Nutritional Assessment and Macronutrient Deficiencies in Liver Disease

Susie Hamlin
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• Prevalence and consequence of malnutrition

• Nutritional screening and assessment

• Calculation and provision of macronutrients
Prevalence of PEM

• Occurs irrespective of aetiology of the cirrhosis

• Found in 65-100% of patients with advanced liver disease
  - 80% decompensated disease
  - 20% compensated disease

• Reported to be as high as 100% in liver transplant candidates (Alvares-da Silva MR et al 2005)

• Direct correlation between progression of liver disease and severity of malnutrition

• 25% prevalence reported in Child- Pugh Class A disease (Henkel and Buchman 2006)
Consequence of Malnutrition

- Higher rates of encephalopathy, infection and variceal bleeding

- Twice as likely to have refractory ascites

- Associated with the progressive deterioration in liver function
  - prolonged length of hospital stay

- More blood products intra-op, longer ventilatory support
Malnutrition is a prognostic indicator of clinical outcome

- Independent risk factor for morbidity and mortality in ESLD patients
- Mortality doubles in malnourished patients
- Short term survival decreases in parallel to the severity of malnutrition
- Post transplant morbidity higher
Scoring systems for assessing the clinical status and severity of chronic liver disease

Model for End-Stage Liver Disease (MELD)
Bilirubin, Creatinine, International normalized ratio for prothrombin time (INR) 6 to ≥40
the higher the MELD score the greater the severity of disease
Minimal listing criteria ≥ 15

UK Model of End-Stage Liver Disease (UKELD)
Uses the above plus serum sodium
Minimal listing criteria ≥ 49

Child-Pugh Classification
Why PEM?

- Inadequate provision of nutrients
- Impaired absorption
- Abnormal substrate utilization
- Diminished synthetic capacity
Inadequate Provision of Nutrients

- Anorexia - ↑ TNF-α ↑ interleukin 1b, interleukin 6
- Nausea and vomiting
- Altered gut motility – delayed gastric emptying
- Early satiety in ascites
- Encephalopathy
- Protein losses – blood loss, LVP
- Abnormal taste? Zinc involved
- Calorie substitution from alcohol
- Dietary restrictions (e.g. low sodium)
- Pain on eating from oesophagitis, gastritis or pancreatitis
- Poor dentition
- Socioeconomic
- Generalised weakness and immobility
- Frequent hospital admissions
Impaired Absorption

• Impaired digestion

• Reduced bile secretions – and compromised hepatic bile synthesis

• Pancreatic insufficiency

• Higher incidence of small bowel bacterial overgrowth - 35-60% in cirrhotic (Bauer et al 2001)

• Co-existing conditions – Coeliac disease, IBD

• Drug related diarrhoea – intestinal hurry
Metabolic alterations leading to malnutrition in ESLD

<table>
<thead>
<tr>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased catabolism</td>
<td>Decreased skeletal muscle and hepatic glycogen synthesis</td>
<td>Increased lipolysis</td>
</tr>
<tr>
<td>Increased use BCAA</td>
<td>Increased gluconeogenesis</td>
<td>Enhanced turnover and oxidation of fatty acids</td>
</tr>
<tr>
<td>Decreased ureagenesis</td>
<td>Glucose intolerance and insulin resistance</td>
<td>Increased ketogenisis</td>
</tr>
</tbody>
</table>
Abnormal Substrate Utilization (i)

Accelerated Starvation

• Starvation type metabolism / Anabolic resistance

• Lack of hepatic and skeletal muscle glycogen

• Early gluconeogenesis from skeletal muscle and increased fat oxidation → muscle wasting in post absorptive state

• Seen after overnight fast  Pattern seen in healthy people only after 3 days

• Increased dependence on alternative fuel source, muscle mass catabolised as short term fuel source = anabolic resistance

• (Owen et al, 1983; Swart et al, 1989; Schneeweiss et al, 1990; Verboeket-van de Venne et al, 1995)
Abnormal Substrate Utilization (ii)

• **Hyperdynamic circulation**
  higher use of macro and micronutrients and demand

• **Hypermetabolic State**
  
  34% cirrhotic are considered hypermetabolic (Muller MJ 1999)
  Mean REE may be similar to controls but complications e.g. infection, GI bleeding, ascites can increase metabolic stresses temporarily

• **Elevated pro-inflammatory cytokines**
  have the potential to lead to a cytokine driven hypermetabolism (von Baehr WD 2000, Tilg H 1992)
Abnormal Substrate Utilization (iii)

- Insulin Resistance
- Diabetes mellitus found in 38% cirrhotic patients
- Impairment of glucose homeostasis due to
  - Hepatic insulin resistance
  - Altered gluconeogenesis
    - Low glycogen stores
    - Impaired glycogenolysis
- Insulin resistance and decreased levels of insulin like growth factor-1 contribute to muscle wasting
Poor dietary intake
Malabsorption of nutrients
↓ protein synthesis
↑ intestinal protein losses
↑ energy expenditure
Disturbed substrate utilisation
↑ pro inflammatory cytokines
Hypermetabolism
Insulin resistance
Nutritional Assessment

• Screening for and treatment of malnutrition is vital in the early stages of disease

• There specific difficulties in liver disease

• Newer screening tools have been developed
Which One Is Malnourished?

Low BMI

Normal BMI

High BMI
Malnutrition Universal Screening Tool (MUST) is not useful in patients with ascites and peripheral oedema
Nutritional screening:

Royal Free Nutritional Prioritization Tool
RF-NPT (Aurora et al., 2011)

• Validated nutritional screening tool for the cirrhotic fluid over loaded patient
• Considers completion of meals
• Decrease in appetite ≥50% previous 5 days
• Weight loss in preceding 3 -6 months
Nutritional Assessment

**Subjective** Global Assessment (SGA) (ESPEN 2006)
History and physical assessment

**Objective** assessment:
Anthropometric measurements
- Mid Arm Circumference (MAC)
- Mid arm muscle circumference (MAMC)
- Triceps Skinfold Thickness (TSF)
- Handgrip
Nutritional Assessment

• **Handgrip** – easy, quick, non-invasive, inexpensive
• Sensitive marker of muscle mass depletion
• Correlates with morbidity and mortality
• Shown to improve with increased nutritional intake
• Use serial measurements
Nutritional Assessment

• Anthropometry – MAC / TSF / MAMC
• Easy to measure muscle mass and body fat
Handgrip superior to SGA PNI in identifying malnutrition in ESLD (Alvares-da-Silva, 2005)

Handgrip predicted poorer clinical outcome at 1 year (ascites, HE, SBP, HRS)
Nutritional Assessment: Royal Free Hospital –Global Assessment (RFH-GA)

• A global assessment scheme using subjective and objective variables Morgan et al (2006)

• Devised and validated for use in the cirrhotic population

• Internal and external validity, repeatability against accurate measurement of body composition and predictive validity

• Accepted gold standard for nutritional assessment for patients with cirrhosis in the UK
RFH - GA

- Clinical information – anorexia, N&V, dysphagia, bowel function, infections, HE, weight loss, activity

- Dietary intake – appetite, early satiety, taste changes

- Estimated kcal/protein dietary intake from dietary history
  - negligible below 500kcal
  - inadequate between 500kcal and calculated nutritional requirements
  - adequate - met calculated nutritional requirements

- Physical status – fat and muscles stores, presence of oedema/ ascites

- Anthropometric measurements – MAC, TSF, MAMC in relation to 5th centile

- Use algorithm to categorise
RFH-GA

- Significant predictor of survival

- Nutritional status defined using the RFH-GA in those moderately malnourished and severely malnourished significantly worse after adjustment for hepatic impairment

- Gender differences
  - Preferential fat mass loss in women
  - Muscle mass in men
Cumulative survival in 116 patients with cirrhosis by category of nutritional status determined using the RFH GA scheme. The numbers of patients at risk at each time point are tabulated below the figure by nutritional category. Significance of the difference between the groups ($\chi^2 = 15.04; \text{df} = 2; P = .0005$).
Nutritional assessment: Summary

• Cirrhotic patients should be screened using RF-NPT not MUST

• RFH GA accepted gold standard for nutritional assessment in UK liver units
Calculating Requirements

Kcal
• Calculating basal metabolic rate
• + disease related stress factors
• + Activity related stress factors (PENG 2011)

Or

• Calculating kcal / kg dry weight

• Protein g/kg dry weight (ESPEN 2007)
Nutritional Requirements

• Compensated cirrhosis (ESPEN 2006)

Energy  \( \rightarrow \)  25-35kcal/kg dry body weight

Protein  \( \rightarrow \)  1.0-1.2 g/kg dry body weight
Nutritional requirements

- Decompensated cirrhosis (ESPEN 2006)

Energy  \( \rightarrow \) 35-40kcal/kg dry body weight

Protein  \( \rightarrow \) 1.2-1.5g/kg dry body weight
Estimating Dry Weight  (Mendenhall 1992)

<table>
<thead>
<tr>
<th>Severity</th>
<th>Ascites</th>
<th>Oedema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>2.2kg</td>
<td>1.0kg</td>
</tr>
<tr>
<td>Moderate</td>
<td>6.0kg</td>
<td>5.0kg</td>
</tr>
<tr>
<td>Severe</td>
<td>14.0kg</td>
<td>10.0kg</td>
</tr>
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</table>
# Calculating requirements

**Henry Oxford Equations**  
**Basal metabolic rate BMR**

- **W** = Dry weight always used

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>Kcal /day</th>
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</thead>
<tbody>
<tr>
<td>Males</td>
<td>18-30</td>
<td>16.0W + 545</td>
</tr>
<tr>
<td></td>
<td>30-60</td>
<td>14.2W +593</td>
</tr>
<tr>
<td></td>
<td>60-70</td>
<td>13.0W +567</td>
</tr>
<tr>
<td></td>
<td>70+</td>
<td>13.7W +481</td>
</tr>
<tr>
<td>Females</td>
<td>18-30</td>
<td>13.1W +558</td>
</tr>
<tr>
<td></td>
<td>30-60</td>
<td>9.74W +694</td>
</tr>
<tr>
<td></td>
<td>60-70</td>
<td>10.2W +572</td>
</tr>
<tr>
<td></td>
<td>70+</td>
<td>10.0W +57</td>
</tr>
</tbody>
</table>
## Calculating Nutritional Requirements

1) Henry Oxford Equation BMR  
2) Add stress factors  
3) Add activity factors

<table>
<thead>
<tr>
<th>Condition</th>
<th>Stress factor(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compensated</td>
<td>0-20%</td>
</tr>
<tr>
<td>Decompensated</td>
<td>30-40%</td>
</tr>
<tr>
<td>Acute (fulminant) +/− ventilation</td>
<td>20-30%</td>
</tr>
<tr>
<td>Post transplant</td>
<td>30%</td>
</tr>
</tbody>
</table>
Calculating Nutritional Requirements: example

- 40 year old male ALD, ascites, jaundice.
  Mobile on ward
  Actual weight 70kg
  Dry weight (moderate ascites -6kg) = 64kg
  Dry BMI 19.7kg/m2

Kcal requirements  
BMR = 14.2 x 64 + 593
40% stress
25% activity

Requirements for weight maintenance 2479 kcal

OR

35 - 40 kcal/kg = 2240 kcal - 2560 kcal
+ 400 - 100 kcal for weight gain

Protein requirements
1.2 - 1.5g x 64 = 76.8 - 96g protein /day
1.8 x 64 = 123.3g for repletion
Obesity: Compensated disease

- Prevalence of obesity in ESLD patients 21-28% similar to general population

- Compensated liver disease patients – weight loss not exceeding 0.5 -1kg week with close anthropometric monitoring

- Monitor patients for signs of subacute non alcoholic steatohepatitis during weight loss

- Require min 7% wt loss from baseline weight to get histological improvement (Promrat et al., 2010)
Obesity: Decompensated disease

- Metabolic consequence of disease makes estimation of kcal challenging
- Glycogen stores remain low
- Type 2 Diabetes common
- ↓insulin sensitivity and secretion
- Metabolic response to injury – kcal from CHO and protein – less from fat than non obese (Roth JL et al 2005)
- Nutritional support not always recognised → leads to significant protein depletion
- Dry weight often difficult to establish
- Close anthropometric measurement is necessary – handgrip most reproducible
Obesity: Decompensated Disease

Severe metabolic stress
Calculating requirements – dry weight used

Weight excess
BMI 30kg/m2 > 25% LBM 70% fat mass
Stress factors added  20 – 40% BMR
Close monitoring - adjust up or down as necessary (PENG 2012)

Protein Requirements
BMI > 30kg/m2 x 75% of the value from actual weight
BMI > 50kg/m2 x 65%
Close monitoring - adjust up or down as necessary (PENG 2012)

• Area further research is necessary with increasing NAFLD/NASH cirrhosis
Providing Macronutrients

Carbohydrate

• Aim to provide 60 -70% kcal from complex and refined carbohydrate
• Meal pattern – Small frequent meals
• Aggressive use of insulin/OHA as necessary to maintain normoglycaemia
• Aim 6-7 meals/snacks per day
Late Evening Snacks (LES)

- Decreases lipid oxidation
- Improves nitrogen balance
- Decreased skeletal muscle proteolysis overnight

Various doses CHO used in studies 50 - 110g
- 50g CHO minimal amount needed to prevent ketogenesis and nitrogen sparing effect

Should be advised in compensated cirrhosis to preserve existing skeletal muscle mass
50g CHO Late Evening Snack

- 2 crumpets with 200mls milk
- 1 milk based 1.5kcal/ml supplement
- ¾ juice based 1.5kcal/ml supplement
- 2½ thick slices of bread
- Breakfast cereal with milk
- 1 slice fruit cake
- Scone with jam and 300mls of milk
- 5 dried dates and 200mls milk
- Small square of flapjack and 300mls milk
Oral Nutritional Supplements (ONS)

• Nutritional counselling alone can be successful in increasing dietary intake (Le Cornu et al, 2000)

• More frequently nutrition support is required i.e. oral nutritional supplements (ONS) and/or naso-gastric feeding (Plauth et al, 2006)

• ONS used when cannot meet requirements with food and snacks
Oral Nutritional Supplements

- Prescribe at times to minimise post absorptive phase (fasting times)
- Prescribe at a time will not affect meals
- Adjust diabetic medication as necessary to optimise glycaemic control
- Increase in dietary intake in cirrhotic patients after 3-4 weeks on ONS and dietetic input (Campillo et al, 2003)
- Increase in spontaneous dietary intake after 6/52 enteral tube feeding (Campillo et al, 2005)

All ONS are not equal
Enteral Tube Feeding

• To commence enteral tube feeding if patients cannot meet nutritional requirements orally (ESPEN 2007)

• Oesophageal varices not a contraindication to fine bore NG feeding (ESPEN 2006)

• Artificial nutrition should be given early consideration if patients cannot meet nutritional requirements orally

• Increase in spontaneous dietary intake demonstrated after 6/52 enteral tube feeding (Campillo et al, 2005)

• Overnight tube feeding decreases the fasting period
Nasogastric Feeding

- Prescribed according to individual nutritional requirements and tolerance
- Minimise the post absorptive period as much as possible
- 24 hour feeding may be necessary
- Rest periods not always appropriate
- 1.5-2.0kcal/ml feeds often necessary
- Use nasal bridles if patients persistently pulling out tubes
Protein: Low Protein Diets

• Not advised
• Better awareness of the complex metabolic alterations in cirrhosis
• Crucial to maintain muscle mass which aids ammonia removal by conversion to glutamine
• Reduced muscle mass predisposes to hepatic encephalopathy
• Minimising fasting periods and provision of adequate protein and kcal during episodes of HE
• Nitrogenous products from skeletal muscle breakdown can exacerbate HE
• Tight glycaemic control if necessary to optimise protein/BCAA utilisation Bachmann C et al 2004, Bemeur et al 2010
Protein

• Requirement = 1.2 - 1.5g kg dry weight/day
• No protein restrictions
• Up to 1.8g/kg per day for repletion
• Cirrhotic patients need at least 1.2 - 1.3g/protein/kg/day to remain in positive N₂ balance
• Evenly distribute protein throughout the day
• Stable cirrhotics are capable of positive nitrogen balance and formation of LBM
Protein

- ESPEN 1997 recommended that in severely protein intolerant patients (particularly grades III-IV HE protein) may be reduced for short periods only after excluding all other precipitating causes of HE.

- 0.5 - 1.2g protein/kg until the acute episode resolves

+-/- BCAA solutions
Figure 2: Inter-organ trafficking of ammonia in normal physiological conditions, in well-nourished patients with end-stage liver failure compared to malnourished end-stage liver failure patients.

Bemeur et al., Journal of Nutrition and Metabolism 2010

↑muscle glutamine synthetase
↑ammonia removal as glutamine
↓muscle mass common
Branched Chain Amino Acids

HE

leucine, isoleucine and valine

• $\downarrow$ BCAA : AAA in liver cirrhosis 3:5:1→1.1

• Impaired hepatic deamination of AAA

• BCAA utilization to support muscle glutamine synthesis, therefore ammonia detoxification

• $\uparrow$ aromatic AA = proposed cause of HE acting as precursors for false neurotransmitters as octopamine

• Correction of amino acid ratio may improve HE
Protein Branched Chain Amino Acids

- Inhibit protein degradation
- Enhance protein synthesis
- Prevention progression liver failure stimulating hepatic regeneration
- Improve nutritional status and prevent HE and promote recovery from HE

Short term:
- Improve liver function and nutritional status
- Achieve positive nitrogen balance and improve HE

Long term:
- Improve liver function and nutritional status
BCAA – the evidence (i)

Cochrane review 2003 Als-Nielsen

- 11 RCT reviewed
- Unconvincing evidence of significant benefit to advocate using BCAAs with HE patients
- More RCT’s needed
2 Large RCTs since Cochrane review Marchesini 2003

- 172 patients 14.4g BCAA/d 1 year
- No difference in HE scores

However
- ↓ end point of death or deterioration
- ↓ hospital admission rate
- ↓ Child Pugh Score
- Improved LFT
- Improved quality of life
BCAA – the evidence (iii)

Muto 2005

• LOTUS group – long term survival study
• 646 patients decompensated cirrhosis
• 12g BCAA /d + adequate kcal + protein intake
• Reduced incidence of events improvement
  serum albumin increased
• Increase quality of life
• ESPEN 2006 (Plauth et al, 2006)

- BCAA–enriched formula should be used in patients with HE arising during enteral nutrition (A)

- Long-term (i.e. 12-24 months) nutritional supplementation with oral BCAA granulate is useful in slowing progression of hepatic failure and prolonging event-free survival

- Oral BCAA supplementation can improve clinical outcome in advanced cirrhosis (B)
BCAA products

Fresubin Hepa
44%BCAA

Not used in liver UK liver transplant centres

Availability limited

Oral preparations unpalatable and expensive

No consensus on recommended dose
Marchesini et al, 2005

Vegetable sources? LES?

Hepatical (SHS)
31%BCAA
Fat

- Aim to provide 20-40% Kcal from fat
- Valuable source kcal 9kcal/gram

Problems
- Reduced bile secretion $\rightarrow$ ↓micelle formation
- Pancreatic exocrine insufficiency especially in alcoholic liver disease
- Common in cholestatic diseases

Impaired absorption of fat soluble vitamins A,D,E,K
Fat

- Fat reduced only in patients with steatorrhoea
- Only restricted to tolerance
- Medium Chain Triglyceride products used as kcal replacement
- Fat soluble vitamins require supplementation if necessary
Future Developments

- Use of pre and probiotics to improve gut immune function (Bianchi 2008)
- Use of omega 3 fatty acids - anti-inflammatory action
- Branched chain amino acids
- Late evening snack composition
- Glutamine – myostatin inhibition
Summary

Supportive nutritional intervention is indicated in most patients with ESLD with high and low BMI

Nutritional support can and does improve morbidity and mortality

Malnutrition should be identified and treated early

Close and regular monitoring is essential

Dietary restrictions are rarely indicated

Anthropometry is essential and skilled interpretation of nutritional data is necessary (dry weight, obesity)
THINK NUTRITION
&
FEED