The Specific Role of Enteral Nutrition to Improve Health Condition in Cirrhotic Patient

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OUTLINE

- Metabolic and nutrient changes in liver cirrhosis patient.
- Malnutrition and Sarcopenia in liver cirrhosis patient.
- Frailty in liver cirrhosis patient.
- Liver cirrhosis patient management.
- Late evening snack.
- BCAA for liver cirrhosis.
- Hepatosol lola for liver cirrhosis.
Metabolic and nutrient changes and in liver cirrhosis patient

- GLUCOSE
- LIPID
- PROTEIN
- MICRO NUTRIENT

Metabolic changes in liver cirrhosis patient

Disorders of carbohydrate metabolism
- Disorders of glycogen storage
- Increased insulin resistance
- Hepatic diabetes mellitus
- Impaired gluconeogenesis
- Increased catabolism

Disorders of protein metabolism
- Hypoalbuminemia
- Decreased colloid osmotic pressure
- Disorders of substance transportation
- Delayed wound healing
- Decreased blood coagulation factor concentrations
- Bleeding tendency
- Disorders of amino acid metabolism
- Hepatic encephalopathy

Disorders of fat metabolism
- Disorders of fat absorption
- Decreased polyunsaturated fatty acid concentrations
- Increased saturated fatty acid concentrations
- Hypcholesterolemia
- Increased serum LDL concentration

Liver cirrhosis

Water retention
- Decreased effective circulating plasma volume
- Decreased GFR
- Pseudohypoaldosteronism
- Increased Na reabsorption
- Increased secretion and decreased decomposition of ADH
- Decreased kallikrein-kinin system
- Inhibition of estrogen inactivation

Glucose metabolic in liver cirrhosis patient

HOMA-Insulin Resistance index (8.38 vs 3.52) were significantly higher in patients with hepatogenous diabetes.

→ insulin resistance in liver cirrhosis is higher than in type 2 DM, and impairment of hepatic insulin degradation may be an important mechanism of hyperinsulinemia in liver cirrhosis.

80-90% of patients with liver cirrhosis have abnormal glucose and hyperinsulinemia.
Causes of abnormal Glucose Tolerance Test

- Insulin resistance (due to ↑ insulin secretion by pankreas)
- ↓ the number of liver parenchyma cells (liver insulin clearance ↓)
- ↑ counter insulin concentration (growth hormon, cortisol, epinephrine)

Hiperinsulinemia
Diabetes Melitus

Glikogen reserves in liver ↓ ➔ Glucose supply at night until morning is interrupted ➔ Free fatty acids ↑ ketone ↑

1 day fasting in liver cirrhosis patient

Equal to 3 days of fasting in normal people

Distribution of daily food intake more than 3 times a day, without increasing the number of calories, is useful for increasing protein metabolism in liver cirrhosis patients.
Lipid Metabolism

Normal people

Cirrhosis patient

Arakawa, Yasuyuki., et al. Liver Cirrhosis and Metabolism (sugar, protein, fat, and tarce element). 2004
Protein Metabolism in Liver Cirrhosis Patient

↑ protein catabolism

↑ ammonia

↓ protein synthesis

↓ essential amino acids

↓ daily protein intake

↓ absorption in the intestine

Arakawa, Yasuyuki., et al. Liver Cirrhosis and Metabolism (sugar, protein, fat, and tarce element). 2004
Protein Metabolism in Liver Cirrhosis Patient

BCAA is metabolized in skeletal muscle, while AAA is metabolized in the liver.

Liver cirrhosis → AAA will ↑ because it can not be metabolized in the liver.

Fig. 5. Amino acid kinetics in the blood.
## AAA Concentrations Differences in Liver Disease


<table>
<thead>
<tr>
<th>Disease name</th>
<th>Plasma AAA concentration (mean±SD)</th>
<th>μ moles/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy adults</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute hepatitis</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Fulminant hepatitis</td>
<td></td>
<td>***</td>
</tr>
<tr>
<td>Chronic inactive hepatitis</td>
<td></td>
<td>***</td>
</tr>
<tr>
<td>Chronic active hepatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compensated liver cirrhosis</td>
<td></td>
<td>***</td>
</tr>
<tr>
<td>Uncompensated liver cirrhosis</td>
<td></td>
<td>***</td>
</tr>
<tr>
<td>Primary liver carcinoma</td>
<td></td>
<td>***</td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-alcoholic fatty liver</td>
<td></td>
<td>**</td>
</tr>
</tbody>
</table>

Significant differences compared to healthy adults: * P<0.05, ** P<0.01, *** P<0.001

Arakawa, Yasuyuki., et al. Liver Cirrhosis and Metabolism (sugar, protein, fat, and tarce element). 2004
Causes of BCAA Concentration Decreased

Fig. 6. Causes of decreased blood branched-chain amino acid (BCAA) concentrations in patients with liver cirrhosis.

*This depends on the balance between hyperinsulinemia and decreased insulin sensitivity.
# Fat-Soluble Vitamin Deficiency

<table>
<thead>
<tr>
<th>VITAMIN DEFICIENCY</th>
<th>SYMPTOMPS</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Nyctalopia</td>
<td>25,000 IU/day vitamin A 4-8 weeks</td>
</tr>
<tr>
<td>D</td>
<td>osteopenia, osteoporosis, and osteomalacia</td>
<td>Daily recommendation: 2000 IU vitamin D2 or D3 and 1200 - 1500 mg Ca.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Untuk defisiensi: 50,000 IU vit D/weeks 8 - 12 weeks (target: 25-hydroxyvitamin D</td>
</tr>
<tr>
<td></td>
<td></td>
<td>level minimal 30 ng/mL).</td>
</tr>
<tr>
<td>E</td>
<td>hemolytic anemia, neuropathy, and creatinuria.</td>
<td></td>
</tr>
<tr>
<td>K</td>
<td>PT prolonged&gt; increased risk of bleeding</td>
<td>Depends on the clinical patient.</td>
</tr>
</tbody>
</table>

### Other Micronutrient Deficiencies

<table>
<thead>
<tr>
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<th>SYMPTOMS</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zn</td>
<td>Dysgeusia, acrodermatitis, glossitis, hypogonadism, and impaired wound healing</td>
<td>50 mg elemental iron / day (220 mg of zinc sulfate)</td>
</tr>
<tr>
<td>Mg</td>
<td>muscle cramps</td>
<td>Supplementation with 400 mg of magnesium oxide is commonly performed in clinical practice</td>
</tr>
<tr>
<td>Mn and Cu</td>
<td>are excreted in bile and may be elevated in patients with chronic liver disease and should not be included in total parenteral nutrition in patients with cholestasis</td>
<td></td>
</tr>
</tbody>
</table>
Metabolic and nutrient changes in liver cirrhosis patient.

Malnutrition and Sarcopenia in liver cirrhosis patient.

Frailty in liver cirrhosis patient.

Liver cirrhosis patient management

Late evening snack.

BCAA for liver cirrhosis.

Hepatosol lola for liver cirrhosis.
Fig. 2. Mechanisms and potential targets for anabolic resistance and dysregulated proteostasis resulting in sarcopenia and/or failure to respond to standard supplementation. Adapted from Dasarathy S. et al. 2016. BCAA, branched chain amino acid; ROS, reactive oxygen species; Tx, treatment.
Complications of Malnutrition in Cirrhosis Patients

- Ascites
- Variceal Bleeding
- Hepatic Encephalopathy
- Liver function ↓
- Vulnerable to infection
- Poor wound healing
- ↑mortality
- ↑mortality

Sarcopenia in Cirrhosis Patients

**Sarcopenia** → the degenerative loss of skeletal muscle mass that is involuntary and age related.

Two types of sarcopenia:

1. **Primary sarcopenia**: resulting from advance age.

2. **Secondary sarcopenia**: caused by chronic conditions such as liver cirrhosis or malignancy.

Lack of Protein Energy: 25.1% - 65.6%

Sarcopenia: 30-70%

Naseer, Maliha., et al. Interventions to Improve Sarcopenia in Cirrhosis. 2019
Sarcopenia in Cirrhosis Patients

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Frailty in Cirrhosis Patients

Frailty →

is a complex syndrome characterised by functional decline and reduced physiologic reserve.

50% with advanced liver disease

↑ morbidity

↑ mortality
Frailty in Cirrhosis Patients

Laube Robyn, et al. Fraility in advanced Liver Disease. 2018
The main domains of decline in Frailty Cirrhosis Patients

Neurologic Changes
- Neuron loss (esp. hippocampus)
- Impaired synapse function
- Altered protein transport

Immune System Changes
- Chronic low-grade inflammation
- Increased neutrophils
- Elevated CRP, IL-6 and TNF-α

Skeletal Muscle Changes
- Increased protein demand
- Muscle breakdown and mobilisation of skeletal muscle amino acids

Gut Microbiome Changes
- Reduced diversity
- Increased Eubacterium dolichum and Eggerthella lenta
- Reduced Faecalibacterium prausnitzii

Endocrine Changes
- Reduced oestradiol and testosterone
- Reduced GH, IGF-1, DHEAS
- Reduced vitamin D levels
Various Scoring on Frailty

1. Physical strength (gait speed, grip strength and chair stands),
2. Self-reported measures of fatigue and functional ability.
3. Mini-Mental State Examination for cognition,
4. Mini Nutritional Assessment for nutritional status,
5. Liver Frailty Index (grip, chair stands, balance)

Management in Patients with Frailty

Table 3. Management approaches to frailty

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
</tr>
<tr>
<td>- Aerobic exercise</td>
</tr>
<tr>
<td>- Resistance training</td>
</tr>
<tr>
<td>- Prehabilitation program prior to surgery or liver transplantation</td>
</tr>
<tr>
<td>Nutrition</td>
</tr>
<tr>
<td>- Adequate caloric intake to meet daily requirements</td>
</tr>
<tr>
<td>- Protein supplementation</td>
</tr>
<tr>
<td>- Late night snacks</td>
</tr>
<tr>
<td>Pharmacologic</td>
</tr>
<tr>
<td>- Consider testosterone supplemendation in patients with low serum testosterone levels</td>
</tr>
<tr>
<td>Cognitive</td>
</tr>
<tr>
<td>- Cognitive training programs including memory, attention and problem-solving tasks</td>
</tr>
</tbody>
</table>
Correlation Between Hand Grip Strength with Child Pugh Score and Muscle Mass in Liver Cirrhosis

The strength of the hand grip is positively correlated with the muscle mass of liver cirrhosis patient, but does not correlate with the Child Pugh score of the liver cirrhosis patient.

<table>
<thead>
<tr>
<th>Table 5.7: Correlation between Hand Grip Strength (KGT) with Muscle Mass (analisis subgrup)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameter</strong></td>
</tr>
<tr>
<td>&lt;50 tahun</td>
</tr>
<tr>
<td>≥50 tahun</td>
</tr>
<tr>
<td><strong>Jenis Kelamin</strong></td>
</tr>
<tr>
<td>Laki-laki</td>
</tr>
<tr>
<td>Perempuan</td>
</tr>
<tr>
<td><strong>Komorbid</strong></td>
</tr>
<tr>
<td>Komorbid (+)</td>
</tr>
<tr>
<td>Komorbid (-)</td>
</tr>
<tr>
<td><strong>Hemoglobin</strong></td>
</tr>
<tr>
<td>Anemia</td>
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<td>Tidak Anemia</td>
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Screening and Assessment of Cirrhosis Patient Nutrition Status
Parameters for Malnutrition Assessment

1. Nutrition screening by using *Nutrition Screening Initiative (NSI)* checklist (global standard).

2. Comprehensively evaluated with:
   - *Subjective Global Assessment* (SGA),
   - Physical examination (*Mid Arm Muscle Circumference* dan *Triceps Skin Fold Thickness*)
   - Urine and blood test (*albumin*)
   - Immunology test
   - Muscle strength test
   - Measurement of calorie value using indirect calorimeter (*Respiratory Quotient*).
If nutritional requirements cannot be met through oral feeding, the next line of therapy is tube feeding.

Contraindications in using PEG (Percutaneous Endoscopic Gastrostomy):

1. ascites,
2. bleeding varices,
3. coagulopathy or other sequela of decompensated cirrhosis.

Due to this, clinicians are rarely inclined to use a PEG tube for cirrhotic patients.

If nutritional status continues to decline → patients begin tube feeding within 1 wk of inadequate oral intake.

Delaying the onset of tube feeding is associated with worse outcomes and delayed improvement in nutritional status.

NG tubes are recommended, since PEG tubes are often contraindicated in chronic liver disease patients.
Nutritional recommendation

Optimizing the Nutritional Support of Adult Patients in the Setting of Cirrhosis

Brandon J. Perumpail, Andrew A. Li, George Cholankeril, Radhika Kumari and Aijaz Ahmed.

Nutritional Recommendations for Malnutrition in Cirrhosis

<table>
<thead>
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<tbody>
<tr>
<td>Daily Calories</td>
</tr>
<tr>
<td>Proteins</td>
</tr>
<tr>
<td>Carbohydrates</td>
</tr>
<tr>
<td>Lipids</td>
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Special Considerations

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<tr>
<td>Hepatic Encephalopathy</td>
</tr>
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<td>Ascites</td>
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Late evening snack

**Results:** Late evening snack decreased lipid oxidation and improved nitrogen balance, irrespective of the composition or type of formulation used. Daytime isocaloric isonitrogenous snacks did not have the metabolic or clinical benefit of LES. LES decreased skeletal muscle proteolysis. No studies have examined its effect on muscle protein synthesis. There was inconsistent translation into an increase in lean body or skeletal muscle mass. Improved quality of life occurs but decreased mortality or need for transplantation has not been reported. The optimal composition of LES has not been defined, but based on mechanistic considerations, a branched chain supplemented LES holds most promise.

**Conclusions:** Late evening snack holds the most promise as an intervention to reverse anabolic resistance and sarcopenia of cirrhosis with improved quality of life in patients with cirrhosis. Long term benefit and improved survival need critical evaluation.
There was a significant changes in Albumin given LES (MD = 0.77, 95% CI: 0.09–1.45, P = 0.03)

**Figure 2: Forest plot for ALB (RCTs).**
There was a significant changes in Prealbumin given LES (MD = 85.84, 95% CI: 41.33-130.34, P = 0.0002)
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The mechanism of increasing albumin by BCAA

Branched-Chain Amino Acids as Pharmacological Nutrients in Chronic Liver Disease

Takumi Kawaguchi,1 Namiki Izumi,2 Michael R. Charlton,3 and Michio Sata1

Branched-chain amino acids (BCAAs) are a group of essential amino acids comprising valine, leucine, and isoleucine. A low ratio of plasma BCAAs to aromatic amino acids is a physiological hallmark of liver cirrhosis, and BCAA supplementation was originally devised with the intention of normalizing amino acid profiles and nutritional status. However, recent studies on BCAAs have revealed that, in addition to their role as protein constituents, they may have a role as pharmacological nutrients for patients with chronic liver disease. Large-scale, multicenter, randomized, double-blinded, controlled trials on BCAA supplementation have been performed in Italy and Japan, and results demonstrate that BCAA supplementation improves not only nutritional status, but also prognosis and quality of life in patients with liver cirrhosis. Moreover, accumulating experimental evidence suggests that the favorable effects of BCAA supplementation on prognosis may be supported by unforeseen pharmacological actions of BCAAs. This review summarizes the possible effects of BCAAs on albumin synthesis and insulin resistance from clinical and basic viewpoints. We also review the newly discovered clinical impact of BCAAs on hepatocellular carcinoma and the prognosis and quality of life of patients with liver cirrhosis. (Hepatology 2011;54:1063-1070)
Albumin Repair Mechanism by BCAA
Cirrhosis Patient Outcome Treated with BCAA

Effects of Oral Branched-Chain Amino Acids on Hepatic Encephalopathy and Outcome in Patients With Liver Cirrhosis

Takumi Kawaguchi, MD, PhD\textsuperscript{1,2}; Eitaro Taniguchi, MD, PhD\textsuperscript{1}; and Michio Sata, MD\textsuperscript{1,2}

Table 2. Randomized Control Trials of Oral BCAA Supplementation on MHE in Cirrhotic Patients.

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Control</th>
<th>Dose of BCAAs</th>
<th>Trial Period</th>
<th>Improvement of MHE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plauth et al\textsuperscript{3}</td>
<td>17</td>
<td>No amino acids</td>
<td>3 g/day</td>
<td>8 weeks</td>
<td>Yes</td>
</tr>
<tr>
<td>Les et al\textsuperscript{4}</td>
<td>116</td>
<td>Maltodextrin</td>
<td>30 g/day/day</td>
<td>56 weeks</td>
<td>Yes</td>
</tr>
</tbody>
</table>

BCAAs, branched-chain amino acids; MHE, minimal hepatic encephalopathy.
Protein intake should not be restricted in cirrhotic patients with hepatic encephalopathy as it increase catabolism

Grade of recommendation B – Consensus 100 % agreement

Long-term oral BCAA supplements (0.25 g/kg/day) should be prescribed in patients with advance cirrhosis in order to improve event-free survival or quality of live

Grade of recommendation B – Consensus 89 % agreement

After an episode of HE, BCAA supplementation for 12 months improved minimal HE and muscle mass, improved sarcopenia
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The Effect of L-ornithine L-aspartate and Branch Chain Amino Acids on Encephalopathy and Nutritional Status in Liver Cirrhosis with Malnutrition

Suzanna Ndraha, Irsan Hasan, Marcellus Simadibrata

Department of Internal Medicine, Faculty of Medicine, University of Indonesia - Dr. Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta Pusat 10410, Indonesia.

Correspondence mail to: susen.ndraha@yahoo.co.id
Perbaikan prealbumin sesudah perbaikan gizi dengan substitusi BCAA pada EHM (p=0,005)

Tidak ada perbaikan CFF sesudah perbaikan gizi dengan substitusi BCAA pada EHM (p=0.246)
Perbaikan prealbumin sesudah perbaikan gizi dengan substitusi BCAA + LOLA pada EHM (p = 0,008)

Perbaikan CFF sesudah perbaikan gizi dengan substitusi BCAA + LOLA pada EHM (p = <0,001)
Simpulan

• Pasien sirosis hati cenderung mengalami malnutrisi
• Pengelolaan nutrisi pada pasien sirosis hati sangat penting karena berhubungan dengan ketahanan hidup pasien
• Pasien sirosis hati harus di nilai malnutrisi, sarcopenia dan fraility sebagai bagian yang
• Komprehensif dalam tatalaksana pasien sirosis hati
• Kecukupan energi, protein, lemak dan micronutrien perlu di jaga
• BCAA dapat digunakan apabila pasien sirosis tidak bisa mentolerir masukan protein
• Pemberian LOLA dapat mengurangi Ensefalopati hepatik
Thankyou
GOLDEN AGE OF HEPATOLOGY
MARCH, 4TH-8TH 2020
BALI NUSA DUA CONVENTION CENTER

Website: apasl2020.org | Email: info@apasl2020.org