BCAA-enriched solution specifically designed for liver disease.[66, 67] It is unusual to require either PN or BCAA formulas, and the primary goal is always aggressive enteral support.

Obese, very ill patients with liver disease represent a unique nutritional challenge. These patients are predisposed to develop problems with fuel utilization which makes them more susceptible to loss of lean body mass. They are also at greater risk for insulin resistance and altered lipid metabolism. Current guidelines recommend the use of hypocaloric, high protein nutrition therapy in an attempt to preserve lean body mass, to mobilize fat stores, and to minimize the risk of overfeeding complications in these at-risk obese patients with liver disease.[65] Energy targets are low in patients with BMIs of 30-50, usually 65-70% of requirements as measured by indirect calorimetry or approximately 11-14 kcal/kg of actual body weight per day. However, protein requirements are high, usually projected at 2.0-2.5 g/kg of ideal body weight per day.[65]

b. Out Patient

Patients with cirrhosis require nutritional assessment and a nutritional plan, not only as inpatients, but also as part of long term outpatient therapy. Several studies support the concept of improved outpatient outcome with nutritional support in patients with cirrhosis. An outpatient study from Japan studied two groups of over 100 cirrhotics. The first group of patients received no dietary counseling, and the second group received both nutritional assessment and nutritional counseling by a registered dietitian every one to three months. Patients were advised to eat a late-evening snack and administered branched-chain amino acid supplements, if appropriate. Mortality was significantly lower in the subjects receiving dietary counseling / intervention at the end of the study (approximately five years). Patients with milder disease (Child-Pugh Class A) derived the most benefit.[68]

An important component of the dietary management of the patient with advanced liver disease is to minimize periods without food intake because these patients rapidly enter into "starvation mode" with decreased glucose oxidation and increased protein and fat catabolism[69]. Owen and co-workers demonstrated that cirrhoticscan develop a 'starvation' metabolic state in one night, while it takes a healthy person approximately 2-3 days of fasting to enter into a similar metabolic state. To prevent this starvation, the diet should optimally be divided into 3 meals (the first early in the morning), three snacks if possible, and one critical bedtime supplement. The early breakfast improves cognitive function in patients with subclinical (minimal) hepatic encephalopathy[70], and the bedtime supplement improves body protein stores / muscle mass. The improvement in muscle mass with nighttime supplements was convincingly documented by Plank, et al. who randomized 103 cirrhotic patients to receive two cans of Ensure Plus (710 kcal with 26g of protein) or two cans of Diabetic Resource (500 kcal with 30g of protein) either during the day or at bedtime, for a total of 12 months[71]. The bedtime supplement group showed a gain in muscle mass over a 12-month period while a similar improvement was not seen in the other group, which consumed the daytime supplement. Energy and protein intake was increased by a similar amount in both groups. This benefit was observed not only in decompensated but also in compensated Child's A cirrhosis. There was also significant improvement in quality of life for subjects eating the nighttime snack compared to the daytime snack. This important study confirms similar results from several shorter or smaller trials. Thus, nighttime snacks are vital for helping to maintain muscle mass and quality of life.

Unfortunately, there is a long tradition of protein restriction for patients with advanced liver disease who also have hepatic encephalopathy (HE). This tradition has no solid scientific basis, and multiple studies refute this approach. Cordoba, et al., in a

prospective randomized study, treated 30 cirrhotic patients who suffered episodic overt hepatic encephalopathy with either a low-protein enteral formula or a normal protein formula from the first day. The incidence of episodes of hepatic encephalopathy was similar with both formulas.[72] In a second study, Gheorghe, et al. treated 153 consecutive cirrhotic patients with overt HE with a diet providing 30 kcal/kg/day and 1.2 g protein/kg/day. Most patients showed improvement in their HE, with the best results seen in the patients with more severe HE.[73] The HE should be treated with lactulose and with rifaximin, if needed. If the HE persists, despite maximal medical therapy and evaluation for other causes of changes in mentation, then protein intake can be decreased to the maximal tolerated, and a BCAA - enriched formula supplement can be administered to complete the nitrogen needs.

CONCLUSIONS :

There is no standardized definition of malnutrition in the setting of cirrhosis, but it generally represents a state of nutritional imbalance that occurs with undernutrition (inadequate protein/calorie intake) leading to sarcopenia, or over-nutrition due to excess caloric intake (fat and/or carbohydrate) leading to sarcopenic obesity. Each patient should have a nutritional plan as detailed above and should undergo follow-up nutritional assessment to monitor progress.

References :

1. Patek AJ, Jr., Post J, et al. Dietary treatment of cirrhosis of the liver; results in 124 patients observed during a 10 year period. J Am Med Assoc. 1948;138(8):543-9. Epub 1948/10/23. PubMed PMID: 18886770.
2. Mendenhall C, Roselle GA, Gartside P, Moritz T. Relationship of protein calorie malnutrition to alcoholic liver disease: a reexamination of data from two Veterans Administration Cooperative Studies. Alcohol Clin Exp Res. 1995;19(3):635-41. Epub 1995/06/01. PubMed PMID: 7573786.
3. Mendenhall CL, Anderson S, Weesner RE, Goldberg SJ, Crolic KA. Protein-calorie malnutrition associated with alcoholic hepatitis. Veterans Administration Cooperative Study Group on Alcoholic Hepatitis. Am J Med. 1984;76(2):211-22. Epub 1984/02/01. PubMed PMID: 6421159.
4. Mendenhall CL, Moritz TE, Roselle GA, Morgan TR, Nemchausky BA, Tamburro CH, Schiff ER, McClain CJ, Marsano LS, Allen JI, et al. Protein energy malnutrition in severe alcoholic hepatitis: diagnosis and response to treatment. The VA Cooperative Study Group #275. JPEN J Parenter Enteral Nutr. 1995;19(4):258-65. Epub 1995/07/01. doi: 10.1177/0148607195019004258. PubMed PMID: 8523623.
5. Mendenhall CL, Tosch T, Weesner RE, Garcia-Pont P, Goldberg SJ, Kiernan T, Seeff LB, Sorell M, Tamburro C, Zetterman R, et al. VA cooperative study on alcoholic hepatitis. II: Prognostic significance of protein-calorie malnutrition. Am J Clin Nutr. 1986;43(2):213-8. Epub 1986/02/01. doi: 10.1093/ajcn/43.2.213. PubMed PMID: 3080866.
6. Mendenhall CL, Moritz TE, Roselle GA, Morgan TR, Nemchausky BA, Tamburro CH, Schiff ER, McClain CJ, Marsano LS, Allen JI, et al. A study of oral nutritional support with oxandrolone in malnourished patients with alcoholic hepatitis: results of a Department of Veterans Affairs cooperative study. Hepatology. 1993;17(4):564-76. Epub 1993/04/01. PubMed PMID: 8477961.
7. Sinclair M, Grossmann M, Gow PJ, Angus PW. Testosterone in men with advanced liver disease: abnormalities and implications. J Gastroenterol Hepatol. 2015;30(2):244-51. Epub 2014/08/05. doi: 10.1111/jgh.12695. PubMed PMID: 25087838.
8. Bonefeld K, Moller S. Insulin-like growth factor-I and the liver. Liver Int. 2011;31(7):911-9. Epub 2011/07/08. doi: 10.1111/j.1478-3231.2010.02428.x. PubMed PMID: 21733081.
9. Arturi F, Succurro E, Procopio C, Pedace E, Mannino GC, Lugara M, Procopio T, Andreozzi F, Sciacqua A, Hribal ML, Perticone F, Sesti G. Nonalcoholic fatty liver disease is associated with low circulating levels of insulin-like growth factor-I. J Clin Endocrinol Metab. 2011;96(10):E1640-4. Epub 2011/08/06. doi: 10.1210/jc.2011-1227. PubMed PMID: 21816784.
10. Moller S, Becker U, Juul A, Skakkebaek NE, Christensen E. Prognostic value of insulinlike growth factor I and its binding protein in patients with alcohol-induced liver disease. EMALD group. Hepatology. 1996;23(5):1073-8. Epub 1996/05/01. doi: 10.1002/hep.510230521. PubMed PMID: 8621136.
11. Kearns PJ, Young H, Garcia G, Blaschke T, O'Hanlon G, Rinki M, Sucher K, Gregory P. Accelerated improvement of alcoholic liver disease with enteral nutrition. Gastroenterology. 1992;102(1):200-5. Epub 1992/01/01. PubMed PMID: 1727754.
12. Cabre E, Rodriguez-Iglesias P, Caballeria J, Quer JC, Sanchez-Lombrana JL, Pares A, Papo M, Planas R, Gassull MA. Short- and long-term outcome of severe alcohol-induced hepatitis treated with steroids or enteral nutrition: a multicenter randomized trial. Hepatology. 2000;32(1):36-42. Epub 2000/06/28. doi: 10.1053/jhep.2000.8627. PubMed PMID: 10869286.
13. Moreno C, Deltenre P, Senterre C, Louvet A, Gustot T, Bastens B, Hittelet A, Piquet MA, Laleman W, Orlent H, Lasser L, Serste T, Starkel P, De Koninck X, Negrin Dastis S, Delwaide J, Colle I, de Galocsy C, Francque S, Langlet P, Putzeys V, Reynaert H, Degre D, Trepo E. Intensive Enteral Nutrition Is Ineffective for Patients With Severe Alcoholic Hepatitis Treated With Corticosteroids. Gastroenterology. 2016;150(4):903-10 e8. Epub 2016/01/15. doi: 10.1053/j.gastro.2015.12.038. PubMed PMID: 26764182.
14. Antonow DR, McClain CJ. Nutrition and Alcoholism. In: Tarter RE, van Thiel DH, editors. Alcohol and the Brain: Chronic Effects. Boston, MA: Springer US; 1985.
15. Sarin SK, Dhingra N, Bansal A, Malhotra S, Guptan RC. Dietary and nutritional abnormalities in alcoholic liver disease: a comparison with chronic alcoholics without liver disease. Am J Gastroenterol. 1997;92(5):777-83. Epub 1997/05/01. PubMed PMID: 9149184.
16. Caregaro L, Alberino F, Amodio P, Merkel C, Bolognesi M, Angeli P, Gatta A. Malnutrition in alcoholic and virus-related cirrhosis. Am J Clin Nutr. 1996;63(4):602-9. Epub 1996/04/01. doi: 10.1093/ajcn/63.4.602. PubMed PMID: 8599326.

17. Lolli R, Marchesini G, Bianchi G, Fabbri A, Bugianesi E, Zoli M, Pisi E. Anthropometric assessment of the nutritional status of patients with liver cirrhosis in an Italian population. Ital J Gastroenterol. 1992;24(8):429-35. Epub 1992/10/01. PubMed PMID: 1421444.
18. Thuluvath PJ, Triger DR. Autonomic neuropathy and chronic liver disease. Q J Med. 1989;72(268):737-47. Epub 1989/08/01. PubMed PMID: 2602555.
19. DiCecco SR, Wieners EJ, Wiesner RH, Southorn PA, Plevak DJ, Krom RA. Assessment of nutritional status of patients with end-stage liver disease undergoing liver transplantation. Mayo Clin Proc. 1989;64(1):95-102. Epub 1989/01/01. PubMed PMID: 2492064.
20. Peng S, Plank LD, McCall JL, Gillanders LK, McIlroy K, Gane EJ. Body composition, muscle function, and energy expenditure in patients with liver cirrhosis: a comprehensive study. Am J Clin Nutr. 2007;85(5):1257-66. Epub 2007/05/11. doi: 10.1093/ajcn/85.5.1257. PubMed PMID: 17490961.
21. Ray S, Khanra D, Sonthalia N, Kundu S, Biswas K, Talukdar A, Saha M, Bera H. Clinico-biochemical correlation to histological findings in alcoholic liver disease: a single centre study from eastern India. J Clin Diagn Res. 2014;8(10):MC01-5. Epub 2014/12/06. doi: 10.7860/JCDR/2014/8763.4968. PubMed PMID: 25478382; PMCID: PMC4253200.
22. Poonja Z, Brisebois A, van Zanten SV, Tandon P, Meeberg G, Karvellas CJ. Patients with cirrhosis and denied liver transplants rarely receive adequate palliative care or appropriate management. Clin Gastroenterol Hepatol. 2014;12(4):692-8. Epub 2013/08/28. doi: 10.1016/j.cgh.2013.08.027. PubMed PMID: 23978345.
23. Chesta J, Silva M, Thompson L, del Canto E, Defilippi C. [Bacterial overgrowth in small intestine in patients with liver cirrhosis]. Rev Med Chil. 1991;119(6):626-32. Epub 1991/06/01. PubMed PMID: 1844365.
24. Stewart JJ, Battarbee HD, Farrar GE, Betzing KW. Intestinal myoelectrical activity and transit time in chronic portal hypertension. Am J Physiol. 1992;263(4 Pt 1):G474-9. Epub 1992/10/01. doi: 10.1152/ajpgi.1992.263.4.G474. PubMed PMID: 1415706.
25. Zhang Y, Feng Y, Cao B, Tian Q. The effect of small intestinal bacterial overgrowth on minimal hepatic encephalopathy in patients with cirrhosis. Arch Med Sci. 2016;12(3):592-6. Epub 2016/06/10. doi: 10.5114/aoms.2015.55675. PubMed PMID: 27279853; PMCID: PMC4889679.
26. Sinclair M, Grossmann M, Hoermann R, Angus PW, Gow PJ. Testosterone therapy increases muscle mass in men with cirrhosis and low testosterone: A randomised controlled trial. J Hepatol. 2016;65(5):906-13. Epub 2016/10/19. doi: 10.1016/j.jhep.2016.06.007. PubMed PMID: 27312945.
27. Jeejeebhoy KN. Malnutrition, fatigue, frailty, vulnerability, sarcopenia and cachexia: overlap of clinical features. Curr Opin Clin Nutr Metab Care. 2012;15(3):213-9. Epub 2012/03/28. doi: 10.1097/MCO.0b013e328352694f. PubMed PMID: 22450775.
28. John WJ, Phillips R, Ott L, Adams LJ, McClain CJ. Resting energy expenditure in patients with alcoholic hepatitis. JPEN J Parenter Enteral Nutr. 1989;13(2):124-7. Epub 1989/03/01. doi: 10.1177/0148607189013002124. PubMed PMID: 2709599.
29. Prieto-Frias C, Conchillo M, Payeras M, Inarrairaegui M, Davola D, Fruhbeck G, Salvador J, Rodriguez M, Richter JA, Mugueta C, Gil MJ, Herrero I, Prieto J, Sangro B, Quiroga J. Factors related to increased resting energy expenditure in men with liver cirrhosis. Eur J Gastroenterol Hepatol. 2016;28(2):139-45. Epub 2015/11/13. doi: 10.1097/MEG.0000000000000516. PubMed PMID: 26560751.
30. Arabi YM, Aldawood AS, Solaiman O. Permissive Underfeeding or Standard Enteral Feeding in Critical Illness. N Engl J Med. 2015;373(12):1175-6. Epub 2015/09/17. doi: 10.1056/NEJMc1509259. PubMed PMID: 26376142.
31. Merli M, Giusto M, Lucidi C, Giannelli V, Pentassuglio I, Di Gregorio V, Lattanzi B, Riggio O. Muscle depletion increases the risk of overt and minimal hepatic encephalopathy: results of a prospective study. Metab Brain Dis. 2013;28(2):281-4. Epub 2012/12/12. doi: 10.1007/s11011-012-9365-z. PubMed PMID: 23224378.
32. Huisman EJ, Trip EJ, Siersema PD, van Hoek B, van Erpecum KJ. Protein energy malnutrition predicts complications in liver cirrhosis. Eur J Gastroenterol Hepatol. 2011;23(11):982-9. Epub 2011/10/06. doi: 10.1097/MEG.0b013e32834aa4bb. PubMed PMID: 21971339.
33. Hanai T, Shiraki M, Nishimura K, Ohnishi S, Imai K, Suetsugu A, Takai K, Shimizu M, Moriwaki H. Sarcopenia impairs prognosis of patients with liver cirrhosis. Nutrition. 2015;31(1):193-9. Epub 2014/12/03. doi: 10.1016/j.nut.2014.07.005. PubMed PMID: 25441595.
34. Sinclair M, Gow PJ, Grossmann M, Angus PW. Review article: sarcopenia in cirrhosis--aetiology, implications and potential therapeutic interventions. Aliment Pharmacol Ther. 2016;43(7):765-77. Epub 2016/02/06. doi: 10.1111/apt.13549. PubMed PMID: 26847265.
35. Hara N, Iwasa M, Sugimoto R, Mifuji-Moroka R, Yoshikawa K, Terasaka E, Hattori A, Ishidome M, Kobayashi Y, Hasegawa H, Iwata K, Takei Y. Sarcopenia and Sarcopenic Obesity Are Prognostic Factors for Overall Survival in Patients with Cirrhosis. Intern Med. 2016;55(8):863-70. Epub 2016/04/19. doi: 10.2169/internalmedicine.55.5676. PubMed PMID: 27086797.
36. Lee YH, Kim SU, Song K, Park JY, Kim DY, Ahn SH, Lee BW, Kang ES, Cha BS, Han KH. Sarcopenia is associated with significant liver fibrosis independently of obesity and insulin resistance in nonalcoholic fatty liver disease: Nationwide surveys (KNHANES 2008-2011)(1527-3350 (Electronic)).
37. Dasarathy S. Cause and management of muscle wasting in chronic liver disease. Curr Opin Gastroenterol. 2016;32(3):159-65. Epub 2016/03/15. doi: 10.1097/MOG.0000000000000261. PubMed PMID: 26974417; PMCID: PMC5653274.
38. Dasarathy S. Posttransplant sarcopenia: an underrecognized early consequence of liver transplantation. Dig Dis Sci. 2013;58(11):3103-11. Epub 2013/08/06. doi: 10.1007/s10620-013-2791-x. PubMed PMID: 23912247; PMCID: PMC4066193.
39. Dasarathy S, Merli M. Sarcopenia from mechanism to diagnosis and treatment in liver disease. J Hepatol. 2016;65(6):1232-44. Epub 2016/08/16. doi: 10.1016/j.jhep.2016.07.040. PubMed PMID: 27515775; PMCID: PMC5116259.
40. Davuluri G, Allawy A, Thapaliya S, Rennison JH, Singh D, Kumar A, Sandlers Y, Van Wagoner DR, Flask CA, Hoppel C, Kasumov T, Dasarathy S. Hyperammonaemia-induced skeletal muscle mitochondrial dysfunction results in cataplerosis and oxidative stress. J Physiol. 2016;594(24):7341-60. Epub 2016/10/25. doi: 10.1113/JP272796. PubMed PMID: 27558544; PMCID: PMC5157075.
41. Davuluri G, Krokowski D, Guan BJ, Kumar A, Thapaliya S, Singh D, Hatzoglou M, Dasarathy S. Metabolic adaptation of skeletal muscle to hyperammonemia drives the beneficial effects of l-leucine in cirrhosis. J Hepatol. 2016;65(5):929-37. Epub 2016/10/19. doi: 10.1016/j.jhep.2016.06.004. PubMed PMID: 27318325; PMCID: PMC5069194.

42. McDaniel J, Davuluri G, Hill EA, Moyer M, Runkana A, Prayson R, van Lunteren E, Dasarathy S. Hyperammonemia results in reduced muscle function independent of muscle mass. Am J Physiol Gastrointest Liver Physiol. 2016;310(3):G163-70. Epub 2015/12/05. doi: 10.1152/ajpgi.00322.2015. PubMed PMID: 26635319; PMCID: PMC4971815.
43. Fischer JE, Rosen HM, Ebeid AM, James JH, Keane JM, Soeters PB. The effect of normalization of plasma amino acids on hepatic encephalopathy in man. Surgery. 1976;80(1):77-91. Epub 1976/07/01. PubMed PMID: 818729.
44. Tsien C, Davuluri G, Singh D, Allawy A, Ten Have GA, Thapaliya S, Schulze JM, Barnes D, McCullough AJ, Engelen MP, Deutz NE, Dasarathy S. Metabolic and molecular responses to leucine-enriched branched chain amino acid supplementation in the skeletal muscle of alcoholic cirrhosis. Hepatology. 2015;61(6):2018-29. Epub 2015/01/24. doi: 10.1002/hep.27717. PubMed PMID: 25613922; PMCID: PMC4441611.
45. Leamy AK, Egnatchik RA, Young JD. Molecular mechanisms and the role of saturated fatty acids in the progression of non-alcoholic fatty liver disease. Prog Lipid Res. 2013;52(1):165-74. Epub 2012/11/28. doi: 10.1016/j.plipres.2012.10.004. PubMed PMID: 23178552; PMCID: PMC3868987.
46. Nanji AA, French SW. Dietary factors and alcoholic cirrhosis. Alcohol Clin Exp Res. 1986;10(3):271-3. Epub 1986/06/01. PubMed PMID: 3526949.
47. Tappy L, Le KA. Metabolic effects of fructose and the worldwide increase in obesity. Physiol Rev. 2010;90(1):23-46. Epub 2010/01/21. doi: 10.1152/physrev.00019.2009. PubMed PMID: 20086073.
48. Spruss A, Kanuri G, Wagnerberger S, Haub S, Bischoff SC, Bergheim I. Toll-like receptor 4 is involved in the development of fructose-induced hepatic steatosis in mice. Hepatology. 2009;50(4):1094-104. Epub 2009/07/29. doi: 10.1002/hep.23122. PubMed PMID: 19637282.
49. Wada T, Kenmochi H, Miyashita Y, Sasaki M, Ojima M, Sasahara M, Koya D, Tsuneki H, Sasaoka T. Spironolactone improves glucose and lipid metabolism by ameliorating hepatic steatosis and inflammation and suppressing enhanced gluconeogenesis induced by high-fat and high-fructose diet. Endocrinology. 2010;151(5):2040-9. Epub 2010/03/10. doi: 10.1210/en.2009-0869. PubMed PMID: 20211973.
50. Kelley GL, Allan G, Azhar S. High dietary fructose induces a hepatic stress response resulting in cholesterol and lipid dysregulation. Endocrinology. 2004;145(2):548-55. Epub 2003/10/25. doi: 10.1210/en.2003-1167. PubMed PMID: 14576175.
51. Park OJ, Cesar D, Faix D, Wu K, Shackleton CH, Hellerstein MK. Mechanisms of fructose-induced hypertriglyceridaemia in the rat. Activation of hepatic pyruvate dehydrogenase through inhibition of pyruvate dehydrogenase kinase. Biochem J. 1992;282 (Pt 3):753-7. Epub 1992/03/15. PubMed PMID: 1554357; PMCID: PMC1130852.
52. Abdelmalek MF, Lazo M, Horska A, Bonekamp S, Lipkin EW, Balasubramanyam A, Bantle JP, Johnson RJ, Diehl AM, Clark JM, Fatty Liver Subgroup of Look ARG. Higher dietary fructose is associated with impaired hepatic adenosine triphosphate homeostasis in obese individuals with type 2 diabetes. Hepatology. 2012;56(3):952-60. Epub 2012/04/03. doi: 10.1002/hep.25741. PubMed PMID: 22467259; PMCID: PMC3406258.
53. Abdelmalek MF, Suzuki A, Guy C, Unalp-Arida A, Colvin R, Johnson RJ, Diehl AM, Nonalcoholic Steatohepatitis Clinical Research N. Increased fructose consumption is associated with fibrosis severity in patients with nonalcoholic fatty liver disease. Hepatology. 2010;51(6):1961-71. Epub 2010/03/20. doi: 10.1002/hep.23535. PubMed PMID: 20301112; PMCID: PMC2922495.
54. Chaves GV, Peres WA, Goncalves JC, Ramalho A. Vitamin A and retinol-binding protein deficiency among chronic liver disease patients. Nutrition. 2015;31(5):664-8. Epub 2015/04/04. doi: 10.1016/j.nut.2014.10.016. PubMed PMID: 25837210.
55. Abbott-Johnson WJ, Kerlin P, Abiad G, Clague AE, Cuneo RC. Dark adaptation in vitamin A-deficient adults awaiting liver transplantation: improvement with intramuscular vitamin A treatment. Br J Ophthalmol. 2011;95(4):544-8. Epub 2010/08/10. doi: 10.1136/bjo.2009.179176. PubMed PMID: 20693552.
56. Medici V, Halsted CH. Folate, alcohol, and liver disease. Mol Nutr Food Res. 2013;57(4):596-606. Epub 2012/11/09. doi: 10.1002/mnfr.201200077. PubMed PMID: 23136133; PMCID: PMC3736728.
57. Welzel TM, Katki HA, Sakoda LC, Evans AA, London WT, Chen G, O'Broin S, Shen FM, Lin WY, McGlynn KA. Blood folate levels and risk of liver damage and hepatocellular carcinoma in a prospective high-risk cohort. Cancer Epidemiol Biomarkers Prev. 2007;16(6):1279-82. Epub 2007/06/06. doi: 10.1158/1055-9965.EPI-06-0853. PubMed PMID: 17548697.
58. Hoyumpa AM, Jr. Mechanisms of thiamin deficiency in chronic alcoholism. Am J Clin Nutr. 1980;33(12):2750-61. Epub 1980/12/01. doi: 10.1093/ajcn/33.12.2750. PubMed PMID: 6254354.
59. Mohammad MK, Zhou Z, Cave M, Barve A, McClain CJ. Zinc and liver disease. Nutr Clin Pract. 2012;27(1):8-20. Epub 2012/02/07. doi: 10.1177/0884533611433534. PubMed PMID: 22307488.
60. Johnson TM, Overgard EB, Cohen AE, DiBaise JK. Nutrition assessment and management in advanced liver disease. Nutr Clin Pract. 2013;28(1):15-29. Epub 2013/01/16. doi: 10.1177/0884533612469027. PubMed PMID: 23319353.
61. Bharadwaj S, Ginoya S, Tandon P, Gohel TD, Guirguis J, Vallabh H, Jevenn A, Hanouneh I. Malnutrition: laboratory markers vs nutritional assessment. Gastroenterol Rep (Oxf). 2016;4(4):272-80. Epub 2016/05/14. doi: 10.1093/gastro/gow013. PubMed PMID: 27174435; PMCID: PMC5193064.
62. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, Jeejeebhoy KN. What is subjective global assessment of nutritional status? JPEN J Parenter Enteral Nutr. 1987;11(1):8-13. Epub 1987/01/01. doi: 10.1177/014860718701100108. PubMed PMID: 3820522.
63. da Silva Fink J, de Mello ED, Beghetto MG, Luft VC, de Jezus Castro SM, de Mello PD. Nutritional Assessment Score: A new tool derived from Subjective Global Assessment for hospitalized adults(1532-1983 (Electronic)).
64. Plauth M, Cabre E, Riggio O, Assis-Camilo M, Pirlich M, Kondrup J, Dgem, Ferenci P, Holm E, Vom Dahl S, Muller MJ, Nolte W, Espen. ESPEN Guidelines on Enteral Nutrition: Liver disease. Clin Nutr. 2006;25(2):285-94. Epub 2006/05/19. doi: 10.1016/j.clnu.2006.01.018. PubMed PMID: 16707194.
65. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, McCarthy MS, Davanos E, Rice TW, Cresci GA, Gervasio JM, Sacks GS, Roberts PR, Compher C, Society of Critical Care M, American Society for P, Enteral N. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2016;40(2):159-211. Epub 2016/01/17. doi: 10.1177/0148607115621863. PubMed PMID: 26773077.

66. Marchesini G, Bianchi G, Merli M, Amodio P, Panella C, Loguercio C, Rossi Fanelli F, Abbiati R, Italian BSG. Nutritional supplementation with branched-chain amino acids in advanced cirrhosis: a double-blind, randomized trial. Gastroenterology. 2003;124(7):1792-801. Epub 2003/06/14. PubMed PMID: 12806613.

67. Charlton M. Branched-chain amino acid-enriched supplements as therapy for liver disease: Rasputin lives. Gastroenterology. 2003;124(7):1980-2. Epub 2003/06/14. PubMed PMID: 12806634.

68. Iwasa M, Iwata K, Hara N, Hattori A, Ishidome M, Sekoguchi-Fujikawa N, Mifuji-Moroka R, Sugimoto R, Fujita N, Kobayashi Y, Takei Y. Nutrition therapy using a multidisciplinary team improves survival rates in patients with liver cirrhosis. Nutrition. 2013;29(11-12):1418-21. Epub 2013/10/10. doi: 10.1016/j.nut.2013.05.016. PubMed PMID: 24103520.

69. Owen OE, Trapp VE, Reichard GA, Jr., Mozzoli MA, Moctezuma J, Paul P, Skutches CL, Boden G. Nature and quantity of fuels consumed in patients with alcoholic cirrhosis. J Clin Invest. 1983;72(5):1821-32. Epub 1983/11/01. doi: 10.1172/JCI111142. PubMed PMID: 6630528; PMCID: PMC370471.

70. Vaisman N, Katzman H, Carmiel-Haggai M, Lusthaus M, Niv E. Breakfast improves cognitive function in cirrhotic patients with cognitive impairment. Am J Clin Nutr. 2010;92(1):137-40. Epub 2010/05/07. doi: 10.3945/ajcn.2010.29211. PubMed PMID: 20444959.

71. Plank LD, Gane EJ, Peng S, Muthu C, Mathur S, Gillanders L, McIlroy K, Donaghy AJ, McCall JL. Nocturnal nutritional supplementation improves total body protein status of patients with liver cirrhosis: a randomized 12-month trial. Hepatology. 2008;48(2):557-66. Epub 2008/07/16. doi: 10.1002/hep.22367. PubMed PMID: 18627001.

72. Cordoba J, Lopez-Hellin J, Planas M, Sabin P, Sanpedro F, Castro F, Esteban R, Guardia J. Normal protein diet for episodic hepatic encephalopathy: results of a randomized study. J Hepatol. 2004;41(1):38-43. Epub 2004/07/13. doi: 10.1016/j.jhep.2004.03.023. PubMed PMID: 15246205.

73. Gheorghe L, Iacob R, Vadan R, Iacob S, Gheorghe C. Improvement of hepatic encephalopathy using a modified high-calorie high-protein diet. Rom J Gastroenterol. 2005;14(3):231-8. Epub 2005/10/04. PubMed PMID: 16200232.