Alcoholic liver disease

Role of nutrition as risk factor and therapeutic options

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Risk factors for ALD

Other risk factors
- nutritional status
- gender (female)
- overweight >10 yrs
- genetic factors
- ethnic differences

Alcoholic liver disease (ALD)

- Major health issue
- No FDA-approved treatments
- Treating complications remains the mainstay of therapy
Overview: Chronic changes in liver disease

- 90% fatty liver
- 10-30% alcoholic hepatitis
- 8-20% cirrhosis

Of heavy long-term drinkers:
- 90% fatty liver
- 10-30% alcoholic hepatitis
- 8-20% cirrhosis
In the 80s...

...nutrition was seen as primary cause of liver injury in ALD.

Although, experimentally, malnutrition may not be essential for the development of alcoholic hepatitis, clinically, it appears to precede the development of the liver injury, which suggests an interaction.

<table>
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<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>9.5</td>
<td>46.2</td>
<td>63.0</td>
<td>65.7</td>
</tr>
<tr>
<td>Weight loss** †</td>
<td>9.5</td>
<td>36.8</td>
<td>27.1</td>
<td>16.2 **</td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
<td>18.0</td>
<td>26.2</td>
<td>19.2</td>
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<tr>
<td>Hepatomegaly</td>
<td>0</td>
<td>85.9</td>
<td>97.1</td>
<td>88.9</td>
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<tr>
<td>Splenomegaly †</td>
<td>4.8</td>
<td>24.5</td>
<td>38.6</td>
<td>46.2</td>
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<tr>
<td>Infection</td>
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<td>5.2</td>
<td>16.8</td>
<td>8.1</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>4.8</td>
<td>13.6</td>
<td>10.3</td>
<td>10.1</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>0</td>
<td>10.4</td>
<td>7.5</td>
<td>14.1</td>
</tr>
</tbody>
</table>

† p < 0.005

** increasing incidence of ascites

Nowadays...

...it is accepted that ALD can develop in well-nourished individuals.

➢ Causative factor:
Critical „threshold“

Threshold for alcohol intake, which must be reached:

- Daily intake of alcohol for 10-12 years
- Doses in excess of:
  - 40-80 g/day for males
  - 20-40 g/day for females

Frazier et al. Ther Adv Gastroenterol 2011;4:63-81
Alcoholic «front runners»

The world's top drinkers

- Estonia
- Lithuania
- Germany
- Latvia
- Finland
- Czech Republic
- Russia

https://epianalysis.wordpress.com/2012/02/28/alcohol/
Slovenia: a good example

- Slovenia on second position
- Big fall despite proximity to other Eastern European nations with large increases
- Social support and alcoholic policy

https://epianalysis.wordpress.com/2012/02/28/alcohol/
Critical drinking pattern

- Drinking alcohol outside mealtimes
- Drinking multiple different alcoholic beverages

Increased prevalence in alcohol related liver disease

Bellentani et al. Gut 1997;41:845-850
Stewart SF,+ Day CP. Alcohol and the Liver in Sherlock’s Diseases of the Biliary System
Malnutrition in ALD

- Prevalence: 20-90% (65% viral hepatitis)

- Most frequent complication in liver disease and cirrhosis

- n = 60
- Patients with end stage liver disease prior to liver transplantation
- Comparison of different nutritional assessments

Monsef et al. Open J Gastroenterol 2014;4:159-169
In Frigo Veritas

Ausmass des Problems

Clinical Nutrition 29 (2010) 38–41

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Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original Article

Prevalence of undernutrition on admission to Swiss hospitals

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7 Hospitals, 32’837 Patients
Ausmass des Problems

8% 11% 22% 28%

< 45 45 - 64 65 - 84 ≥ 85

Ausmass des Problems

Malnutrition

- Immune status ↓
  - Infections ↑
  - Complications ↑

- LOS ↑
  - Costs ↑

- Treatment tolerance ↓
  - Mental state ↓
  - QoL ↓

- Prognosis ↓
  - Morbidity ↑
  - Mortality ↑
Malnutrition in ALD

- Malnutrition = most frequent complication of ALD
- Severity of malnutrition depends on:

Prognostic relevance

Dietary intake

- Data from two Veterans Administration Cooperative Studies
- n = 245
- Patients with alcoholic hepatitis
- 6-month mortality associated with 1-month daily dietary intake

Prognostic relevance

Subjective global assessment (SGA)

Huynh et al. World J Gastroenterol 2015;21:12835-42
Prognostic relevance

Body mass index (BMI) vs. Sarcopenia

- Two cirrhotic patients
- Identical BMI (32 kg/m²)
- Abdominal CT images L3

Sarcopenic
L3 SMI 50 cm²/m²
(SMI=Skeletal Muscle Index)

Not sarcopenic
L3 SMI 71 cm²/m²

Prognostic relevance

Body mass index (BMI) vs. Sarcopenia

- Retrospective study
- \( n = 120 \)
- Patients with liver cirrhosis
- Abdominal CT scan

Prognostic relevance

- Sarcopenia is independently associated with mortality

Potential mechanisms of sarcopenia

Cirrhosis

Portacaval
Shunting

Hepatocellular
dysfunction

Hyperammonemia

↓ Branched chain amino acid concentration

Reduced protein synthesis

Sarcopenia

Treat primary etiology (antivirals, insulin sensitizers etc.)
Transplantation

Ammonia lowering measures (lactulose, rifaximin)

Leucine supplementation, leucine enriched branched chain or essential amino acid supplementation

Myostatin antagonists
Exercise
Malnutrition in ALD

Signs and Symptoms:
- Decreased lean body mass
- Various vitamin deficiencies
- Decrease serum proteins

Basis:
- Decreased food intake
- High caloric content of alcohol (7.1 kcal/g = empty calories)
- Decreased processing and storage of nutrients
- Poor absorption and digestion

Role of nutrition as therapeutic option

- Abstinence
- Agents to suppress inflammation
- Nutritional improvement
  - Promoters of hepatic regeneration
  - Modifiers of metabolism
  - Fibrosis inhibitors
  - Anabolic steroids
  - Hypertension
Treatment of ALD

Abstinence!

Bell et al. Scandinavian J of Gastroenterol 2004;39:858-863
Treatment of ALD

Nutritional support

- Caloric intake → 2000 kcal (35-40 kcal per kg BW per day)
- Protein intake → 1.2 – 1.5 g per kg BW per day
- Encourage late evening snacks and short intervals between meals → decreases post-absorptive state
- 6 to 7 meals/snacks per day, late evening snacks (50 g CHO) → CHO oxidation increase, lipid & protein oxidation decrease

Treatment of ALD ff.

- Late evening snacks high in protein → anabolism at night, preventing muscle loss
- Enteral tube feeding → well-tolerated, may improve hepatic function but no conclusive effect on skeletal muscle
- Parenteral nutrition → long-term effects unknown
- AA, BCAA, leucine supplementation: *see later*

Nutritional therapy in cirrhosis/alcoholic hepatitis – Meta-analysis

- 13 controlled trials (1980 bis 2012)
- n = 329
- 9 enteral, 4 intravenous trials
- at least 75 % of nutritional demands

- **Reduced mortality** (RR 0.80, 95% CI 0.64-0.99)
- **Prevented hepatic encephalopathy** (RR 0.73, 95% CI 0.55-0.96)
- **Prevented infection** (RR 0.66, 95% CI 0.45-0.98)

Fialla AD et al. Liver International 2015;1-7
Route of nutritional support

Route of nutritional support:

- Normal food
- Enrichment
- Oral Nutritional Supplements - ONS
- Enteral nutrition
- Parenteral nutrition

- Parenteral nutrition is rarely indicated
- ONS may be not effective because of poor intake and compliance
- However ONS are effective when consumed!

Route of nutritional support ff.

Oral Nutritional Supplements

(Synonyme in Deutsch)

- Trinknahrung
- Zusatztrinknahrung (sondenfreie enterale Ernährung)
- Orale Supplemente
- Trinknahrungssupplemente
## Effect of increase in nutrition

### Oral Nutritional Supplements

<table>
<thead>
<tr>
<th></th>
<th>ONS (Dietary counseling &amp; ONS)</th>
<th>DC (Dietary Counseling)</th>
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<tr>
<td>Hand grip</td>
<td><img src="%E2%96%B3" alt="Increase" /></td>
<td><img src="%E2%96%BC" alt="Decrease" /></td>
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<td><img src="%E2%96%BC" alt="Decrease" /></td>
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<tr>
<td>QoL</td>
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<td>3 x <img src="%E2%96%B3" alt="Increase" /></td>
</tr>
<tr>
<td>Re-admissions</td>
<td>26 %</td>
<td>48 %</td>
</tr>
</tbody>
</table>

*Norman et al. Clin Nutr 2008;27:48-56*
Today…

Oral Nutritional Supplements

- > 4,000 randomised clinical studies
- > 360,000 participants
Improvement of nutritional status

- 81-90% Studies: improvement
- 46-60% Studies: significant improvement

- Highly effective wenn BMI < 20 kg/m²
- Irrespective of place (hospital, nursing home, community)

Oral Nutritional Supplements
Decrease in LOS

Average decrease:

2 Days
Surgical patients

33 Days
Orthopaedic patients

Significant Improvement

Stratton et al. Wallingford, CABI Publishing; 2003
Leberschutz durch Kaffee?

Schützt Kaffee die Leber – oder doch viel mehr?
Vom Gift zum rezeptfreien Allheilmittel: Kaffee macht Karriere
Decrease in liver cirrhosis by coffee consumption (Meta-Analysis)

Relation between cups of coffee & liver cirrhosis

Liver-associated mortality & coffee consumption

Decrease in mortality by 46 % if daily consumption is 2-3 Tassen coffee
(RR 0.54, 95% CI 0.17-0.50)

HCC risk & coffee consumption

- RR 0.60 any coffee consumption
- RR 0.72 low consumption Konsum (~ 1-3 Tassen?)
- RR 0.44 high consumption (~ 3- >8 Tassen?)

(versus no consumption)

Coffee consumption and cancer development

- **Liver cancer** (RR 0.50)
- **Colorectal cancer** (RR 0.83)
- **Postmenopausal breast cancer**
- **Advanced prostate cancer**
- **Survivors with breast or prostate cancer**
Potential mechanisms of plant chemicals
(Phytochemicals, e.g. Polyphenole)

- Decrease in oxidative damage
- Regulation of DNA-repair
- Antiproliferative
- Antiangiogenic
- Antimetastatic
- Etc.

Treatment of ALD

NAS (No Added Salt) Diet

- No salt cooking
- Up to 100 g hard cheese per wk
- Up to 4 slices bread per d
- Limit processed foods/salty foods (sauces, soups, crisps, cured meats etc.)
Type of formula - BCAA

Branched-chain amino acids:
➢ "Use BCAA-enriched formulae in patients with hepatic encephalopathy arising during enteral nutrition." [ESPEN guidelines]
➢ Improvement in hepatic encephalopathy:

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>BCAA Events</th>
<th>BCAA Total</th>
<th>Other supplement Events</th>
<th>Other supplement Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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<tbody>
<tr>
<td>Hayashi 1991</td>
<td>22</td>
<td>32</td>
<td>5</td>
<td>26</td>
<td>26.2%</td>
<td>3.58 [1.57, 8.13]</td>
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<tr>
<td>Marchesini 1990</td>
<td>24</td>
<td>30</td>
<td>12</td>
<td>34</td>
<td>73.8%</td>
<td>2.27 [1.39, 3.70]</td>
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<tr>
<td>Total (95% CI)</td>
<td>62</td>
<td></td>
<td>60</td>
<td>100.0%</td>
<td>2.55</td>
<td>1.68, 3.89</td>
<td></td>
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<tr>
<td>Total events</td>
<td>46</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Therapeutic relevance

Effect of BCAA supplementation – Nutritional intervention!

- BCAA > 1 yr
- BCAA granules 3x daily after meals
- BCAA = 4 g
  - 952 mg isoleucine
  - 1904 mg leucine
  - 1144 mg valine

- Retrospective study (n = 120), abdominal computed tomography scan

BCAA – The Evidence

Hepatic Encephalopathy (HE)

- No convincing evidence for BCAA
- Meta-Analysis: Improvement of mental state, no benefit for survival
- Postoperative (liver resection) no increase HE with conventional AA solution
- Liver adapted AA solution (increased BCAA) in more severe HE (III-IV)

## Type of formula – Fatty acids

### Dietary fatty acids – investigated in animal models:

<table>
<thead>
<tr>
<th>Saturated fat, % energy</th>
<th>Treatment</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Corn oil</th>
<th>Saturated fat&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Ethanol</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>g/L</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Control</td>
<td>133</td>
<td>115</td>
<td>52</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Ethanol</td>
<td>133</td>
<td>5</td>
<td>52</td>
<td>0</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>Control</td>
<td>133</td>
<td>115</td>
<td>40</td>
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<td>Ethanol</td>
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<td>5</td>
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<tr>
<td></td>
<td>Ethanol</td>
<td>133</td>
<td>5</td>
<td>16</td>
<td>36</td>
<td>90</td>
</tr>
</tbody>
</table>

<sup>1</sup> Saturated fat = beef tallow:MCT oil (18:82, v:v).

- Rats fed intragastrically by total enteral nutrition
- Diets with or without alcohol
- Difference in saturated fatty acid

Type of formula – Fatty acids

Control diet, 0% saturated FA

Ethanol diet, 0% saturated FA

Ethanol diet, 30% saturated FA

Vesicular steatosis / macrophage infiltration

Type of formula – Fatty acids

Unsaturated fatty acids:
- increase oxidative stress

Saturated fatty acids
- are protective

In ALD – things may be different

GOOD Saturated Fats VS BAD Unsaturated Fats
Nutritional therapy– health effects

Very likely:
- Nutritional status ↑

Probable:
- Mortality ↓
- Cell mediated immunity ↑
- Liver injury (glycoproteins, caseine, various polyphenols)
- Infectious complications (serotonin, the calming transmitter ↑)
- Hospitalizations ↓

Conclusion

Nutrition is a risk factor for and in ALD:

- Nutritional status, especially overweight, increases the risk for developing ALD.

- Malnutrition is the most frequent complication and adversely affects mortality (and morbidity).

- Data investigating the effect of nutritional therapy on clinical parameters are sparse. **Giving ONS have to be considered!**

- There is a need for standardized assessments of nutritional parameters in ALD.
Conclusion

Considering the risk versus benefit:

- Nutritional therapy is an essential therapeutic intervention in ALD!
Besten Dank für Ihre Aufmerksamkeit