Cirrhosis: Let’s get moving!

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Objectives

Physical Deconditioning in Cirrhosis
• What is it?
• Why does it happen?
• Clinical Relevance
• Potential therapies
  – Exercise
  – Nutrition

Cirrhosis is associated with a high disease burden

• 12th leading cause of death in the US
• 1 million clinic visits and 300,000 hospitalizations per year
• Sicker patients on the transplant list

Davis GL et al. Gastroenterol 2010
Goals of care

• Identify and treat modifiable prognostic factors in an attempt to maintain health and optimize outcomes
  – Etiology based treatment (HCV, HBV, Etoh, Hemochromatosis, AIH)
  – Guideline based management to reduce acute hits to the liver (Variceal bleed, Infection, HCC)
  – Optimize functional status so patients are less vulnerable when exposed to a stressor

TAKE HOME POINT #1
- Patients with cirrhosis are deconditioned
- Etiology of this deconditioning is multifactorial

Exercise capacity 101

• Peak exercise capacity – “the maximum ability of the CV system to deliver O₂ to exercising skeletal muscle and of the muscle to extract O₂ from the blood”

\[ \text{VO}_{2} = (SV \times HR) \times (\text{CaO}_{2} - \text{CvO}_{2}) \text{ in mL/min} \]

• \( \text{VO}_{2} \) normalized for body weight
  – 3.5 mL/kg/min (resting seated O₂ uptake)
  – Equivalent to 1 MET

Albouaini K et al. Heart 2007
Cardiopulmonary exercise testing

Albousini K et al. Heart 2007

Peak VO₂ across age & fitness continuum

Maximal or Peak VO₂ (ml/kg/min)


Activities of daily living as a percent of peak VO₂ in Decompensated Cirrhosis

Percent peak VO₂

MET data from Ainsworth et al. MSSE. 2011
Multiple factors impact the VO₂ in cirrhosis

TAKE HOME POINT #1
- Patients with cirrhosis are deconditioned
- Etiology of this deconditioning is multifactorial

TAKE HOME POINT #2
- VO₂ and its determinants / “correlates” are strong independent predictors of poor outcome
• 6213 men referred for treadmill exercise testing.

• After adjustment, the peak exercise capacity was the strongest predictor of death, each 1-MET increase in capacity conferring a 12% improvement in survival

The VO₂ also has excellent prognostic value in cirrhosis

• N=135 to 399

• Independent of MELD in the prediction of mortality pre-transplantation

• Independent predictor of post-transplant mortality, hospital and ICU length of stay

Components/correlates of VO₂ also have prognostic value

- Mitochondrial dysfunction
- Decoiling
- Muscle weakness
- Malnutrition
- Cachexia
- Anemia
- Chylotho-cardiopathy
- Cirrhosis
- Hydrothorax
- Intestinal lung disease
- Portal-pulmonary hypertension

Lemyze M et al. Digestive and Liver Disease 2012
**Muscle mass loss: MAMC**

N=1053
MAMC <5th% in 38% M, 8% F

Merli M Hepatology 1996

**Muscle mass loss: L3 Skeletal Muscle Index**

N=142
Sarcopenia in 54% M, 21% F

Tandon, Myers et al. Liver Transpl 2012

**Limitations with considering size alone**

Figure 2. Declines in leg lean mass and muscle strength over 3 years by quartiles of baseline strength, stratified by gender. Values of p, analysis of variance between quartiles within the same gender.

Goodpaster BH Gerontology 2006
Cruz-Jentoft A et al. Age and Ageing 2010
**Hand-grip strength**

- Prospective, cross-sectional study of 50 patients with cirrhosis. 88% CP-A
  - Abnormal hand grip predicted a composite endpoint of ascites, HE, SBP, HRS at 1 year of follow-up
  - 66% versus 12% of patients

*Ahoraes DaSilva MR, Nutrition 2005*

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**Six-minute walk distance predicts mortality in liver transplant candidates**

- ~50% increase in survival for every 100 meter increase in the 6MWD
- <2 miles/hour VO2 of 9 mL/kg/min

*Carey EL Liver Transplantation 2010*

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**Frailty – Multidimensional model**

- Frail: ≥ 3 criteria

*Morely JF et al. JAMDA 2013*
TAKE HOME POINT #2
- VO₂ and its determinants / “correlates” are strong independent predictors of poor outcome

TAKE HOME POINT #3
- Exercise + Nutritional Therapy is a promising intervention for MODIFYING exercise capacity and its determinants/correlates
Exercise effects in healthy controls

- Increases SV, lowers HR, improves large arterial compliance
- $\Delta$ A-v $O_2$ content difference
  - Increases muscle mass and quality, $\Delta$ capillary density, $\Delta$ mitochondrial number and oxidative capacity
- Improves QOL, mood and reduces fatigue, beneficial metabolic effects

Alhousaini K et al. Heart 2007

Exercise in cirrhosis

- Limited data evaluating impact on muscle mass or exercise capacity
- 5 patients examined at baseline and after 6 and 12 weeks of an exercise program. VO$_2$ max increased by 19% and 29%
- 4 patients underwent a 4-5 week exercise program. 2 increased their VO$_2$ peak (by 21% and 27%) and 2 had no change

Ritland S et al. Scand J Gastroenterol 1983
Campillo B et al. J Hepatol 1990

Concerns about exercise in cirrhosis -1

Exercise trial: Pilot RCT

- 19 cirrhotics (74% Child Pugh A), 79% men, mean age 58, mean MELD 10

- Randomized to 8-weeks of cycle ergometer exercise training 3 days a week (at 60-80% of baseline peak VO₂) versus usual care

- All patients received regular follow-up with a dietician and had variceal proph if needed


Exercise trial: Pilot RCT

- Primary outcome – Peak VO₂

- Secondary outcomes –
  - Ultrasound measured quadriceps thickness
  - Thigh circumference
  - 6 minute walk distance
  - Fatigue
  - Self-perceived health status (VAS)
  - Adverse outcomes


Zenith L et al. CDDW 2013

Results - 1

Table 1. Baseline and Study End measurements – exercise capacity and anthropometric measures

<table>
<thead>
<tr>
<th>Table 1. Baseline and Study End measurements – exercise capacity and anthropometric measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exercise Group</strong></td>
</tr>
<tr>
<td>Peak VO₂ (liters/min)</td>
</tr>
<tr>
<td>Peak VO₂ (ml/kg/min)</td>
</tr>
<tr>
<td>6-Minute walk distance (m)</td>
</tr>
</tbody>
</table>

Results - 1

Table 1. Baseline and Study End Measurements – Exercise Capacity and Anthropometric Measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Exercise Group Baseline</th>
<th>Exercise Group Study End</th>
<th>Control Group Baseline</th>
<th>Control Group Study End</th>
<th>Difference between means (95% CI)</th>
<th><strong>p</strong> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO2 (L/min)</td>
<td>1.99 ± 0.35</td>
<td>2.30 ± 0.79</td>
<td>2.21 ± 0.52</td>
<td>2.14 ± 0.62</td>
<td>0.48 (0.30 to 0.65)</td>
<td>0.001</td>
</tr>
<tr>
<td>Peak VO2 (mL/kg/min)</td>
<td>23.2 ± 7.7</td>
<td>27.3 ± 5.2</td>
<td>26.2 ± 6.7</td>
<td>25.3 ± 4.6</td>
<td>5.5 (2.29 to 7.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>60-Minute Walk Distance (m)</td>
<td>359.1 ± 15.8</td>
<td>376.5 ± 11.0</td>
<td>329.3 ± 84.6</td>
<td>340.0 ± 97.7</td>
<td>23.6 (12.4 to 34.4)</td>
<td>0.19</td>
</tr>
<tr>
<td>Total Protein (g/dl)</td>
<td>51.7 ± 23.3</td>
<td>51.3 ± 12.1</td>
<td>51.2 ± 36.2</td>
<td>51.9 ± 31.6</td>
<td>1.5 (0.61 to 1.3)</td>
<td>0.63</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>160 ± 475</td>
<td>211 ± 175</td>
<td>226 ± 832</td>
<td>220 ± 488</td>
<td>4.6 (0.01 to 0.91)</td>
<td>0.006</td>
</tr>
<tr>
<td>Hip Circumference (cm)</td>
<td>52.4 ± 6.7</td>
<td>52.4 ± 6.7</td>
<td>52.4 ± 6.7</td>
<td>52.4 ± 6.7</td>
<td>0.0 (0.84 to 1.84)</td>
<td>1.00</td>
</tr>
<tr>
<td>Body Mass Index (BMI)</td>
<td>27.7 ± 5.8</td>
<td>26.0 ± 5.0</td>
<td>26.4 ± 4.7</td>
<td>26.5 ± 4.0</td>
<td>-0.05 (0.07 to 0.03)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Results - 2

Table 2. Baseline and Study End Measurements – Quality of Life, Liver Function and Liver Enzymes

<table>
<thead>
<tr>
<th>Measure</th>
<th>Exercise Group Baseline</th>
<th>Exercise Group Study End</th>
<th>Control Group Baseline</th>
<th>Control Group Study End</th>
<th>Difference between means (95% CI)</th>
<th><strong>p</strong> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLUO (Total)</td>
<td>57.3 ± 0.83</td>
<td>60.1 ± 0.85</td>
<td>54.3 ± 0.91</td>
<td>53.9 ± 0.96</td>
<td>0.5 (14.0 to 3.85)</td>
<td>0.52</td>
</tr>
<tr>
<td>GGT (IU/L)</td>
<td>104 ± 11.5</td>
<td>100 ± 11.1</td>
<td>102 ± 13.3</td>
<td>106 ± 13.0</td>
<td>0.05 (2.0 to 21.3)</td>
<td>0.92</td>
</tr>
<tr>
<td>ALT (UI/L)</td>
<td>36.2 ± 16.8</td>
<td>40.4 ± 37.1</td>
<td>46.7 ± 75.9</td>
<td>46.2 ± 67.3</td>
<td>1.5 (10.1 to 9.6)</td>
<td>0.63</td>
</tr>
<tr>
<td>AST (UI/L)</td>
<td>33.8 ± 33.6</td>
<td>34.1 ± 37.4</td>
<td>33.2 ± 22.2</td>
<td>33.7 ± 15.0</td>
<td>0.01 (8.8 to 1.65)</td>
<td>0.03</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>26.7 ± 10.3</td>
<td>27.5 ± 8.8</td>
<td>27.6 ± 13.7</td>
<td>31.2 ± 15.3</td>
<td>1.7 (13.2 to 4.5)</td>
<td>0.64</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.8 ± 0.52</td>
<td>3.8 ± 0.51</td>
<td>3.8 ± 0.43</td>
<td>3.8 ± 0.33</td>
<td>0.0 (1.2 to 3.6)</td>
<td>0.50</td>
</tr>
</tbody>
</table>
Conclusions

• Impaired Exercise Tolerance in Cirrhosis
  – Common and associated with poor outcomes
  – Potentially modifiable
• Nutrition + Exercise therapy require further study
  – Likely to have different benefits at different CP classes.
    May be particularly beneficial with NAFLD
  – Improving pre and post transplant outcomes,
    functionality, QOL, fatigue
  – Point of futility?