NUTRITIONAL OPTIMIZATION IN PRE LIVER TRANSPLANT PATIENTS

ACHIEVING NUTRITIONAL ADEQUACY

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NUTRITION IN LIVER FAILURE

extent of problem and consequences

MALNUTRITION IN LIVER CIRRHOSIS
PREVALENCE AND OUTCOMES

PREVALENCE OF MALNUTRITION IN CHRONIC LIVER DISEASE

- Early cirrhosis - protein deficiency
- Late cirrhosis - protein energy malnutrition (PEM)

Child A - 20%

Child B and C - 50 to 70%

Before liver transplant 80 to 100%

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- more prevalent in alcoholic vs. non alcoholic
- alcoholics - malabsorption, pancreatic insufficiency
- cholestatic - more calorie deficient, loss of fat soluble vitamins
- obesity - in up to 20% of non alcoholic patients
- women lose more body fat; men have reduced lean body mass

CONSEQUENCES OF MALNUTRITION

MALNUTRITION IN LIVER CIRRHOSIS

- increases morbidity and mortality
- increased risk of complications - twice or more - infections, refractory ascites, hepatic encephalopathy and variceal bleed
- independent predictor of mortality in end stage liver cirrhosis
- increased complications and mortality after liver transplantation

Henkel and Buchman. Nutritional support in chronic liver disease. Nature 2006.

Table 4 Relationship between nutritional status and outcome after liver transplantation.

Authors and reference no.	Patients (*n*)	Parameters used for the assessment of nutritional status	Prevalence of malnutrition (%)	Outcomes related to malnutrition
Pikul et al[39]	68	SGA	79	Prolonged ventilator support Increased incidence of tracheostomy More days in intensive care unit and hospital
Selberg et al[41]	150	Anthropometry Body composition analysis Indirect calorimetry	41–53	Low survival 5 years after liver transplantation
Harrison et al[42]	102	Anthropometry Dietary intake	79	Higher risk of infections
Figueridо et al[40]	53	SGA Hand-grip strength Body composition analysis	87	More days in intensive care unit Increased incidence of infections
Stephenson et al[33]	99	SGA	100	Increased blood product requirements More days in hospital
Shahid et al[43]	61	Hand-grip strength Anthropometry	Not defined	No correlation
De Luis et al[44]	31	SGA Body composition analysis Dietary intake	Not defined	No correlation
Merli et al[34]	38	SGA Anthropometry Indirect calorimetry Dietary intake	53	More days in intensive care unit and hospital Increased incidence of infections

MALNUTRITION OUTCOMES AFTER LIVER TRANSPLANT

- higher rate of post transplant complications - infections, bleeding
- require more blood products intra-operatively
- need longer ventilatory support
- increased length of hospital stay
- higher incidence of liver graft failure
- decreased survival rate

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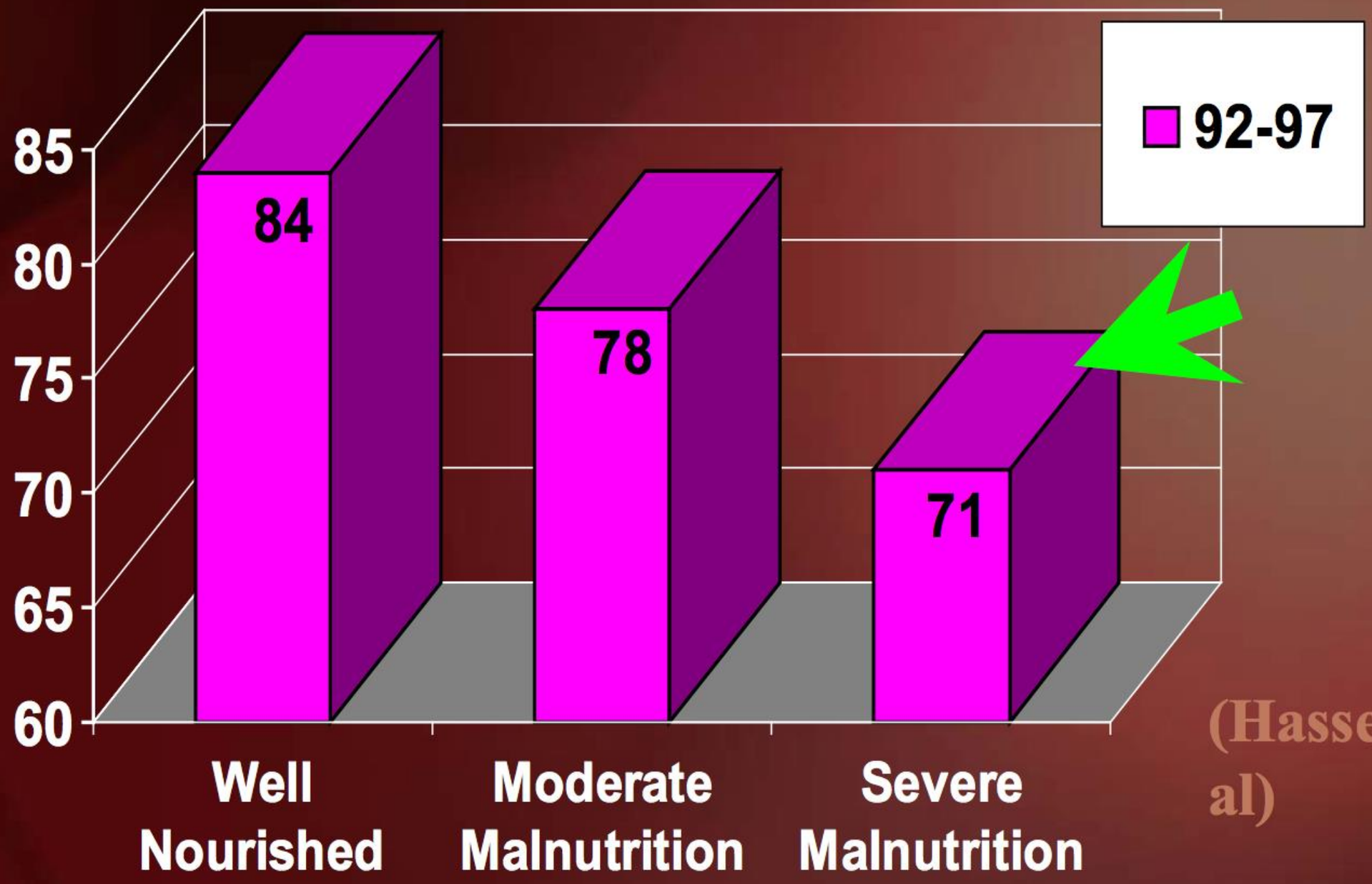
Effect of Malnutrition

3-Year Survival

1224 Liver Transplant Patients

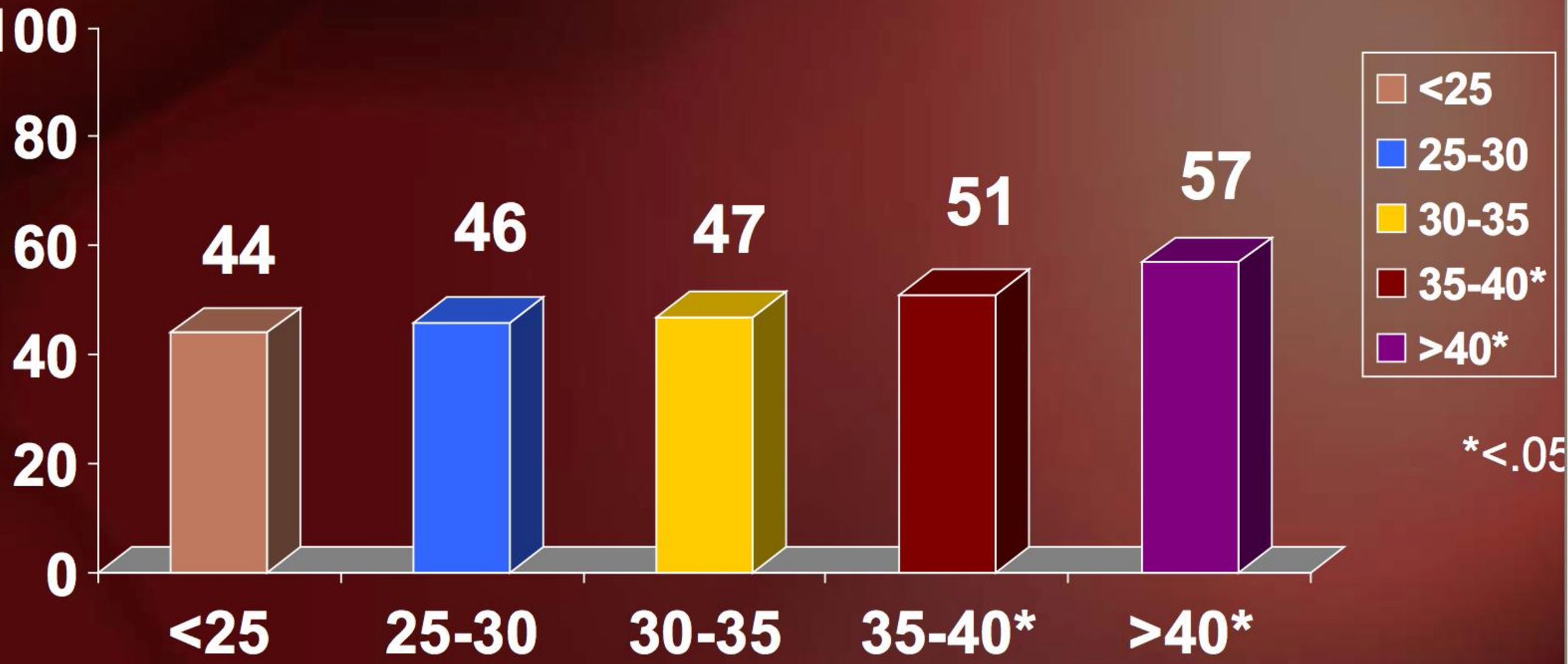


(Hasse et al)

OBESITY AND LIVER TRANSPLANT

LTx and Obesity

UNOS database 1988-1996 – 5-yr mortality by BMI



Nair. Hepatol. 2002;35:105.

CAUSES OF PROTEIN ENERGY MALNUTRITION IN LIVER CIRRHOSIS

TABLE 1. Etiology of Malnutrition in ESLD

- Poor dietary intake
  - Anorexia and early satiety
  - Dietary restriction (sodium and protein)
  - Ascites/encephalopathy
  - Leptin levels
  - Increased proinflammatory cytokines (tumor necrosis factor α, interleukin 1)
  - Gastroparesis, nausea and vomiting
- Nutrient malabsorption
  - Pancreatic insufficiency
  - Cholestatic liver disease
- Drug-induced losses
  - Neomycin, lactulose, diuretics, antimetabolites, cholestyramine
- Iatrogenic
  - Large-volume paracentesis

Table 1 Causes and mechanisms of malnutrition in end-stage liver disease.

Reduced nutrient intake	• Decreased appetite and anorexia	– Unpalatable diet (sodium and water restriction for peripheral edema and ascites, protein restriction for hepatic encephalopathy) – Disgeusia due to micronutrient deficiencies (zinc or magnesium) – Anorexic effect caused by increased levels of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and leptin
	• Nausea and early satiety	– Tense ascites – Gastroparesis – Small bowel dismotility – Bacterial overgrowth
	• Starvation	– Hospitalization – Invasive diagnostic procedures requiring fasting – Gastrointestinal bleeding and endoscopic therapies
Reduced intestinal absorption	• Maldigestion • Bacterial overgrowth • Diarrhea	– Pancreatic insufficiency in alcohol abuse and/or cholestasis – Intestinal dismotility and increased transit time – Drugs (i.e., nonabsorbable disaccharides, antibiotics, and cholestyramine)
Metabolic alterations	• Protein catabolism • Increased energy expenditure	– Reduced hepatic protein synthesis and increased protein breakdown – During ascites and bacterial infections – Hepatocellular carcinoma
	• Insulin resistance • Increased fat turnover	– Hyperinsulinemia and reduced nonoxidative glucose metabolism – Increased lipolysis due to more rapid transition to starvation – Fats are utilized as alternative energy source

ENERGY METABOLISM IN CLD

- Hypermetabolic state seen in up to 34% (BEE measured by Harris Benedict equation)
- Hypermetabolic state caused by - infections, presence of ascites, increase in pro inflammatory cytokines
- Altered pattern of fuel consumption - starvation mode - fat used as metabolic substrate
- particularly seen after overnight fast (in up to 58%)
- ‘accelerated starvation’ phenomenon - deprived glycogen stores, and increased gluconeogenesis

NUTRITIONAL ASSESSMENT BEFORE LIVER TRANSPLANT

ASSESSMENT OF NUTRITIONAL STATUS

- Thorough nutritional assessment very important in every patient

PROBLEMS IN LIVER DISEASE

- weight may not reflect lean body mass - ascites and edema
- albumin / prealbumin low due to liver disease
- presence of edema interferes with measurements

Table 2 Factors influencing the accuracy of common indices used for nutritional assessment in patients with chronic liver disease.

Body weight	• Water restriction and fluid accumulation • Changes in body composition
Visceral proteins	• Decreased liver synthesis • Increased volume of distribution
Anthropometry	• Fluid retention (barely influential)
Immunological status	• Hypersplenism • Abnormal immunological reactivity
Creatinine excretion	• Renal insufficiency
Bioelectrical impedance analysis	• Presence of ascites

Table 3 Advices for nutritional assessment in a cirrhotic subject.

Physical examination and anthropometry	• Consider body weight modification in the last months with particular attention at the last 2 weeks. • Calculate body mass index using the estimated dry weight if needed. • Evaluate subcutaneous fat and muscle mass (arm circumference and triceps skinfold). • Measure hand-grip strength as a tool to identify patients at nutritional risk.
Dietary interview	• Perform a detailed diet history to evaluate the recent reduction or modification (intentional/unintentional). • Estimate the amount of calorie and protein intake in the diet. • Evaluate the presence of gastrointestinal symptoms (anorexia, vomiting, nausea, diarrhea, and dysphagia).
Subjective global assessment (SGA) of nutrition	• Integrate objective and subjective data to obtain SGA.
Total energy balance	• Estimate calorie needs with formulas or measure resting energy expenditure in difficult case by indirect calorimetry. • Calculate energy balance as: total energy intake subtracted total energy expenditure.

NUTRITIONAL ASSESSMENT TOOLS

- Anthropometry
- Subjective Global Assessment (SGA)
- Hand grip strength
- Body Cell Mass (BCM) depletion - techniques are: isotope dilution; measurement of whole body potassium; in vivo neutron activation analysis - cumbersome, only for research
- Bioelectric impedance - reliable tool to estimate BCM

ANTHROPOMETRY

- Triceps skin-fold thickness - to assess fat storage
- mid-arm circumference - assess skeletal muscle mass
- poor inter-observer variability
- overestimation if there is significant edema
- however, studies show good correlation with outcomes and mortality in liver transplant patients

AASLD 2006

SUBJECTIVE GLOBAL ASSESSMENT

- most reliable method in patients undergoing liver transplant
- specificity 96%, low sensitivity
- inter-observer reproducibility more than 80%
- accurate in predicting outcomes before and after liver transplant
- should be preferred method

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nts of subjective global assessment for liver transplan

History

Weight changes (consider ascites and edema)

Appetite, early satiety, and taste changes

Diet history and adequacy of intake

GI symptoms: persistent nausea, vomiting, diarrhea, or constipation

Energy and activity levels

Physical

Muscle wasting

Fat stores

Ascites, edema

Rating

Well nourished

Moderately (or suspected of being) malnourished

Severely malnourished

TABLE 2. Methods for Nutritional Status Evaluation

	Anthropometrics Malnutrition (calorie reserves)		
Triceps Skinfold	Normal	Moderate	Severe
Men	7.5-12.5 mm	4-6 mm	<4 mm
Women	10-16.5 mm	5-8 mm	<5 mm
Mid-arm Muscle Circumference			
Men	23.0-25.5 cm	18-20 cm	<18 cm
Women	21-23 cm	16-18.5 cm	<16 cm
24-Hour Urinary Creatinine Excretion			
		Men 23 mg/kg of ideal body weight	<60% of normal
		Women 18 mg/kg of ideal body weight	<60% of normal
Resting Energy Expenditure			
Harris-Benedict equation BEE × 1.2 kcal/d			>20% of BEE
Indirect calorimetry			>20% of predicted
	Subjective Global Assessment		
History			
Weight changes			
Appetite and early satiety			
Diet history			
Gastrointestinal symptoms: nausea, vomiting, diarrhea, or constipation			
Activity level			
Physical exam			
Muscle wasting			
Fat stores			
Rating			
Well nourished			
Moderate malnutrition			
Severe malnutrition			

Abbreviation: BEE, basal energy expenditure; RDA, recommended daily allowance.

TREATMENT

nutritional intervention improves outcomes

Hirsch study. JPEN 1993.

- effect of nutritional supplementation in alcoholic cirrhosis
- daily supplement of 1000 kcal / 34 gm protein
- better hospital outcomes, better nutritional parameters (mid arm circumference)

Mendenhall study. Hepatology 1993.

- nutritional supplementation in alcoholic hepatitis.
- 2500 kcal / day vs. inadequate diet intake - mortality 19 vs. 51%

- BEE calculated with ideal body weight
- calorie intake 1.2 times of BEE / 30 to 35 kcal / kg / day (up to 40 kcal / kg / day in severe malnutrition)
- 60 to 70% should be simple plus complex carbohydrates
- protein 1.2 to 1.5 gm / kg / day
- standard protein / vegetable and milk based protein in HE
- branched chain amino acids in intolerant patients

PROTEIN REQUIREMENT

- Uncomplicated hepatitis or cirrhosis: 0.8 -1 g/kg
- To promote positive nitrogen balance: 1.2-1.3 g/kg
- Alcoholic hepatitis, decompensated liver disease, or malnutrition: up to 1.5 g/kg

BRANCHED CHAIN AMINO ACIDS - BCAA

- BCAA (valine, leucine, isoleucine) are catabolized by skeletal muscle and kidney

  - AAA have impaired hepatic deamination

    - AAA accessing CNS are metabolized to false neurotransmitters (octopamine, phenylethanolamine)

- BCAA can be used as nutritional supplement, to treat hepatic encephalopathy or long term use in cirrhosis

BCAA to treat hepatic encephalopathy

11 trials, 556 patients
Results:

– 59% BCAA improved at end of treatment vs. 41% control (RR 1.31, 9 trials)

– NS difference in improvement when only studies w/ hi methodological quality evaluated

– NS difference in time to improvement

– NS difference in survival

BCAA supplement in cirrhosis

646 decompensated cirrhotics • BCAA 12 g/d x 2 years vs diet

– Reduced primary end points (composite of death, HCC, rupture of EV, progress of hepatic failure) - hazard ratio 0.67, p= 0.015

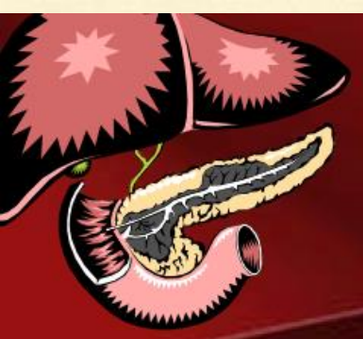
– Increased albumin (p= 0.018)

– Improved health perception in SF-36 (p= 0.003)

Muto. Clin Gastroenterol Hepatol. 2005;3:705

Nutrient Supplementation

- **Cholestatic liver disease:** A, D, E
- **Alcoholic liver disease:** A, B_6, B_{12}, Folate, Niacin, Thiamine, Magnesium, Phosphorus, Zinc
- **Diuresis:** Magnesium, Zinc, Potassium
- **Refeeding:** Magnesium, Phosphorus, Potassium



Nutrient Restrictions

- **Potassium** - some diuretics, renal failure
- **Iron** - hemosiderosis, hemochromatosis
- **Copper** - Wilson's disease
- **Phosphorus** - renal failure

Liver osteodystrophy

- highly prevalent in ESLD - 35 to 40% (Apollo Chennai study)
- Serum calcium, phosphate, Vitamin D levels, Bone Densitometry
- Calcium 1000 to 1200 mg and vitamin 0.25 mcg daily
- Osteopenia - calcium and vitamin D
- Osteoporosis - with alendronate

Salt and water restriction

- EASL Guidelines 2012
- Ascites - salt restriction 88 meq/l ; 2000 mg sodium per day
- Refractory ascites maybe less
- Water restriction not necessary
- Hyponatremia (excess ADH activity) - sodium less than 125 mmol / L = restrict water to 1000 ml daily

Fasting and protein catabolism

- Fat is a preferred fuel - due to alterations in insulin, glucagon, cortisol, and epinephrine levels

- Overnight fast in cirrhotic pt is like 2-3 day fast in normals

- high contribution from fat in energy metabolism

BCAA nocturnal supplements

- randomized trials

- complete nutritional supplementation (710 Kcal and 26 g protein) - given in the late evening hours (from 9 pm to 7 am)

- improved total body protein (neutron activation analysis)

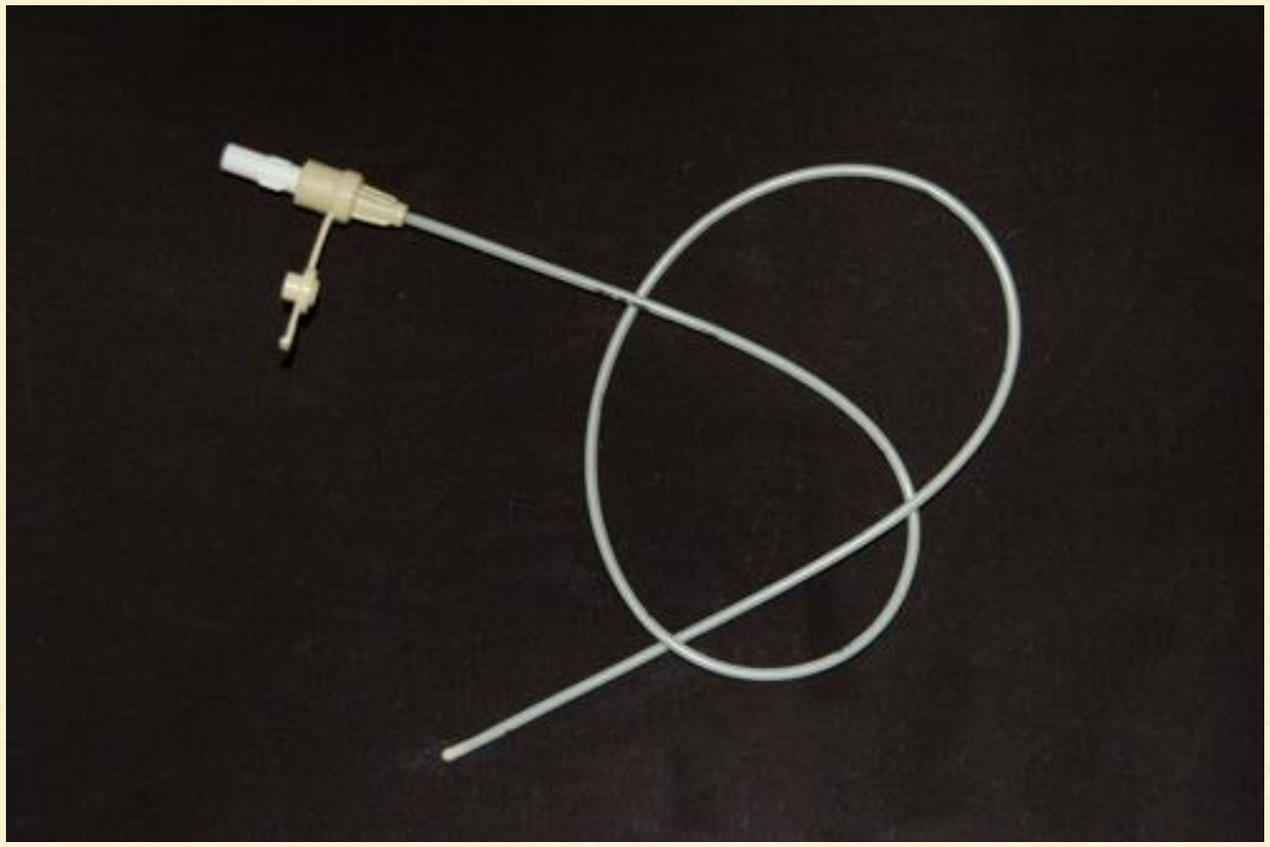
- Nocturnal supplement with snacks enriched with BCAA improved nutritional status - better than food intake

Henkel. Hepatology 2008; Yamouchi. Hepatol Res 2001.

method of nutritional support

- oral - predominantly food intake
- frequent small meals, every 3 to 4 hours, nocturnal feed
- oral - nutritional supplement
- nasogastric / nasoenteral tube
- parenteral
- in ascites and renal impairment - calorie dense feeds

TUBE FEEDING



soft polyurethane feeding tubes

8 to 12 Fr available

nasogastric or nasoenteral

Table 5 Main nutritional recommendations in end-stage liver disease.

Energy intake	Provide 30–35 Kcal/Kg dry body weight/day. Provide 50–60% of calories as carbohydrates. Provide 20–30% of calories as fat. Avoid unnecessary dietary restrictions.
Frequency of meals	4–6 meals every day including a late evening snack.
Protein intake	Provide 1–1.5 g of protein per Kg of weight/day. In patients with hepatic encephalopathy, if the patient is protein-intolerant, consider to reach the protein need including vegetable proteins, dairy proteins, and/or branched chain amino acids oral supplementation.
Vitamins and trace elements	Consider the need of vitamins (A, D, E, and K) or trace elements (zinc and calcium) supplements based on patient's symptoms or serum levels.
Artificial nutrition	Patients who are unable to take adequate nutrition through diet or nutrition supplementation may require enteral or parenteral nutrition for maintenance.

TABLE 3. General Nutritional Recommendations for Patients With ESLD Before LT

Hepatic encephalopathy should be treated aggressively before protein restriction is instituted.
Protein restriction should not be performed routinely, to prevent aggravating protein deficiency.
Smaller and more frequent meals are better tolerated especially at nighttime to prevent further starvation.
Monitor calorie count frequently and consider enteral feeding supplementation if oral intake if suboptimal.
Water restriction is not recommended, unless serum sodium is less than 125 mEq/L.
Dietary sodium restriction to 2 g/day in patients with ascites.
Branch-chained amino acids should be considered only for patients with refractory hepatic encephalopathy.
BEE should be measured and not predicted in patients with edema and ascites.
Energy needs are highly variable and best determined by indirect calorimetry
Patients should take a daily multivitamin.
Calcium supplementation (1,200-1,500 mg/day) in patients with osteopenia and osteoporosis.

TABLE 4. Goals of Nutritional Therapy in Patients With ESLD Waiting for LT

Correct malnutrition and prevent metabolic complications.
Educate patients and caregivers on individual plan for nutrition and level of activity.
Improve quality of life.
Reduce perioperative complications after transplantation.

CONCLUSIONS

- impaired nutrition is very common in patients with end stage liver disease
- malnutrition leads to adverse outcomes in liver transplantation
- thorough assessment of very patients is very important
- malnourished patients should be given adequate calories
- nutritional supplementation as required, tailored to individual needs
- team approach - concerned doctors, nutrition team, nurses, primary care givers - to achieve success