

## Protein Recommendations for Older Adults with Cirrhosis: A Review

Jennifer Iames, John V Logomarsino

Jennifer Iames, MS, RD, Central Michigan University, 5115 Troy, Urbana Rd, Casstown, OH 45312, the United States

John V Logomarsino, PhD, RD, LD/N, Central Michigan University, Dept of Human Environmental Studies, Mt. Pleasant, MI 48859, the United States

Correspondence to: Jennifer Iames, 5115 Troy Urbana Rd, Casstown, OH 45312, the United States

Email: [Henry1jn@cmich.edu](mailto:Henry1jn@cmich.edu)

Telephone: +1-937-765-0731

Fax: +1-937-723-5859

Received: January 1, 2015

Revised: January 30, 2015

Accepted: February 2, 2015

Published online: April 21, 2015

### ABSTRACT

Protein intake has a key role in liver cirrhosis in older adults. However, types and amounts of protein intake in cirrhosis have been controversial. The aim of this paper is to investigate the optimal protein intake for management of cirrhosis and prevention of hepatic encephalopathy in older adults. Protein restriction of 0.6 g/kg/d has traditionally been used as medical nutrition therapy in liver cirrhosis. However, recent evidence has shown that protein restrictions have many negative consequences for older adults with cirrhosis. Current research indicates protein intakes of 1.2-1.5 g/kg/d in liver cirrhosis; however, many older adults do not consume this amount. Strategies to help increase protein intake and manage cirrhosis include ensuring adequate protein at every meal through either regular intake or supplementation, protein supplementation prior to bedtime or overnight, and supplementation with branched-chain amino acids. An emphasis on vegetable protein versus animal protein is probably not an advantageous treatment option because of lack of conclusive evidence regarding benefits and potential negative side effects.

© 2015 ACT. All rights reserved.

**Key words:** Liver cirrhosis; Dietary Protein; Aged

Iames J, Logomarsino JV. Protein Recommendations for Older Adults with Cirrhosis: A Review. *Journal of Gastroenterology and Hepatology Research* 2015; 4(4): 1546-1556 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/1014>

### INTRODUCTION

Nutrition management is a critical component of managing cirrhosis. Poor nutritional status in cirrhosis is strongly associated with life-threatening complications, deterioration of liver function, and decreased survival<sup>[1,2]</sup>. This is especially true in older adults that are already at greater risk of malnutrition, poor quality of life, and increased morbidity and mortality<sup>[3-5]</sup>. Due to the fact that nutrition plays such a critical role in cirrhosis and older adulthood, it would seem that protein intake would be encouraged. However, this has not always been the case.

Types and amounts of protein intake in cirrhosis have long been debated with various recommendations. A review completed in 2013 by Bauer *et al*<sup>[6]</sup> specifically addressed protein needs in both healthy older adults and particular acute and chronic diseases; however cirrhosis was not addressed<sup>[6]</sup>. The aim of this paper is to review the different protein recommendations for management of cirrhosis and prevention of hepatic encephalopathy in older adults. A literature search was conducted in PubMed and CINAHL using the search terms dietary protein, older adults, liver cirrhosis, hepatic encephalopathy, sarcopenia, nutrition, and age 65+. Studies were considered for inclusion if they were written in English and had relevant applications to older adults with cirrhosis. Additional publications were identified by searching through the reference lists of retrieved articles.

#### Development of cirrhosis in older adults

In 2010, chronic liver disease was the fifth leading cause of death in men for all age groups in the United States<sup>[7]</sup>; in 1989 it was the ninth leading cause of death<sup>[8]</sup>, suggesting an overall increase in prevalence. In addition, the most rapidly increasing population of patients with cirrhosis is over the age of fifty<sup>[9]</sup>. This is not surprising given the fact that many characteristics of old age lend themselves to development

and progression of chronic liver disease and cirrhosis.

There are several different factors that naturally occur in older adulthood that help contribute to the development of chronic liver disease and cirrhosis. After reaching maximum size in early adulthood, the liver steadily decreases in both size and the amount of blood flow it receives, leading to decreased function and efficiency over time<sup>[10]</sup>. Also, increased ammonia production and bacterial overgrowth are common in older adulthood, both of which are thought to play a key role in development of hepatic encephalopathy<sup>[11]</sup>. Older adults tend to have chronic constipation, intestinal dysmotility, and increased colonic transit time, which predisposes them to increased ammonia production<sup>[12]</sup>. Finally, older adulthood is associated with a higher incidence of diabetes, which is strongly correlated to progression of liver cirrhosis<sup>[13]</sup>.

#### Pathogenesis of malnutrition in older adults with cirrhosis

It is estimated that 20% of patients with compensated cirrhosis and 60% of patients with decompensated cirrhosis have malnutrition<sup>[14]</sup>. In older adults, protein energy malnutrition is associated with high health care costs, increased frequency of infection and bedsores, increased morbidity and mortality, and poor physical functioning<sup>[4,5]</sup>. In canine trials, poor nutritional status has been shown to encourage the development of hepatic encephalopathy<sup>[15]</sup>. In addition, malnutrition in cirrhosis is positively associated with old age<sup>[14]</sup>. Multiple factors help contribute to the development of malnutrition in older adults with cirrhosis, including inadequate intake, altered absorption, sarcopenia, and altered metabolism. All causes must be explored and taken into consideration when developing treatment and prevention strategies.

In older adults, food intake naturally decreases over time<sup>[16]</sup>, which promotes the development of malnutrition. Other reasons for decreased intake in both older adults and patient with cirrhosis include anorexia, early satiety secondary to ascites or increased leptin, altered mental status, unpalatable diets, physical dependence, polypharmacy, altered taste perceptions, and inadequate nutrient intake during treatments or testing<sup>[3,4,16-18]</sup>.

Altered absorption is another factor that encourages development of malnutrition. In cirrhosis, it is caused by small bowel bacterial overgrowth, imbalance of gut microflora, impaired pancreatic exocrine function, portosystemic shunting, bile acid deficiency, and competition with medications<sup>[19-21]</sup>. One study that examined the fecal content of patients with cirrhosis and healthy controls found evidence of impaired fatty acid metabolism, which may further contribute to malabsorption<sup>[19]</sup>. Furthermore, reduction of gastric acid and atrophic gastritis are both common in older adults and can further contribute to malabsorption, especially if they are precipitated by bacterial overgrowth<sup>[4]</sup>.

Altered metabolism is another major contributing factor in the development of malnutrition in cirrhosis. One of the main features of cirrhosis is insulin resistance. Insulin resistance leads to decreased glucose disposal and glycogen formation and thus overall diminished hepatic and muscle glycogen stores. This leads to increased fat oxidation and gluconeogenesis with protein catabolism from muscle for energy use. There is also an overall loss of protein from reduced synthesis of urea and hepatic proteins, as well as increased urinary nitrogen excretion<sup>[20,22-27]</sup>. Furthermore, it has been shown that healthy patients require 3 days of fasting to enter a starvation state whereas patients with cirrhosis will switch to gluconeogenesis from amino acids after only an overnight fast<sup>[28]</sup>.

Sarcopenia, or loss of skeletal muscle mass, is the most common complication in cirrhosis and is thought to be a major contributor to the development of malnutrition in cirrhosis<sup>[29]</sup>. Development of

sarcopenia is accelerated by physical inactivity and inadequate protein intake, both of which are common in cirrhosis and older adults<sup>[30]</sup>. It has been shown that 7.2-8.6% of older adult women consume protein levels below 0.66 g/kg/d and approximately 10-25% of older adults consume less than the recommended dietary allowance of protein of 0.8 g/kg/d<sup>[31]</sup>. After the age of 50 there is a 1% loss of muscle mass per year<sup>[9]</sup>. In addition, decreased physical activity and bed rest associated with hospitalization are very common in older adulthood and cirrhosis and contribute to loss of muscle mass<sup>[32]</sup>. Loss of lean tissue in healthy older adults during bed rest far exceeds the losses experienced by younger adults<sup>[32]</sup>. In cirrhosis as in older adults, skeletal muscle protein synthesis is decreased and impaired compared to younger healthy individuals, whereas total muscle protein breakdown is increased, further contributing to decreased muscle mass<sup>[14,16]</sup>.

Hypermetabolism does not occur in every case of cirrhosis, but it has been shown to occur in 16-34% of cases, which further contributes to malnutrition<sup>[17,18]</sup>. Furthermore, increased protein is required to offset inflammatory and catabolic conditions associated with chronic and acute diseases<sup>[34]</sup>, and inflammation has been noted in patients with even minimal hepatic encephalopathy<sup>[28]</sup>. Experts currently recommend protein intakes of 1.2-1.5 g/kg/day to maintain muscle mass and physical functioning in older adults<sup>[30]</sup>. However, this recommendation is contradictory to the protein restrictions that have been common in treatment of cirrhosis and hepatic encephalopathy.

## PROTEIN RESTRICTIONS AS A TREATMENT AND PREVENTION STRATEGY IN CIRRHOSIS

Protein restrictions in cirrhosis to prevent and manage hepatic encephalopathy (HE) have been commonplace for more than half a century. In 1893, it was observed that dogs with porto-caval shunts developed neurological symptoms after eating meat. In the 1930s, the same types of dogs were noted to improve when fed bread and milk instead of meat<sup>[27]</sup>. In the mid-20th century, protein restriction was found to decrease HE in patients with surgical creation of a portosystemic shunt. The theory was that decreased protein intake led to decreased ammonia productions and therefore less HE. The practice was then expanded to all patients with cirrhosis, with or without HE<sup>[35]</sup>. A study in 2006 indicated that 58% of dietitians continue to restrict dietary protein and 64% received requests for inappropriate protein restrictions for patients with HE<sup>[35]</sup>. Even though there is plenty of observational data to support the theory that protein is harmful in HE, results from experimental data suggested that this is not case. In fact, since the 1970's, a significant amount of research has shown protein restrictions can be detrimental in HE, especially in older adults.

#### Effects of protein restrictions on progression of liver disease

Since the 1970's, multiple studies have been done that have proven that protein restriction is not beneficial in HE; a summary of these studies can be found in table 1<sup>[24,36-45]</sup>. As far back as 1977, Greenberger *et al.*<sup>[36]</sup> described a case of one woman with chronic HE who tolerated up to 90 g of vegetable protein and up to 70 g of a combination of animal and vegetable protein with no adverse effects on her clinical status<sup>[36]</sup>. The study itself had multiple flaws, including the fact that it had only 3 subjects, but the fact that this woman was able to tolerate such a large amount of protein was unheard of at the time. In the 1980's, 4 studies were completed that demonstrated that up to 78 g of protein (1.5 g/kg/day) is well tolerated. Compared to control groups consuming 40 g of protein, the higher intake of protein did not result in increased progression of liver failure or incidence

of HE<sup>[37-40]</sup>. Similar studies continued in the 1990's, showing that higher amounts of protein intake do not lead to worsening of hepatic encephalopathy<sup>[41,42,45]</sup>. In 2004 and 2005, two more studies were done to completely remove any doubt as to whether or not dietary protein is harmful in HE. In 2004, Cordoba *et al*<sup>[43]</sup> provided enteral nutrition to cirrhotic patients with chronic HE. The first group followed the same protein restricted requirements that have been commonplace for decades (0g for 3 days, then gradually increased every 3 days up to 1.2 g/kg/d) while the second group received 1.2 g protein/kg/day throughout the study. No significant differences in course of HE between the two groups were noted. On the second day, protein breakdown was exacerbated in the first group. No difference in protein breakdown was noted at the end of study when dietary protein content was the same<sup>[43]</sup>. Although the study only included 21 subjects, the results helped to strengthen the theory that increased protein intake is safe and could even be beneficial in preventing protein catabolism. In 2005, Gheorghe *et al*<sup>[44]</sup> provided 153 stable patients with overt HE a diet of vegetable and milk proteins at 30 kcal/kg and 1.2 g protein/kg/day. Results of the study showed that 79.7% of all patients showed improvement in mental status, while patients with severe impairment showed the most improvement. All patients showed decreases in blood ammonia level, regardless of tolerance to diet. Also, because of the high fiber content of the diet, 67% of patients were able to either decrease or discontinue their lactulose regimen<sup>[44]</sup>. For the last four decades, an overwhelming amount of evidence has come out indicating that protein restrictions are not beneficial in preventing development of HE in liver cirrhosis. Moreover, restricting protein has been shown to cause many negative consequences in older adults with cirrhosis.

#### **Negative consequences of protein restrictions in older adults with cirrhosis**

Protein restrictions in cirrhosis may lead to negative consequences, including higher rates of malnutrition, muscle wasting, and increased serum ammonia levels. This is especially concerning in older adults with cirrhosis who are already at increased risk of malnutrition. Bunout *et al*<sup>[39]</sup> demonstrated that at a protein intake of 40 g/day, an individual is in negative nitrogen balance<sup>[39]</sup>. Negative nitrogen balance can lead to muscle wasting<sup>[46]</sup>, which has been noted to be in up to one-third of patients with cirrhosis<sup>[27]</sup>. As the muscle is broken down it releases more ammonia into the body from the skeletal muscle<sup>[43]</sup>. Moreover, because ammonia is metabolized in the skeletal muscle, the less muscle that is available means higher amounts of ammonia remain circulating in the body. Also, protein-restricted diets are considered unpalatable and difficult for the patient to maintain, which may contribute to poor intake. In fact, in one study, 4 of the 6 participants were found to be consuming 60-77 g protein/day, well above their prescribed 40 g/day<sup>[37]</sup>. Overall, low protein intake has been shown to be associated with worsening of hepatic encephalopathy while a higher protein intake correlates with improvement in clinical status<sup>[47]</sup>. Since the 1950's, more research has come out to demonstrate that factors other than ammonia may be responsible for the development of HE, indicating there is a low correlation between plasma ammonia and HE<sup>[44]</sup>. In light of this overwhelming evidence, it is clear that protein restrictions are no longer a useful or safe practice in the treatment of cirrhosis or HE.

#### **BENEFITS OF INCREASED PROTEIN INTAKE IN OLDER ADULTS WITH CIRRHOSIS**

Multiple studies have shown benefits to increasing protein intake in older adults, especially those with liver cirrhosis. The Recommended

Dietary Allowance (RDA) for protein in older adults is 0.8 g/kg. However, this amount has been shown to only prevent deficiency. Furthermore, it is the same as the RDA for younger adults and does not take into account changes that occur with aging including reduced muscle mass, increased fat mass, changes in food intake and physical activity, and more-frequent illness<sup>[48]</sup>. Higher protein intake in older adults has been associated with reduced risk of strength loss and incident frailty<sup>[4]</sup>. Also, women aged 60 and older with protein intakes of 1.2-1.76 g/kg/day tended to have fewer health problems than those with protein intakes of <0.8 g/kg/day<sup>[49]</sup>. General protein supplementation in bed rest studies has shown further evidence of the benefits of increased protein intake. Studies that did show benefit from protein supplementation had baseline diets of 0.6-0.8 g/kg/d and increased the protein given to 1-1.4 g/kg/d during the experimental phase. Studies with no benefit had baseline diet already at 1.0-1.2, further supporting the theory that an increased protein intake has a positive impact on older adults<sup>[50]</sup>. While it is evident that increased protein intake has a beneficial effect on older adults in general, the same may also hold true for individuals with liver cirrhosis.

Multiple benefits have been shown with cirrhotic patients consuming increased amounts of protein. Patients with a positive nitrogen balance, as a result of consuming 60-80 g of protein, saw their physical condition improve<sup>[40]</sup>. At protein intakes of 1-1.8 g/kg/day, improved liver function has been noted<sup>[42]</sup> and at protein intakes of 1.5 g/kg, subjects improved more rapidly compared to a control group that consumed only 0.7 g/kg/d<sup>[24]</sup>. Gheorghe *et al*<sup>[44]</sup> has also demonstrated that at intakes of 1.2 g/kg/day, 79.7% of all patients showed improvement in mental status and decreases in blood ammonia level, regardless of tolerance to diet. Also, because of the high fiber content of the diet, 67% of patients were able to either decrease or discontinue their lactulose regimen<sup>[44]</sup>. Finally, a meta-analysis of studies providing either oral or intravenous nutrition supplementation showed either improvement or resolution of hepatic encephalopathy compared to standard hospital diet<sup>[51]</sup>. Although the meta-analysis only focused on patients with alcoholic hepatitis and did not include age information, it included 262 subjects and did not result in any negative outcomes, suggesting the possibility of being beneficial in all types of liver disease and all age groups.

#### **VEGETABLE VERSUS ANIMAL PROTEIN AS A TREATMENT AND PREVENTION STRATEGY IN CIRRHOSIS**

Another treatment option that is popular in cirrhosis and hepatic encephalopathy is the focus of more vegetable protein and less animal protein. Mercaptans are by-products of methionine metabolism and are thought to contribute to development of HE in cirrhotic patients. It has been shown that vegetable proteins have significantly less methionine than animal protein<sup>[36]</sup>. Vegetable proteins also have the benefit of having a higher fiber content, which causes decreased transit time and fecal ammonia excretion. Plasma arginine and citrulline concentrations are also higher in vegetable protein which facilitates ammonia removal via the Krebs-Henseleit cycle<sup>[44]</sup>. It is because of these factors that some studies have examined whether vegetable proteins are better tolerated in HE than animal proteins.

Unfortunately, only a few inconclusive studies have examined animal protein versus vegetable protein in cirrhosis. To date, only 7 studies have been completed that examined vegetable protein versus animal protein and their effects on hepatic encephalopathy<sup>[36,37,41,52-55]</sup>. Six of the studies showed positive results on vegetable protein, including improved HE, improved mental status, larger bowel

movements, EEG improvements, a trend toward positive nitrogen balance, improved branched-chain amino acid to aromatic amino acid ratio, lower urine nitrogen concentrations, and lower plasma ammonia levels<sup>[36,37,41,52-54]</sup>. One of the studies showed no significant differences in grade of HE, nitrogen balance, or plasma amino acids<sup>[55]</sup>. However, all of the studies included a very small sample size ( $N=3-8$ ), and the characteristics of the studies varied widely, making it difficult to draw strong conclusions. Moreover, in each of the studies, the average age of the participants was less than 60, making it impossible to draw conclusions as to the effect of vegetable protein on older adults. A more recent study was completed by Gheorghe *et al*<sup>[44]</sup> in 2005. It did not compare vegetable protein versus animal protein, but 153 subjects, average age of 54, were provided with a vegetable protein diet comprised of 75 g protein, or 1.2 g/kg/d. The majority of patients showed improvements in mental status, decreases in blood ammonia level, and decreased or discontinued lactulose regimen<sup>[44]</sup>. However, the positive results could be attributed to the higher protein content of the diet and not necessarily the vegetable protein alone.

In addition to lack of conclusive evidence relating to the benefit of vegetable protein diets in HE, there is some evidence that they may be contraindicated and unfavorable, especially with older adults. Diets high in vegetable protein are notoriously high in fiber, which can cause abdominal discomfort, bloating, and flatulence. In fact, many of the study participants had low levels of compliance due to these negative side effects. In addition, older patients that already struggle with decreased intake overall due to early satiety would be at a disadvantage because the high fiber content would cause delayed gastric emptying and in turn decreased appetite<sup>[20]</sup>. In a study of healthy older women, animal protein intake was able to predict muscle mass index, but the vegetable protein was not<sup>[56]</sup>. Vegetable proteins are high in branched-chain amino acids (BCAA). However, a high protein diet with a focus on vegetable protein has been shown to lead to a decreased BCAA/aromatic amino acid (AAA) ratio and increased plasma AAA<sup>[37]</sup>. Finally, a diet high in fiber can potentially lead to decreased absorption of nitrogen<sup>[25]</sup>, thus potentially exacerbating a diminished nutritional status. Due to lack of conclusive evidence regarding the benefits of vegetable protein and the potential negative side effects, vegetable protein is not an advantageous treatment option in HE.

## STRATEGIES TO INCREASE PROTEIN INTAKE IN OLDER ADULTS WITH CIRRHOSIS

Due to the altered metabolism seen in cirrhosis, simply increasing calorie intake is not adequate enough to improve a patient's nutritional status. Moreover, excessive calories may confer negative consequences on glycemic control, obesity rates, and steatosis<sup>[57]</sup>. It is evident that increased protein intake is effective at managing cirrhosis, preventing complications of cirrhosis, and beneficial in preserving muscle mass and strength in older adults. Additionally, increased protein intake would bypass the potential complications seen with increased energy intake alone. Several different strategies have been explored as options to increase protein and amino acid intake in both older adults and cirrhosis.

### Minimum Protein Intake at Every Meal

Different researchers have theorized whether giving a certain minimum amount, or threshold, of protein at each meal could be beneficial to maintaining muscle mass. It has been shown that older adults require 25-40 g protein/meal to maximally stimulate muscle protein synthesis<sup>[58-60]</sup>. Additionally, research has shown that nonfrail elderly individuals tend to have a more even protein distribution

across daily meals, whereas frail and prefrail individuals tend to skew their protein intake toward noon meal while consuming significantly less at other meals<sup>[61]</sup>. Both of these factors help support the theory that a threshold amount of protein at each meal could be beneficial to maintaining muscle mass. So far, research has yielded conflicting results as to whether this theory is true or not. Mamerow *et al*<sup>[62]</sup> showed that when protein was evenly distributed across all 3 meals compared to skewed toward the evening meal in healthy adults, muscle protein synthesis was 25% higher. In addition, they also demonstrated that muscle protein synthesis was approximately 30% higher in the breakfast meal that contained 30 g protein compared to the breakfast that contained 10 g protein<sup>[62]</sup>.

Although there has been some research that supports this theory, there has been some that contradicts it. In a study completed by Bouillane *et al*<sup>[63]</sup>, elderly hospitalized subjects were given a diet of either even protein distribution of approximately 21.2 g/meal or a skewed diet with protein intake ranging from 10-47.8 g. The patients on the skewed diet had significant improvements in lean mass compared to an even distribution diet<sup>[63]</sup>. However, as noted by Paddon-Jones *et al*<sup>[64]</sup>, the even distribution diet was less than the suggested protein threshold of 25-30 g of protein, and most likely did not provide an adequate amount of amino acids to promote muscle synthesis. Although, the skewed diet did contain one meal that was well above the threshold which would have been sufficient to encourage muscle synthesis<sup>[64]</sup>. Another study that had opposing results to this theory was a study completed by Arnal *et al*<sup>[65]</sup> in 1999. Fifteen healthy, elderly women were given either a diet comprised of an even distribution of protein at every meal (20-32 g/meal), or a skewed protein distribution with a significantly higher amount of protein at the noon meal (8-83 g/meal). The individuals on the skewed protein diet exhibited more positive nitrogen balance, higher protein rates, and higher rates of protein synthesis compared to the evenly distributed protein diet. The evenly distributed protein diet did reach the protein threshold for 2 of the daily meals and the overall protein intake was 1.7 g/kg/d, indicating that the subjects had more than adequate protein intake<sup>[65]</sup>.

Even though there are some contradictory results, providing minimum protein at every meal should not be ruled out as a potential treatment option. Possible explanations for differences in results of these studies could be explained by differences in study design, number of subjects, and ages of the subjects. Additionally, all of these studies only examined the short term-benefits of protein distribution, leaving the question of potential long term benefits unanswered. Although none of these studies explored the benefit of protein threshold at meals in patients with cirrhosis, their subjects did have very similar characteristics to those of patients with cirrhosis. Results of the studies and a lack of negative outcomes indicate that providing a minimum amount of protein at every meal would be worthwhile to explore in older adults with cirrhosis, especially studies that look at long term benefits.

### Timing of Protein Supplementation

One strategy that has been examined is different timing of protein supplementations, specifically at breakfast and prior to bedtime. It has been shown that elderly individuals tend to ingest only 5-10 g protein at breakfast, which is far below the threshold, and may benefit from additional protein supplementation at breakfast<sup>[66]</sup>. However, very few studies have specifically investigated the impact of protein supplementation at breakfast in patients with cirrhosis. In a short-term bed rest study, healthy older men were given a protein supplement of 20 g after breakfast and before sleep versus no supplement. Results

showed no difference between the treatment group and control group in terms of preserving muscle mass or strength. However, the subjects' baseline diet was 1.0-1.1 g/kg. The average weight of the subjects was 81 kg, indicating they were already consuming 81-89 g/day, or 27-30 g/meal. Additionally, the supplement provided only contained 20 g/meal, below the threshold amount required to stimulate muscle synthesis in older adults<sup>[69]</sup>. In another study of cirrhotic patients, average age of 56, subjects were either provided with a 500 kcal and 21 g protein breakfast or fasted. The subjects that consumed breakfast showed improvements in overall cognitive function compared to the fasting group<sup>[70]</sup>. Even though the amount of protein provided at breakfast was slightly lower than the proposed protein threshold for older adults, it was higher than the amount typically consumed at breakfast in older adults, suggesting benefit to increasing the amount of protein at breakfast. Although few studies have been completed that examined protein supplementation with breakfast, results are encouraging. However, much more research is needed before all the benefits of protein intake at breakfast in older adults with cirrhosis are known.

Another potential beneficial time for protein supplementation in older adults with cirrhosis is at bedtime and overnight. Research has shown that muscle protein synthesis rates are very low during overnight sleep<sup>[67]</sup>, and overnight fasting in cirrhosis can lead to hepatic glycogen depletion and impaired metabolism<sup>[68]</sup>. Several studies have shown that protein supplementation given prior to and during sleep in healthy older adults resulted in substantial increases in overnight rates of muscle protein synthesis<sup>[67]</sup>. In one study completed in 2012, healthy elderly men were provided with either casein protein or a placebo via nasogastric tube while sleeping. Baseline diet for the participants provided 0.9 g/kg/d; and the protein supplement provided an additional 40 g of protein. The experimental group was noted to have increases in plasma amino acid concentrations as well as increases in overall protein synthesis compared to the control group. The experimental group did report decreased hunger the morning following protein administration, but this did not seem to affect energy or protein intake at breakfast<sup>[67]</sup>, suggesting that nocturnal supplementation may have little to no effect on nutrient intake during the day. A recent review examined the effect of late evening snacks in cirrhosis in both short and long-term studies. Composition of the snacks varied, and included liquid dietary supplements, high-carbohydrate foods, and branched-chain amino acid (BCAA)-enriched supplements. Results regarding increases in skeletal muscle and decreased mortality were inconclusive. However, positive benefits were noted in improved fuel metabolism in short-term studies and increases in lean body mass in long term studies. The review did attempt to determine the optimal caloric intake of supplements, but did not review protein content of the supplements or age of the subjects<sup>[71]</sup>, making it difficult to draw conclusions regarding evening supplementation in older adults. A summary of studies providing late evening or overnight supplementation to older adults (average age >60) with cirrhosis can be found in table 2. Of the 7 studies completed to date, all showed various positive benefits including improvements in nitrogen balance, ratio of branched chain to aromatic amino acids, serum albumin, fuel metabolism, and quality of life scores and decreases in serum ketone bodies and muscle cramps<sup>[57,68,72-76]</sup>. The majority of the studies lasted 3 months or less, with one being 12 months. One study compared a late-evening snack of branched-chain amino acids versus regular food. Although both groups showed improvements in quality of life scores, only the branched-chain amino acid group showed any improvement in catabolic state, nitrogen balance, or serum albumin, though the difference could be explained by the lower amount of protein provided in the regular food group. Even though all of the results were positive, it is worth

noting that each study had at least one limitation within their study design. Of particular importance is the fact that other than the studies that provided branched-chain amino acids, the protein content of the snacks was somewhat low (3.6-9 g), suggesting that some factor other than the protein content was responsible for the positive results. However, only one study reported a potential negative side effect of some hypoglycemia if the snack was missed<sup>[76]</sup>. This indicates that, overall, providing a late evening snack is safe and has positive effects on older adults with liver cirrhosis. Therefore, it can be considered as a worthwhile treatment option. Future research should focus on long-term benefits, as well as standardization in study design, particularly outcome measures.

### **Branched Chain Amino Acid Supplementation in Older Adults with Cirrhosis**

Supplementation with BCAAs is another treatment option in liver cirrhosis, but study results have been conflicting. Branched-chain amino acids are characteristically low in patients with liver cirrhosis and strongly correlate with degree of hepatic encephalopathy (HE)<sup>[77]</sup>. Additionally, postprandial stimulation of muscle protein synthesis is triggered by availability of plasma amino acids, particularly leucine<sup>[78]</sup>. Meta-analysis of the effect of branched-chain amino acids in liver cirrhosis has been problematic due to conflicting results, differences in study design, duration of treatment, and type of nutritional supplement<sup>[79]</sup>. A review of 11 randomized trials in 2009 revealed that when only including studies of high quality (clearly stated generation of allocation sequence, allocation concealment, and double blinding), BCAA supplementations did not show any benefit in HE, survival, or adverse events<sup>[80]</sup>. Gluud *et al*<sup>[81]</sup> completed a meta-analysis of 8 studies in 2013. It reviewed such a small number of studies because it only included patients that had HE at baseline. The analysis revealed that BCAA supplementation had a beneficial effect on reducing HE manifestations. No difference was found regarding overall mortality, albumin, or nitrogen balance<sup>[81]</sup>. Both of these reviews examined BCAA in liver cirrhosis in general, but so far no reviews have specifically examined BCAA in older adults with cirrhosis.

Table 3 provides a summary of all studies completed that examined BCAA supplementation in older adults (average age >60) with liver cirrhosis. Of the 9 studies completed to date, 7 showed improvements in nitrogen balance, ratio of branched chain to aromatic amino acids, serum albumin, fuel metabolism, quality of life scores, liver function, muscle mass, and survival, as well as decreases in serum ketone bodies and muscle cramps<sup>[72-75,83-85]</sup>. Two of the studies showed no significant differences between the treatment group and the control group<sup>[38,82]</sup>, however, they both included very small sample sizes. Additionally, one of the studies that showed no difference had a baseline diet of only 40 g protein/day, suggesting that increased protein of any kind is beneficial whether it comes from BCAA or casein. Similar to the reviews previously completed, it is difficult to draw strong conclusions due to the fact that several of the studies had limitations including small sample sizes, short study durations, different study protocols, and varying outcome measures. The main drawback to using BCAA supplementation is its high cost and poor taste. However, none of the studies have reported any toxicity or adverse events, suggesting that supplementation with BCAA is safe in advanced liver disease<sup>[26]</sup>. Many questions are still unanswered in regards to BCAA supplementation in liver cirrhosis, including its mechanism and exact benefits. Nevertheless, its overall safety, as well as promising results from previous studies, indicate it is worthwhile to continue exploring in future research. Future research with BCAA would benefit from larger sample sizes, longer study durations, and more standardization between the control group and treatment groups.



**Table 1** Summary of studies examining safety of increased protein intake in liver disease.

Author, Year	N	Clinical Status	Protein Source	Nutrients Provided	Results	Conclusions per Authors
Greenberger <i>et al</i> [36] 1977	3	Postnecrotic cirrhosis, status-post portal systemic shunt, and recurrent HE§.	Vegetable versus animal protein	2310-3240 kcal/day 24-90 g protein/day	Case 1: lower HEc index scores and decreased arterial ammonia on vegetable protein. Case 2: Marked deterioration on the animal protein diet, no improvement with vegetable protein but did not worsen. Case 3: Able to tolerate 90 g of vegetable protein and 70 g of mixed protein.	Vegetable protein diet resulted in clinical improvement, decreased HE§ scores, decreased arterial ammonia, and improved protein tolerance.
Keshavarian <i>et al</i> [37] 1984	6	Moderate chronic portal-systemic encephalopathy	Vegetable versus animal protein	40 g protein (10 g vegetable + 30 g animal) 80 g (50 g vegetable + 3 gm animal)	Participants showed either improvement or no change with clinical performance. 80 g protein diet resulted in decreased BCAA†/AAA‡ ratio and increased plasma AAA†.	Patients with mild, chronic portal-systemic encephalopathy can tolerate dietary supplementation with vegetable proteins.
Christie <i>et al</i> [38] 1985	6	Stable Cirrhosis	BCAA† versus casein	2108-2268 kcal 98-100 g protein	Protein tolerance and increased nitrogen balance was observed in both groups	Patients with liver disease can be given increasing amounts of protein without inducing or worsening encephalopathy.
Bunout D <i>et al</i> [39] 1989	36	Alcoholic cirrhosis and liver failure	Mixed	Control group: Standard diet of 47 g of protein and 1813 kcal/day. Experiment group: 50 kcal/kg/day (~2707 kcal) and 1.5 g protein/kg/day (80 g)	No differences noted in evolution of liver failure, HE§, or nutritional status.	High energy and protein intake does not cause adverse effects; associated with non-significant reduction in mortality.
Swart GR <i>et al</i> [40] 1989	8	Cirrhosis	BCAA† versus natural protein	40, 60 or 80 g protein	Negative nitrogen balance on 40 g diet; positive nitrogen balance at 60 and 80 g. Physical condition of the patients improved when in positive nitrogen balance. Higher amounts of protein were well tolerated without onset of HEc.	Recommend 1.2 g/kg/d of protein, diets less than 60 g/day should not be used.
Cabre E <i>et al</i> [45] 1990	35	Severely malnourished with cirrhosis	Treatment group: Whole protein + BCAA§† Control group: Mixed	2115 kcal	Enteral nutrition well tolerated without complications. Treatment group showed improvements in serum albumin, mental status, and a decreased mortality rate compared to the control group.	Enteral nutrition is safe and effective in improving short-term clinical outcome in severely malnourished patients with cirrhosis.
Bianchi <i>et al</i> [41] 1993	8	Cirrhosis and chronic HE§	Vegetable versus animal protein	25-30 kcal/day, 71 g protein (either 50 g animal and 21 g vegetable or 50 g vegetable and 21 g animal)	Nitrogen balance, clinical grading of encephalopathy, and psychometric tests were significantly improved with the vegetable protein diet.	A vegetable protein diet is beneficial to patients with cirrhosis and chronic HE§.
Keams <i>et al</i> [24] 1995	16	Alcoholic Liver Disease	Casein-based	40 kcal/kg 1.5 g protein/kg	Group with increased protein improved more rapidly, did not worsen in status	Casein-based solutions are an effective supplementation in alcoholic liver disease.
Nielsen <i>et al</i> [42] 1995	15	Malnourished, clinically stable, liver cirrhosis	Mixed	Gradual increase from 1 to 1.8 g/kg/day	Increased liver function by all participants.	Protein requirements are increased in cirrhosis to maintain protein balance. Nutritional therapy by means of food is feasible in clinically stable patients over a long period of time.
Cordoba <i>et al</i> [43] 2004	20	Cirrhotic patients with HE§	Enteral nutrition	30 kcal/kg/d, Low protein group: 0g for 3 days, then gradually increased every 3 days up to 1.2 g/kg/d, Normal protein group: 1.2 g/kg/d from the beginning	No significant difference in course of HE§ between the two groups. On day 2, protein breakdown was exacerbated in low protein group; no difference at end of study when protein content was the same.	Normal protein diet is safe for patients with HE§. No major benefit in restricting protein on course of HE and low protein diet can exacerbate protein breakdown.
Gheorghie <i>et al.</i> 2005 [44]	153	Stable cirrhosis w/ overt HE§	Vegetable and Dairy Products	30 kcal/kg/d, 1.2 g protein/kg/d	79.7% of all patients showed improvement in mental status; patients with severe impairment showed the most improvement. All patients showed decreases in blood ammonia level, regardless of tolerance to diet.	Dietary protein restriction not required

†AAA: Aromatic Amino Acids; ‡BCAA: Branched Chain Amino Acids; §HE: Hepatic Encephalopathy.

**Table 2 Summary of studies providing late evening or overnight supplementation to adults (average age ≥60) with cirrhosis.**

Author, Year	N	Treatment	Protein Content	Results	Length of the Study	Limitations
Miwa <i>et al</i> [57] 2000	26	Oral liquid nutritional supplement in liver cirrhosis patients versus healthy controls	Base diet 1.2 g/kg/d, Supplement 9 g	The cirrhotic patients showed significant improvement in respiratory quotient and substrate oxidation of both fat and glucose, indicating improvements in overall fuel metabolism. No significant differences were noted for nitrogen balance in either group.	2 days	Control group younger than treatment group
Yamauchi <i>et al</i> [75] 2001	14	Supplementation with BCAA† at late evening versus after dinner	Base diet 50 g; BCAA† supplement 13.7 g	Late evening supplementation had significant decreases in urinary 3-methylhistidine and serum free fatty acids.	28 days	Small sample size, more males than females
Yamanaka-Okumura <i>et al</i> [68] 2006	47	High-carbohydrate late evening snack versus no snack in liver cirrhosis patients and healthy controls	Base diet 70-75 g; Snack: 4.3 g	The cirrhotic patients showed significant improvement in respiratory quotient, indicating improvements in overall fuel metabolism.	1 week	Only male subjects
Fukushima <i>et al</i> [72] 2003	12	Nocturnal versus daytime administration of BCAA†	Base diet: 1.3 g/kg/d, 12 g BCAA† granules	After 3 weeks, both groups showed improvements in nitrogen balance and Fischer's ratio¶ with more significance in the nighttime group. At 3 months nighttime group had improvements in serum albumin.	3 weeks and 3 months	Crossover design with no washout period, small sample size
Sako <i>et al</i> [73] 2003	8	BCAA† as nocturnal snack	13.7 g BCAA†	Decreases in serum ketone bodies and muscle cramps, increases in serum albumin and Fischer's ratio¶.	3 months	Daily caloric & protein intake not controlled, small sample size, no control group
Nakaya <i>et al</i> [74] 2007	38	Late evening snack with BCAA† versus Late evening snack with ordinary food	Base diet: 1.2-1.3 g/kg/d Treatment Snack: 13.5 g Control Snack: 9 g	BCAA† mixture improved catabolic state, nitrogen balance, and serum albumin; no changes in control group; improved QOL§ in both groups.	3 months	Protein intake significantly greater in BCAA† group, 1.17 at baseline, 1.33 with BCAA†, control stayed at 1.17; sample size too small to show significant differences, lack of blinding, short duration to measure albumin
Yamanaka-Okumura <i>et al</i> [76] 2010	39	High-carbohydrate late evening snack versus no snack	Base diet: 1.3 g/kg/d, Snack 3.6 g	Control group had decreased QOL§ scores in 2 areas compared to baseline. Treatment group had increased QOL§ scores in 3 areas.	12 months	Low protein content of LES†; hypoglycemia if LES† was missed even once

†BCAA: Branched Chain Amino Acids; ‡LES: Late evening snack; §QOL: Quality of Life; ¶Fischer's Ratio= BCAA/ aromatic amino acid ratio.

**Table 3 Summary of studies providing BCAA† supplementation in older adults (age ≥60) with liver cirrhosis.**

Author, Year	N	Treatment	Results	Length of the Study	Limitations
Christie <i>et al</i> [38] 1985	6	BCAA† versus casein	No differences noted between groups	3 days	Base diet only 40 gm protein; small sample size
Marchesini <i>et al</i> [83] 1990	61	BCAA† versus casein	BCAA† group improved more rapidly; improvement in nitrogen balance, nutritional parameters, and liver function test; subjects in 6 months had significant increases in body weight	3-6 months	Small sample size in 6 month group, low compliance after 3 months
Yamauchi <i>et al</i> [75] 2001	14	Supplementation with BCAA† at late evening versus after dinner	Late evening supplementation had significant decreases in urinary 3-methylhistidine and serum free fatty acids	28 days	Small sample size, more males than females
Fukushima <i>et al</i> [72] 2003	12	Nocturnal versus daytime administration of BCAA†	After 3 weeks, both groups showed improvements in nitrogen balance and Fischer's ratio # with more significance in the nighttime group. At 3 months nighttime group had improvements in serum albumin.	3 weeks and 3 months	Crossover design with no washout period, small sample size
Sako <i>et al</i> [73] 2003	8	BCAA† as nocturnal snack	Decreases in serum ketone bodies and muscle cramps, increases in serum albumin and Fischer's ratio #	3 months	Daily caloric & protein intake not controlled, small sample size, no control group
Muto <i>et al</i> [84] 2005	622	BCAA† granules versus regular diet	Survival rate, incidence of events serum albumin, and general health perception score significantly higher in BCAA† group	2 years	Incidence of HES§ significantly higher in BCAA† group than control, lack of placebo
Nakaya <i>et al</i> [74] 2007	38	Late evening snack with BCAA† versus Late evening snack with ordinary food	BCAA† mixture improved catabolic state, nitrogen balance, and serum albumin; no changes in control group; improved QOL¶ in both groups	3 months	Protein intake significantly greater in BCAA† group, 1.17 at baseline, 1.33 with BCAA†, control stayed at 1.17; sample size too small to show significant differences, lack of blinding, short duration to measure albumin
Fukushima <i>et al</i> [82] 2007	7	BCAA† granules + regular diet	Serum total albumin did not change significantly. Plasma BCAA† and BTR‡ increased significantly	8 weeks	Small sample size, no control group
Les <i>et al</i> [85] 2011	116	BCAA† versus maltodextrin	BCAA improved muscle mass but did not show decrease occurrence of HES.	56 weeks	Standard diet provided only 0.7 g protein/kg/d

†BCAA: Branched Chain Amino Acids; ‡BTR: Ratio of BCAA to tyrosine; §HES, Hepatic Encephalopathy; ¶QOL: Quality of Life, #Fischer's Ratio= BCAA/ aromatic amino acid ratio

## CONCLUSION

Protein intake has a key role to play in the prevention and management of liver cirrhosis in older adults. Overwhelming evidence has shown that protein-restricted diets do not confer any benefit to patients with cirrhosis and have negative side effects, especially in older adults. The evidence is inconclusive as to vegetable protein being superior to animal protein. Additionally, a diet comprised of vegetable protein may be contraindicated as well as unrealistic to maintain in cirrhosis. The evidence points to the fact that BCAAs may be beneficial in liver cirrhosis, but much more research is needed to determine the mechanism behind their benefits and further validate studies that have already been completed. The most promising strategies are ensuring adequate protein at every meal, through either regular intake or supplementation, and protein supplementation prior to bedtime or overnight.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

## REFERENCES

- Merli M, Riggio O, Dally L. Does malnutrition affect survival in cirrhosis? PINC (Policentrica Italiana Nutrizione Cirrosi). *Hepatology* 1996; **23**(5): 1041-1046. <http://dx.doi.org/10.1002/hep.510230516> PMID:8621131
- Alberino F, Gatta A, Amodio P, Merkel C, Di Pascoli L, Boffo G, Caregaro O. Nutrition and survival in patients with liver cirrhosis. *Nutrition* 2001; **17**(6): 445-450. [http://dx.doi.org/10.1016/S0899-9007\(01\)00521-4](http://dx.doi.org/10.1016/S0899-9007(01)00521-4)
- Bernstein M, Munoz N, Dietetics AoNa. Position of the Academy of Nutrition and Dietetics: food and nutrition for older adults: promoting health and wellness. *J Acad Nutr Diet* 2012; **112**(8): 1255-1277. <http://dx.doi.org/10.1016/j.jand.2012.06.015> PMID:22818734
- Pirlich M, Lochs H. Nutrition in the elderly. *Best Pract Res Clin Gastroenterol* 2001; **15**(6): 869-884. <http://dx.doi.org/10.1053/bega.2001.0246> PMID:11866482
- Vijlbrief RV, Wijnhoven HA, Schaap LA, Terwee CB, Visser M. Determinants of protein-energy malnutrition in community dwelling older adults: A systematic review of observational studies. *Ageing Res Rev*. 2014.
- Bauer J, Biolo G, Cederholm T, Cesari M, Cruz-Jentoft AJ, Morley JE, Phillips S, Sieber C, Stehle P, Teta D, Visvanathan R, Volpi E, Boirie Y. Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE Study Group. *J Am Med Dir Assoc* 2013; **14**(8): 542-559. <http://dx.doi.org/10.1016/j.jamda.2013.05.021> PMID:23867520
- Centers for Disease Control. Leading causes of death by age group, *American Indian or Alaska Native Males-United States* 2010. <http://www.cdc.gov/nchs/deaths.htm>. Accessed October 12, 2014.
- Nompleggi DJ, Bonkovsky HL. Nutritional supplementation in chronic liver disease: an analytical review. *Hepatology* 1994; **19**(2): 518-533. <http://dx.doi.org/10.1002/hep.1840190234>
- Dasarathy S. Consilience in sarcopenia of cirrhosis. *J Cachexia Sarcopenia Muscle* 2012; **3**(4):225-237. <http://dx.doi.org/10.1007/s13539-012-0069-3> PMID:22648736 PMID:PMC3505573
- Fox M, Fox J, Davies M. Diagnosis and management of chronic liver disease in older people. *Rev Clin Gerontol* 2011; **21**: 1-15. <http://dx.doi.org/10.1017/S0959259810000365>
- Ampuero J, Ranchal I, del Mar Díaz-Herrero M, del Campo JA, Bautista JD, Romero-Gómez M. Role of diabetes mellitus on hepatic encephalopathy. *Metab Brain Dis* 2013; **28**(2): 277-279. <http://dx.doi.org/10.1007/s11011-012-9354-2> PMID:23180316
- Madsen JL, Graff J. Effects of ageing on gastrointestinal motor function. *Age Ageing* 2004; **33**(2):154-159. <http://dx.doi.org/10.1093/ageing/afh040> PMID:14960431
- Butt Z, Jadoon NA, Salaria ON, Mushtaq K, Riaz IB, Shahzad A, Hashmi AM, Sarwar S. Diabetes mellitus and decompensated cirrhosis: risk of hepatic encephalopathy in different age groups. *J Diabetes* 2013; **5**(4): 449-455. <http://dx.doi.org/10.1111/1753-0407.12067> PMID:23731902
- 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): 982-989. <http://dx.doi.org/10.1097/MEG.0b013e32834aa4bb> PMID:21971339
- Thompson JS, Schafer DF, Haun J, Schafer GJ. Adequate diet prevents hepatic coma in dogs with Eck fistulas. *Surg Gynecol Obstet* 1986; **162**(2): 126-130. PMID:3945890
- Volpi E, Campbell WW, Dwyer JT, Johnson MA, Jensen GL, Morley JE, Wolfe RR. Is the optimal level of protein intake for older adults greater than the recommended dietary allowance? *J Gerontol A Biol Sci Med Sci* 2013; **68**(6): 677-681. <http://dx.doi.org/10.1093/gerona/gls229> PMID:23183903 PMID:PMC3660117
- Müller MJ, Böker KH, Selberg O. Are patients with liver cirrhosis hypermetabolic? *Clin Nutr* 1994; **13**(3): 131-144. [http://dx.doi.org/10.1016/0261-5614\(94\)90092-2](http://dx.doi.org/10.1016/0261-5614(94)90092-2)
- McCullough AJ, Raguso C. Effect of cirrhosis on energy expenditure. *Am J Clin Nutr* 1999; **69**(6): 1066-1068. PMID:10357723
- Huang HJ, Zhang AY, Cao HC, Lu HF, Wang BH, Xie Q, Xu W, Li LJ. Metabolomic analyses of faeces reveals malabsorption in cirrhotic patients. *Dig Liver Dis* 2013; **45**(8): 677-682. <http://dx.doi.org/10.1016/j.dld.2013.01.001> PMID:23384618
- Krenitsky J. Nutrition for patients with hepatic failure. *Pract Gastroenterol* 2003; **6**: 23-42
- Cheung K, Lee SS, Raman M. Prevalence and mechanisms of malnutrition in patients with advanced liver disease, and nutrition management strategies. *Clin Gastroenterol Hepatol* 2012; **10**(2):117-125. <http://dx.doi.org/10.1016/j.cgh.2011.08.016> PMID:21893127
- Bémeur C, Desjardins P, Butterworth RF. Role of nutrition in the management of hepatic encephalopathy in end-stage liver failure. *J Nutr Metab* 2010; **2010**: 489823. <http://dx.doi.org/10.1155/2010/489823> PMID:21234351 PMID:PMC3017957
- Riggio O, Angeloni S, Ciuffa L, Nicolini G, Attili AF, Albanese C, Merli M. Malnutrition is not related to alterations in energy balance in patients with stable liver cirrhosis. *Clin Nutr* 2003; **22**(6): 553-559. [http://dx.doi.org/10.1016/S0261-5614\(03\)00058-X](http://dx.doi.org/10.1016/S0261-5614(03)00058-X)
- 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): 200-205. PMID:1727754
- Cabral CM, Burns DL. Low-protein diets for hepatic encephalopathy debunked: let them eat steak. *Nutr Clin Pract* 2011; **26**(2):155-159. <http://dx.doi.org/10.1177/0884533611400086> PMID:21447768
- Khanna S, Gopalan S. Role of branched-chain amino acids in liver disease: the evidence for and against. *Curr Opin Clin Nutr Metab Care* 2007; **10**(3):297-303. <http://dx.doi.org/10.1097/MCO.0b013e3280d646b8> PMID:17414498
- Amodio P, Caregaro L, Pattenò E, Marcon M, Del Piccolo F, Gatta A. Vegetarian diets in hepatic encephalopathy: facts or



- fantasies? *Dig Liver Dis* 2001; **33(6)**: 492-500. [http://dx.doi.org/10.1016/S1590-8658\(01\)80028-1](http://dx.doi.org/10.1016/S1590-8658(01)80028-1)
- 28 Kachaamy T, Bajaj JS. Diet and cognition in chronic liver disease. *Curr Opin Gastroenterol* 2011; **27(2)**: 174-179. <http://dx.doi.org/10.1097/MOG.0b013e3283409c25> PMID:20975555
- 29 Periyalwar P, Dasarathy S. Malnutrition in cirrhosis: contribution and consequences of sarcopenia on metabolic and clinical responses. *Clin Liver Dis* 2012; **16**: 95-131. <http://dx.doi.org/10.1016/j.cld.2011.12.009> PMID:22321468
- 30 Deutz NE, Bauer JM, Barazzoni R, Biolo G, Boirie Y, Bosy-Westphal A, Cederholm T, Cruz-Jentoft A, Krznaric Z, Nair KS, Singer P, Teta D, Tipton K, Calder PC. Protein intake and exercise for optimal muscle function with aging: Recommendations from the ESPEN Expert Group. *Clin Nutr* 2014. <http://dx.doi.org/10.1016/j.clnu.2014.04.007>
- 31 Fulgoni VL. Current protein intake in America: analysis of the National Health and Nutrition Examination Survey, 2003-2004. *Am J Clin Nutr* 2008; **87(5)**: 1554S-1557S. PMID:18469286
- 32 English KL, Paddon-Jones D. Protecting muscle mass and function in older adults during bed rest. *Curr Opin Clin Nutr Metab Care* 2010; **13(1)**: 34-39. <http://dx.doi.org/10.1097/MCO.0b013e328333aa66> PMID:19898232 PMCid:PMC3276215
- 33 Senkottaiyan N. Nutrition and the older diabetic. *Clin Geriatr Med* 2008; **24(3)**: 503-513, vii. <http://dx.doi.org/10.1016/j.cger.2008.03.010> PMID:18672185
- 34 Walrand S, Guillet C, Salles J, Cano N, Boirie Y. Physiopathological mechanism of sarcopenia. *Clin Geriatr Med* 2011; **27(3)**: 365-385. <http://dx.doi.org/10.1016/j.cger.2011.03.005> PMID:21824553
- 35 Heyman JK, Whitfield CJ, Brock KE, McCaughan GW, Donaghy AJ. Dietary protein intakes in patients with hepatic encephalopathy and cirrhosis: current practice in NSW and ACT. *Med J Aust* 2006; **185(10)**: 542-543. PMID:17115965
- 36 Greenberger NJ, Carley J, Schenker S, Bettinger I, Stamnes C, Beyer P. Effect of vegetable and animal protein diets in chronic hepatic encephalopathy. *Am J Dig Dis* 1977; **22(10)**: 845-855. <http://dx.doi.org/10.1007/BF01076158> PMID:335882
- 37 Keshavarzian A, Meek J, Sutton C, Emery VM, Hughes EA, Hodgson HJ. Dietary protein supplementation from vegetable sources in the management of chronic portal systemic encephalopathy. *Am J Gastroenterol* 1984; **79(12)**: 945-949. PMID:6391154
- 38 Christie ML, Sack DM, Pomposelli J, Horst D. Enriched branched-chain amino acid formula versus a casein-based supplement in the treatment of cirrhosis. *JPEN J Parenter Enteral Nutr* 1985; **9(6)**: 671-678. <http://dx.doi.org/10.1177/0148607185009006671> PMID:3906162
- 39 Bunout D, Aicardi V, Hirsch S, Peterman M, Kelly M, Silva G, Garay P, Ugarte G, Iturriaga H. Nutritional support in hospitalized patients with alcoholic liver disease. *Eur J Clin Nutr* 1989; **43(9)**: 615-621. PMID:2691239
- 40 Swart GR, van den Berg JW, van Vuure JK, Rietveld T, Wattimena DL, Frenkel M. Minimum protein requirements in liver cirrhosis determined by nitrogen balance measurements at three levels of protein intake. *Clin Nutr* 1989; **8(6)**: 329-336. [http://dx.doi.org/10.1016/0261-5614\(89\)90008-3](http://dx.doi.org/10.1016/0261-5614(89)90008-3)
- 41 Bianchi GP, Marchesini G, Fabbri A, Rondelli A, Bugianesi E, Zoli M, Pisi E. Vegetable versus animal protein diet in cirrhotic patients with chronic encephalopathy. A randomized cross-over comparison. *J Intern Med* 1993; **233(5)**: 385-392. <http://dx.doi.org/10.1111/j.1365-2796.1993.tb00689.x> PMID:8068051
- 42 Nielsen K, Kondrup J, Martinsen L, Dossing H, Larrson B, Stilling B, Jensen MG. Long-term oral refeeding of patients with cirrhosis of the liver. *Br J Nutr* 1995; **74(4)**:557-567. <http://dx.doi.org/10.1079/BJN19950158> PMID:7577893
- 43 Córdoba J, López-Hellín J, Planas M, Sabin P, Sanpredo 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. <http://dx.doi.org/10.1016/j.jhep.2004.03.023> PMID:15246205
- 44 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)**: 231-238. PMID:16200232
- 45 Cabre E, Gonzales-Huix F, Abad-Lacruz A, Esteve M, Acero D, Fernandez-Banares F, Xiol X, Gassull M. Effect of total enteral nutrition on the short-term outcome of severely malnourished cirrhotics. A randomized clinical trial. *Gastroenterology*. 1990; **98(3)**: 715-20. PMID:2105256
- 46 Häussinger D. Hepatic encephalopathy. *Acta Gastroenterol Belg* 2010; **73(4)**: 457-464. PMID:21299155
- 47 Morgan TR, Moritz TE, Mendenhall CL, Haas R. Protein consumption and hepatic encephalopathy in alcoholic hepatitis. VA Cooperative Study Group #275. *J Am Coll Nutr* 1995; **14(2)**: 152-158. <http://dx.doi.org/10.1080/07315724.1995.10718487> PMID:7790689
- 48 Gaffney-Stomberg E, Insogna KL, Rodriguez NR, Kerstetter JE. Increasing dietary protein requirements in elderly people for optimal muscle and bone health. *J Am Geriatr Soc* 2009; **57(6)**: 1073-1079. <http://dx.doi.org/10.1111/j.1532-5415.2009.02285.x> PMID:19460090
- 49 Vellas BJ, Hunt WC, Romero LJ, Koehler KM, Baumgartner RN, Garry PJ. Changes in nutritional status and patterns of morbidity among free-living elderly persons: a 10-year longitudinal study. *Nutrition* 1997; **13(6)**: 515-519. [http://dx.doi.org/10.1016/S0899-9007\(97\)00029-4](http://dx.doi.org/10.1016/S0899-9007(97)00029-4)
- 50 Stein TP, Blanc S. Does protein supplementation prevent muscle disuse atrophy and loss of strength? *Crit Rev Food Sci Nutr* 2011; **51(9)**: 828-834. <http://dx.doi.org/10.1080/10408398.2010.482679> PMID:21888533
- 51 Antar R, Wong P, Ghali P. A meta-analysis of nutritional supplementation for management of hospitalized alcoholic hepatitis. *Can J Gastroenterol* 2012; **26(7)**: 463-467. PMID:22803023 PMCid:PMC3395449
- 52 Fenton JC, Knight EJ, Humpherson PL. Milk-and-cheese diet in portal-systemic encephalopathy. *Lancet* 1966; **1(7430)**: 164-166. [http://dx.doi.org/10.1016/S0140-6736\(66\)90696-9](http://dx.doi.org/10.1016/S0140-6736(66)90696-9)
- 53 Uribe M, Márquez MA, Garcia Ramos G, Ramos-Urbe MH, Vargas F, Villalobos A, Ramos C. Treatment of chronic portal-systemic encephalopathy with vegetable and animal protein diets. A controlled crossover study. *Dig Dis Sci* 1982; **27(12)**: 1109-1116. <http://dx.doi.org/10.1007/BF01391449> PMID:6756833
- 54 de Bruijn KM, Blendis LM, Zilm DH, Carlen PL, Anderson GH. Effect of dietary protein manipulation in subclinical portal-systemic encephalopathy. *Gut* 1983; **24(1)**: 53-60. <http://dx.doi.org/10.1136/gut.24.1.53> PMID:6336714 PMCid:PMC1419916
- 55 Shaw S, Worner TM, Lieber CS. Comparison of animal and vegetable protein sources in the dietary management of hepatic encephalopathy. *Am J Clin Nutr* 1983; **38(1)**: 59-63. PMID:6858955
- 56 Lord C, Chaput JP, Aubertin-Leheudre M, Labonté M, Dionne IJ. Dietary animal protein intake: association with muscle mass index in older women. *J Nutr Health Aging* 2007; **11(5)**: 383-387. PMID:17657359
- 57 Miwa Y, Shiraki M, Kato M, Tajika M, Mohri H, Murakami N, Kato T, Ohnishi H, Morioku T, Muto Y, Moriwaki H. Improvement of fuel metabolism by nocturnal energy supplementation in patients with liver cirrhosis. *Hepatol Res* 2000; **18(3)**:184-189. <http://dx.doi.org/10.1016/S1386->

- 6346(99)00100-X
- 58 Pennings B, Groen B, de Lange A, Gijzen AP, Zorenc AH, Senden JM, van Loon LJ. Amino acid absorption and subsequent muscle protein accretion following graded intakes of whey protein in elderly men. *Am J Physiol Endocrinol Metab* 2012; **302(8)**: E992-999. <http://dx.doi.org/10.1152/ajpendo.00517.2011> PMID:22338070
- 59 Yang Y, Breen L, Burd NA, Hector AJ, Churchward-Venne TA, Josse AR, Tarnopolsky MA, Phillips SM. Resistance exercise enhances myofibrillar protein synthesis with graded intakes of whey protein in older men. *Br J Nutr* 2012; **108(10)**: 1780-1788. <http://dx.doi.org/10.1017/S0007114511007422> PMID:22313809
- 60 Symons TB, Sheffield-Moore M, Wolfe RR, Paddon-Jones D. A moderate serving of high-quality protein maximally stimulates skeletal muscle protein synthesis in young and elderly subjects. *J Am Diet Assoc* 2009; **109(9)**: 1582-1586. <http://dx.doi.org/10.1016/j.jada.2009.06.369> PMID:19699838 PMCid:PMC3197704
- 61 Bollwein J, Diekmann R, Kaiser MJ, Mauer JM, Uter W, Sieber CC, Volkert D. Distribution but not amount of protein intake is associated with frailty: a cross-sectional investigation in the region of Nürnberg. *Nutr J* 2013; **12(1)**: 109. <http://dx.doi.org/10.1186/1475-2891-12-109> PMID:23915061 PMCid:PMC3750269
- 62 Mamerow MM, Mettler JA, English KL, Casperson SL, Arentson-Lantz E, Sheffield-Moore M, Layman DK, Paddon-Jones D. Dietary protein distribution positively influences 24-h muscle protein synthesis in healthy adults. *J Nutr* 2014; **144(6)**: 876-880. <http://dx.doi.org/10.3945/jn.113.185280> PMID:24477298 PMCid:PMC4018950
- 63 Bouillanne O, Curis E, Hamon-Vilcot B, Nicolis I, Chretien P, Schauer N, Vincent JP, Cynober L, Aussel C. Impact of protein pulse feeding on lean mass in malnourished and at-risk hospitalized elderly patients: a randomized controlled trial. *Clin Nutr* 2013; **32**: 186-192. <http://dx.doi.org/10.1016/j.clnu.2012.08.015> PMID:22992307
- 64 Paddon-Jones D, Leidy H. Dietary protein and muscle in older persons. *Curr Opin Clin Nutr Metab Care* 2014; **17(1)**: 5-11. <http://dx.doi.org/10.1097/MCO.0000000000000011> PMID:24310053 PMCid:PMC4162481
- 65 Arnal MA, Mosoni L, Boirie Y, Houlier ML, Morin L, Verdier E, Ritz P, Antoine JM, Prugnaud J, Beaufrere B, Mirand PP. Protein pulse feeding improves protein retention in elderly women. *Am J Clin Nutr* 1999; **69(6)**: 1202-1208. PMID:10357740
- 66 Tieland M, Borgonjen-Van den Berg KJ, van Loon LJ, de Groot LC. Dietary protein intake in community-dwelling, frail, and institutionalized elderly people: scope for improvement. *Eur J Nutr* 2012; **51(2)**: 173-179. <http://dx.doi.org/10.1007/s00394-011-0203-6> PMID:21562887
- 67 Groen BB, Res PT, Pennings B, Hertle E, Senden JM, Saris WH, van Loon LJ. Intra-gastric protein administration stimulates overnight muscle protein synthesis in elderly men. *Am J Physiol Endocrinol Metab* 2012; **302(1)**: E52-60. <http://dx.doi.org/10.1152/ajpendo.00321.2011> PMID:21917635
- 68 Yamanaka-Okumura H, Nakamura T, Takeuchi H, Miyake H, Katayama T, Arai H, Taketani Y, Fujii M, Shimada M, Takeda E. Effect of late evening snack with rice ball on energy metabolism in liver cirrhosis. *Eur J Clin Nutr* 2006; **60(9)**: 1067-1072. <http://dx.doi.org/10.1038/sj.ejcn.1602420> PMID:16508643
- 69 Dirks ML, Wall BT, Nilwik R, Weerts DH, Verdijk LB, van Loon LJ. Skeletal muscle disuse atrophy is not attenuated by dietary protein supplementation in healthy older men. *J Nutr* 2014; **144(8)**: 1196-1203. <http://dx.doi.org/10.3945/jn.114.194217> PMID:24919692
- 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)**: 137-140. <http://dx.doi.org/10.3945/ajcn.2010.29211> PMID:20444959
- 71 Tsien C, McCullough A, Dasarathy S. Late evening snack: exploiting a period of anabolic opportunity in cirrhosis. *J Gastroenterol Hepatol* 2012; **27**: 430-441. <http://dx.doi.org/10.1111/j.1440-1746.2011.06951.x> PMID:22004479
- 72 Fukushima H, Miwa Y, Ida E, Kuriyama S, Toda K, Shinomura Y, Sugiyama A, Sugihara J, Tomita E, Moriwaki H. Nocturnal branched-chain amino acid administration improves protein metabolism in patients with liver cirrhosis: comparison with daytime administration. *JPEN J Parenter Enteral Nutr* 2003; **27(5)**: 315-322. <http://dx.doi.org/10.1177/0148607103027005315> PMID:12971730
- 73 Sako K, Imamura Y, Nishimata H, Tahara K, Kubozono O, Tsubouchi H. Branched-chain amino acids supplements in the late evening decrease the frequency of muscle cramps with advanced hepatic cirrhosis. *Hepatol Res* 2003; **26(4)**:327-329.
- 74 Nakaya Y, Okita K, Suzuki K, Moriwaki H, Kato A, Miwa Y, Shiraishi K, Okuda H, Onji M, Kanazawa H, Tsubouchi H, Kato S, Kaito M, Watanabe A, Habu D, Ito S, Ishikawa T, Kawamura N, Arakawa Y; BCAA-enriched snack improves nutritional state of cirrhosis. *Nutrition* 2007; **23(2)**: 113-120. <http://dx.doi.org/10.1016/j.nut.2006.10.008> PMID:17234504
- 75 Yamauchi M, Takeda K, Sakamoto K, Ohata M, Toda G. Effect of oral branched chain amino acid supplementation in the late evening on the nutritional state of patients with liver cirrhosis. *Hepatol Res* 2001; **21(3)**:199-204. [http://dx.doi.org/10.1016/S1386-6346\(01\)00105-X](http://dx.doi.org/10.1016/S1386-6346(01)00105-X)
- 76 Yamanaka-Okumura H, Nakamura T, Miyake H, Takeuchi H, Katayama T, Morine Y, Imura S, Shimada M, Takeda E. Effect of long-term late-evening snack on health-related quality of life in cirrhotic patients. *Hepatol Res* 2010; **40(5)**: 470-476. <http://dx.doi.org/10.1111/j.1872-034X.2010.00637.x> PMID:20412329
- 77 Dam G, Ott P, Aagaard NK, Vilstrup H. Branched-chain amino acids and muscle ammonia detoxification in cirrhosis. *Metab Brain Dis* 2013; **28(2)**: 217-220. <http://dx.doi.org/10.1007/s11011-013-9377-3> PMID:23315357
- 78 Wall BT, van Loon LJ. Nutritional strategies to attenuate muscle disuse atrophy. *Nutr Rev* 2013; **71(4)**: 195-208. <http://dx.doi.org/10.1111/nure.12019> PMID:23550781
- 79 Fabbri A, Magrini N, Bianchi G, Zoli M, Marchesini G. Overview of randomized clinical trials of oral branched-chain amino acid treatment in chronic hepatic encephalopathy. *JPEN J Parenter Enteral Nutr* 1996; **20(2)**: 159-164. <http://dx.doi.org/10.1177/0148607196020002159> PMID:8676537
- 80 Als-Nielsen B, Koretz RL, Kjaergard LL, Gluud C. Branched-chain amino acids for hepatic encephalopathy. *Cochrane Database Syst Rev* 2003(2):CD001939. PMID:12804416
- 81 Gluud LL, Dam G, Borre M, Les I, Cordoba J, Marchesini G, Aagaard NK, Risum N, Vilstrup H. Oral branched-chain amino acids have a beneficial effect on manifestations of hepatic encephalopathy in a systematic review with meta-analyses of randomized controlled trials. *J Nutr* 2013; **143(8)**: 1263-1268. <http://dx.doi.org/10.3945/jn.113.174375> PMID:23739310
- 82 Fukushima H, Miwa Y, Shiraki M, Gomi I, Toda K, Kuriyama S, Nakamura H, Wakahara T, Era S, Moriwaki H. Oral branched-chain amino acid supplementation improves the oxidized/reduced albumin ratio in patients with liver cirrhosis. *Hepatol Res* 2007; **37(9)**: 765-770. <http://dx.doi.org/10.1111/j.1872-034X.2007.00123.x> PMID:17573945
- 83 Marchesini G, Dioguardi FS, Bianchi GP, Zoli M, Bellati G, Roffi L, Martinez D, Abbiati R. Long-term oral branched-chain amino acid treatment in chronic hepatic encephalopathy.

- A randomized double-blind casein-controlled trial. The Italian Multicenter Study Group. *J Hepatol.* 1990; **11**(1): 92-101. [http://dx.doi.org/10.1016/0168-8278\(90\)90278-Y](http://dx.doi.org/10.1016/0168-8278(90)90278-Y)
- 84 Muto Y, Sato S, Watanabe A, Moriwaki H, Suzuki K, Kato A, Kato M, Nakamura T, Higuchi K, Nishiguchi S, Kumada H. Effects of oral branched-chain amino acid granules on event-free survival in patients with liver cirrhosis. *Clin Gastroenterol Hepatol* 2005; **3**(7): 705-713. [http://dx.doi.org/10.1016/S1542-3565\(05\)00017-0](http://dx.doi.org/10.1016/S1542-3565(05)00017-0)
- 85 Les I, Doval E, García-Martínez R, Cárdenas G, Gómez P, Flavià M, Jacas C, Mínguez B, Vergara M, Soriano G, Vila C, Esteban R, Córdoba J. Effects of branched-chain amino acids supplementation in patients with cirrhosis and a previous episode of hepatic encephalopathy: a randomized study. *Am J Gastroenterol* 2011; **106**(6): 1081-1088. <http://dx.doi.org/10.1038/ajg.2011.9> PMID:21326220

**Peer reviewer:** Bulent Baran, MD, Department of Gastroenterohepatology, Istanbul University, Istanbul Faculty of Medicine, Capa, Istanbul, 34093, Turkey.