Nutrition in Cirrhosis

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Protein-calorie malnutrition (PCM) is extremely common in cirrhosis, it is potentially reversible, and negatively affects outcomes.

There is not complete agreement in how to define PCM in cirrhosis, but different parameters have been used:

- Anthropometrics, skinfold thickness (triceps-biceps-subscapular-suprailiac), mid-arm muscle circumference (< 23 cm), hand grip dynamometry, indirect calorimetry, immune response, subjective global assessment, etc.

PCM worsens with disease progression.

- By "body composition analysis" is: Child-A 34%, Child-B 69%, Child-C 94%

Many complications of liver disease, like encephalopathy and ascites, are worsened by negative nitrogen balance.

Muscular mass is important in removing circulating ammonia.

Prevalence of PCM in cirrhosis varies from 6 to 99% depending on which parameters are used and in how severe is the liver disease (degree of decompensation).

Sarcopenia in cirrhosis is more prevalent in males (63%) than in females (28%).
Causes of Malnutrition in Advanced Cirrhosis


- INADEQUATE NUTRIENT INTAKE
  - Anorexia
  - Nausea and/or vomiting
  - Bloating/abdominal distention
  - Abdominal discomfort
  - Ascites
  - Encephalopathy
  - Delayed gastric emptying
  - Restrictive diet (Na, Protein, ...)
  - Dysgeusia (Zn deficiency)
  - Alcohol intake
  - Socioeconomic barriers

- METABOLIC DISTURBANCES
  - Altered glucose, lipid and protein metabolism
  - Altered pattern of energy consumption
  - Insulin resistance

- MALABSORPTION
  - Cholestasis (bile acid deficiency)
  - Small bowel bacterial overgrowth

- DECREASED LIVER STORAGE CAPACITY
The most clinically useful parameters to assess PCM and Sarcopenia are:

- Hand grip dynamometry (< 30 kg) in males,
- Subjective global assessment in both males and females (underestimates malnutrition),
- Royal Free Hospital – Global Assessment (BMI + MAMC + dietary intake history) in males (Hepatology 2006;44:823-835)

Hand grip dynamometry

- predicts development of major complications of cirrhosis in males with well compensated cirrhosis (but not in women), and

Degree of “core muscular mass” sarcopenia, measured by CT Scan or MRI, is associated with waiting-list and post-transplant mortality.
Clinical phenotypes of Malnutrition:

- sarcopenia,
- adipopenia,
- proportional sarcopenia + adipopenia (hepatic cachexia),
- “sarcopenic obesity” (with normal or high visceral and subcutaneous fat), specially in NASH,
- micronutrient deficiencies.
Derivation and validation of a new global method for assessing nutritional status in patients with cirrhosis

Royal Free Hospital – Global Assessment of Nutrition in Cirrhosis
Skeletal mass depends on muscular protein synthesis, protein destruction and in “satellite cell” proliferation.

Satellite cells are myogenically committed stem cells that are needed for maintenance and growth of muscle.

Muscular growth need muscular protein synthesis + satellite cell proliferation (2-4% of muscle mass).

The most important factor causing sarcopenia is decreased protein synthesis.

Increased protein destruction adds to the problem worsening muscle loss.

There are 3 factor affecting muscle synthesis and regeneration:

- IGF (insulin-like growth factor): stimulates protein synthesis and satellite cell proliferation. Decreased in cirrhosis.
- Myostatin: inhibits protein synthesis and satellite cell proliferation: Increased in cirrhosis.
Resting Energy expenditure (corrected by lean body mass) is increased in cirrhosis.

Measured energy expenditure is higher than predicted energy expenditure in 30% of patients with cirrhosis patients.

Cirrhotic patients have decreased glycogen synthesis and glycogen storage.

Cirrhotic patients have “accelerated starvation” with excessive production of energy from fat, and with excessive gluconeogenesis from aminoacids after an overnight fast.

When gluconeogenesis is utilized to cover glucose needs, this causes loss of aminoacids, increases ammonia production, and increases protein needs.

A late evening snack reverses this starvation mode and improves nitrogen balance.

The snack should have at least 50 g of complex carbohydrates;

The addition of 26-30 g of protein will be ideal.

Frequent meals (Vaisman N; Am J Clin Nutr 2010;92:137–140) and improved nutrition are useful in controlling hepatic encephalopathy.
Effect of Late Snack in Substrate Utilization

Substrate Utilization in Cirrhotics Versus Controls

- **Cirrhosis No Late Snack**: Carbohydrate 26, Fat 58, Protein 16
- **Cirrhosis Late Snack**: Carbohydrate 45, Fat 42, Protein 13
- **CONTROL No Late Snack**: Carbohydrate 55, Fat 23, Protein 22
- **CONTROL Late Snack**: Carbohydrate 54, Fat 24, Protein 22

Effect of Bedtime Snack and Meal Frequency in Nitrogen Balance

McCullough AI AASLD Postgraduate Course 2013; 142-150

Nitrogen Balance (g/day)

- 4 Meals
  - No Bedtime Snack
  - Bedtime Snack

- 6 Meals
  - No Bedtime Snack
  - Bedtime Snack
Formulas to calculate Energy Requirements (Benedict-Harris) are specially poor in cirrhosis (ascites, edema, high resting energy expenditure, hyperdynamic state, ...)

Insulin Resistance is universal in cirrhosis, independent of the cause of liver injury.

Hypoglycemia is common in cirrhosis with sepsis.

Lipid formulations can give many calories in low volume and do not add free-water, that can worsen hyponatremia.

Lipids do not precipitate hepatic encephalopathy; 25-30% of calories should come from fat.

Best is to measure Resting Energy Expenditure by Indirect Calorimetry, otherwise

**RECOMMENDATION:** Give 35-40 kcal/kg of Ideal Body Weight
There is great range in protein requirements in cirrhosis when compared with controls.

Compensated cirrhotics should receive at least 1 g/kg IBW of protein to cover nitrogen needs.

Nitrogen retention can be improved up to 1.8-2 g/kg IBW.

Patients with Hepatic Encephalopathy tolerate and benefit from normal protein diets.

- Protein restriction should be avoided.

Dairy protein is better tolerated than protein from mix-sources.

Vegetable protein is better tolerated than animal protein (pre-biotic effect of fiber?).

- When possible give 30-40 g of vegetable protein/day.

BCAAs can be used in patients “protein intolerant”; the high leucine stimulates “hepatocyte growth factor” secretion by stellate cells, muscle protein synthesis and insulin secretion.

RECOMMENDATION: Most cirrhotics should receive 1.2-1.5/kg IBW.
# Recommended Intake in Cirrhosis (With or without Hepatic Encephalopathy)

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<tr>
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<th>Adequately Nourished</th>
<th>Moderately Malnourished</th>
<th>Severely Malnourished</th>
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<td><strong>Body Weight</strong></td>
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<td>Normal-Overweight</td>
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<td><strong>Daily Energy</strong></td>
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<td>(kcal/kg IBW)</td>
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<td><strong>Daily Protein</strong></td>
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<td>(g/kg IBW)</td>
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* Reducing Carbohydrates and Fat
Nutrition in Hepatic Encephalopathy

Low- vs Normal-Protein Diet in HE
Cordoba J; J Hepatol 2004;41:38–43

Probiotic Yogurt in Covert Hepatic Encephalopathy
Bajaj JS; Am J Gastroenterol 2008;103:1707-1715

Diet with “normal protein intake” improves HE equally as “low protein” diet

12 ounces of Probiotic Yogurt a day

Probiotic Yogurt Improves Covert HE & Protects against Overt HE
Branched-chain amino acids for people with hepatic encephalopathy
Cochrane Database Syst Rev. 2015 Feb 25;2

Trial sequential analysis of branched-chain amino acids (BCAA) versus control interventions (placebo, no intervention, neomycin, or lactulose) for hepatic encephalopathy: Beneficial for HE but NOT for mortality.
Day-time vs Night-time Nutrition Supplementation

Plank LD; Hepatology 2008; 48(2):557-66

500-710 kcal
26-30 g protein

After 9 pm (black bars)

7 am-7 pm (white bars)

Bed-time Nutrition Increases Nitrogen Retention & Muscular Mass
(equivalent to 2 kg of muscle, after 12 months)
Prebiotics are selectively fermented ingredients that modify the activity and/or composition of the GI flora. Lactulose and soluble fiber are Prebiotics that improve HE.

Probiotics are live microorganisms that can alter intestinal flora when given in adequate quantity.

Symbiotics are the combination of Pre- and Pro-biotics.

Meta-analysis of the high quality studies of the effect of Probiotics in HE show beneficial effect in decreasing risk of Over HE without increasing adverse events.

Live-culture Yogurt (a symbiotic) has shown to improve Minimal or Covert HE and to protect against Overt HE.

Fiber intake of 25-45 g a day increases fullness and helps in weight control; also works as a prebiotic.
Probiotics decrease the risk of Overt HE

Probiotics did not affect mortality
Thiamine deficiency is common, specially in the alcoholic, and may be subclinical.

Other vitamin deficiencies (A, D, E, K, Folate, B₆, B₁₂, C niacin) may be present and difficult to identify.

- Daily multivitamins will correct deficiencies.

Sodium restriction is needed when ascites or edema are present; usually the diet will be restricted to 88 mMol (2 g) of Na a day.

- To make a liter of ascites are needed 3 g of Na.

Hyponatremia, either dilutional or due to excessive diuretic use is common.

- Is important to avoid intravascular contraction.

- In case of dilutional hyponatremia, total fluid intake will have to be restricted.

Zinc deficiency may worsen HE because ornithine transcarbamylase and glutamine synthetase are Zn dependent enzymes, and both help in ammonia detoxification.

Fe deficiency is common. Se may also be deficient. Leg cramps often improve with supplementation of Ca, Mg and Zn.
# Additional Nutritional Management Recommendations in Cirrhosis


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<tr>
<th>RECOMMENDATION</th>
<th>Small frequent (≥ 6) meals a day while awake</th>
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<tbody>
<tr>
<td>Meal Pattern</td>
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<tr>
<td>Late-Evening Snack</td>
<td>At least 50 g complex carbohydrates (+ optional 26-30 g protein) nightly</td>
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<td>Nitrogen Source</td>
<td>Per patient preference; encourage dairy + vegetable protein as tolerated</td>
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<td>Fiber</td>
<td>25-45 g per day, especially if overweight</td>
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<td>Micronutrients</td>
<td>Daily Multivitamin with minerals (avoid copper and manganese in cholestasis)</td>
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<td>Poorly controlled HE</td>
<td>Consider Probiotics and/or BCAA supplements (at bedtime)</td>
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Oral diet intake +/- oral supplements is always preferred. If patient cannot cover nutrition needs orally, then naso-enteric tube (with aspiration precautions) is indicated even when varices are present (De Ledinghen V; Dig Dis Sci 1997;42:536–541). Avoid PEG (Loser C; Z Gastroenterol 1996;34:404–8)(Baltz JG; Gastrointestinal Endoscopy 2010;72:1072-75). Use standard formula.

In use of intestine is not possible, use parenteral nutrition.

- Glucose should not exceed 5-6 g/kg/d
- Monitor for hyperglycemia
- In hyperglycemia, limit glucose to 2-3 g/kg/d
- Lipids should not exceed 1 g/kg/d
- Limit Na (60-88 mMol/d) and monitor electrolytes
- Use cyclic regimen (decreases liver enzymes elevation)
- Limit copper and manganese in cholestasis