

Cirrhosis: Let's get moving!

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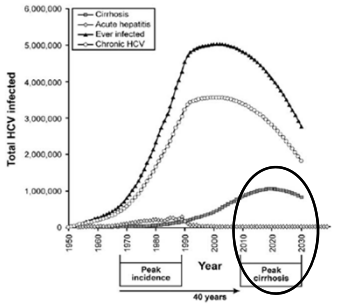
Objectives

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 O_2 to exercising skeletal muscle and of the muscle to extract O_2 from the blood"

$VO_2 = (SV \times HR) \times (CaO_2\text{-}CvO_2)$ in mL/min

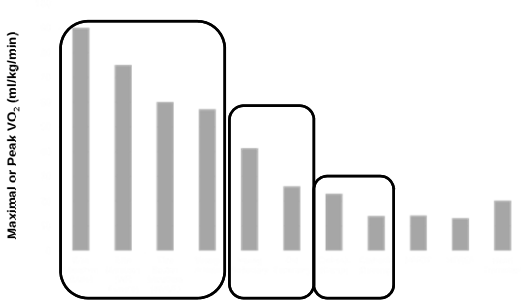
- VO_2 normalized for body weight
  - 3.5 mL/kg/min (resting seated O_2 uptake)
  - Equivalent to 1 MET

Albouaini K et al. Heart 2007

Cardiopulmonary exercise testing

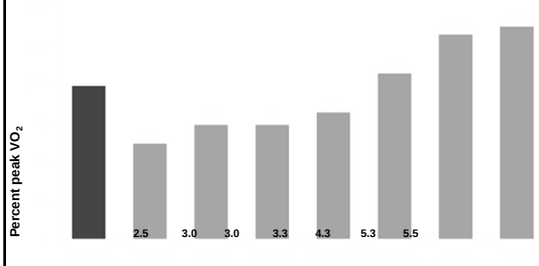
Albouaini K et al. Heart 2007

Peak VO_2 across age & fitness continuum



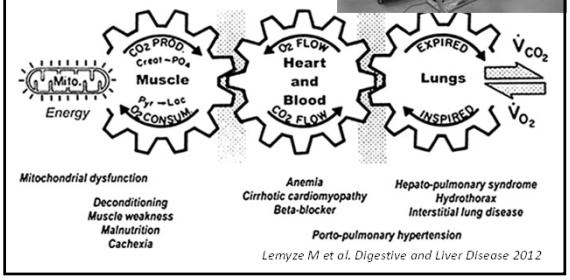
Hagan et al. Med Sc Sports Exerc.1981; Jones A. Int J Sports Sci & Coaching.2006; Wilson & Tanaka. AJP Heart. 2000; Kitzman et al. JAMA. 2002.

Activities of daily living as a percent of peak VO_2 in Decompensated Cirrhosis



MET data from Ainsworth et al. MSSE, 2011

Multiple factors impact the VO_2 in cirrhosis



Lemyze M et al. Digestive and Liver Disease 2012

TAKE HOME POINT #1

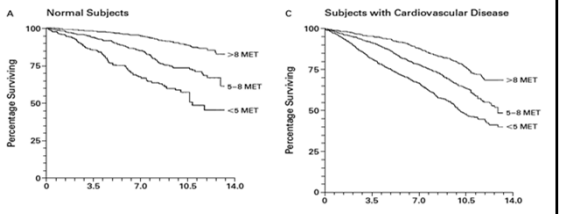
-Patients with cirrhosis are deconditioned

-Etiology of this deconditioning is multifactorial

TAKE HOME POINT #2

-VO_2 and it's 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



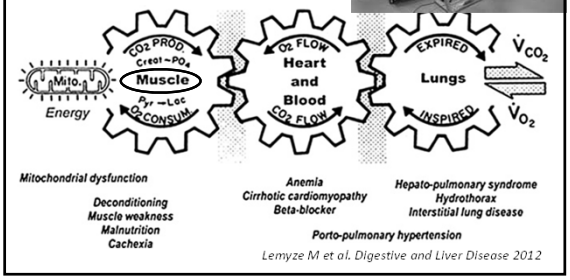
Myers J et al. NEJM 2002

The VO_2 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

Epstein SK et al. Liver Transplantation 2004
Dharancy S et al. Transplantation 2008
Prentis JM et al. Liver Transplantation 2012
Bernal W et al. Liver Transplantation 2013
Neviere R et al. AJT 2013

Components/correlates of VO_2 also have prognostic value



Mitochondrial dysfunction
Deconditioning
Muscle weakness
Malnutrition
Cachexia

Anemia
Cirrhotic cardiomyopathy
Beta-blocker

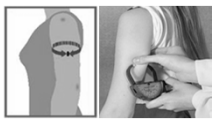
Hepato-pulmonary syndrome
Hydrothorax
Interstitial lung disease

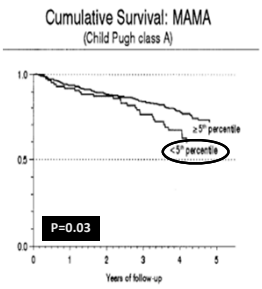
Porto-pulmonary hypertension

Lemyze M et al. Digestive and Liver Disease 2012

Muscle mass loss: MAMC

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

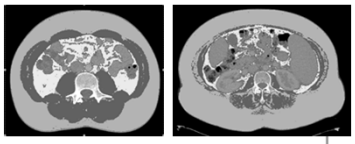


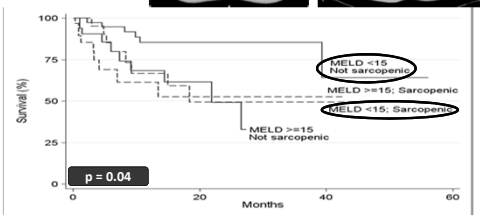


Merli M Hepatology 1996

Muscle mass loss: L3 Skeletal Muscle Index

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





Tandon, Myers et al. Liver Transpl 2012
Montano Loza et al. Clin Gastro Hep 2012

Limitations with considering size alone

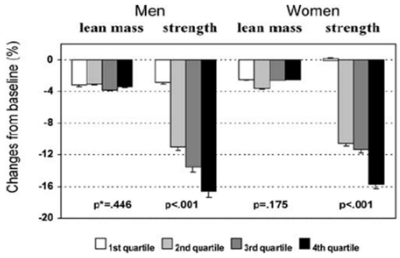


Figure 2. Declines in leg lean mass and muscle strength over 3 years by quartiles of baseline strength, stratified by gender. Values of *p*, analysis of variance between quartiles within the same gender.

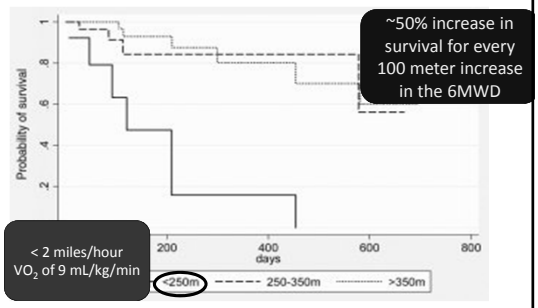
Goodpaster BH Gerentology 2006
Cruz-Jentoft A et al. Age and Ageing 2010

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

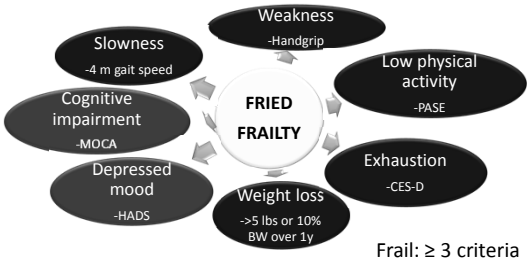
Alvares DaSilva MR, Nutrition 2005

Six-minute walk distance predicts mortality in liver transplant candidates



Carey EJ Liver Transplantation 2010

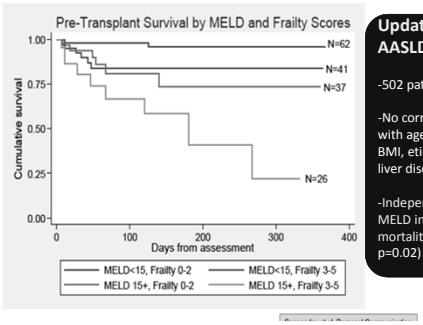
Frailty – Multidimensional model



Frail: ≥ 3 criteria

Moreley JE et al. JAMDA 2013

Frailty and Liver Transplant Candidate Survival



Update at AASLD 2013

-502 patients

-No correlation with age, gender, BMI, etiology of liver disease

-Independent of MELD in predicting mortality (HR = 2.7, p=0.02)

Sonnenday C et al. Hepatology 2010, 2013 (abstracts)

TAKE HOME POINT #2

-VO_2 and it's 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
- ⇧A-v O_2 content difference
  - Increases muscle mass and quality, ⇧ capillary density, ⇧mitochondrial number and oxidative capacity
- Improves QOL, mood and reduces fatigue, beneficial metabolic effects

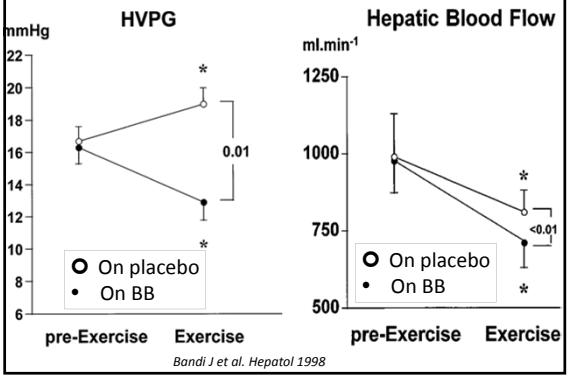
Albouaini K et al. Heart 2007

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



Bandi J et al. Hepatol 1998

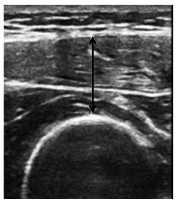
Exercise trial: Pilot RCT

- 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 VO_2) versus usual care
- All patients received regular follow-up with a dietician and had variceal proph if needed

Zenith L et al. Clin Gastroenterol Hepatol (in press)

Exercise trial: Pilot RCT

- Primary outcome – Peak VO_2
- Secondary outcomes –
  - Ultrasound measured quadriceps thickness
  - Thigh circumference
  - 6 minute walk distance
  - Fatigue
  - Self-perceived health status (VAS)
  - Adverse outcomes



Zenith L et al. Clin Gastroenterol Hepatol (in press)
Zenith L et al. CDDW 2013

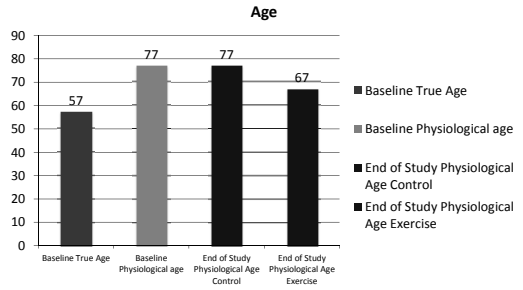
Results - 1

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

	Exercise Group		Control Group		Difference between mean changes (95% CI)	ANCOVA p value
	Baseline	Study End	Baseline	Study End		
Peak VO_2 (L/min)	1.98 ± 0.65	2.35 ± 0.79	2.21 ± 0.52	2.14 ± 0.62	0.48 (0.30 to 0.65)	0.001
Peak VO_2 (mL/kg/min)	23.3 ± 7.7	27.3 ± 6.2	25.2 ± 6.7	23.3 ± 4.8	5.3 (2.9 to 7.8)	0.001
6-Minute walk distance (m)	529.1 ± 131.8	570.5 ± 112.0	529.0 ± 84. 6	546.0 ± 97.7	23.5 (-12.4 to 59.4)	0.19

Zenith L et al. Clin Gastroenterol Hepatol (in press)

Improvement in physiological age



Zenith L et al. Clin Gastroenterol Hepatol (in press)

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Nutritional Intake						
Total protein (g/day)	81.7 ± 20.3	107.5 ± 32.0	102.1 ± 39.2	108.9 ± 31.6	10.4 (-17.1 to 37.9)	0.43
Total calories (kcal/day)	1630 ± 475	2112 ± 705	2024 ± 612	2356 ± 646	60 (-501 to 621)	0.82
Thigh Circumference (cm)	52.4 ± 4.7	53.6 ± 4.4	52.9 ± 4.7	53.1 ± 4.7	1.05 (0.54 to 1.56)	0.001
Avg. Feather Index (cm/m^2)	1.27 ± 0.38	1.37 ± 0.33	1.10 ± 0.21	1.13 ± 0.19	0.11 (-0.02 to 0.25)	0.10
Avg. Compression Index (cm/m^2)	0.58 ± 0.19	0.63 ± 0.18	0.53 ± 0.15	0.53 ± 0.11	0.06 (0.01 to 0.11)	0.01
BMI (kg/m^2)	27.7 ± 3.8	28.0 ± 3.6	28.9 ± 4.1	29.1 ± 4.0	-0.05 (-0.7 to 0.6)	0.86
Body Weight (kg)	83.7 ± 13.0	84.4 ± 12.3	89.7 ± 20.5	90.5 ± 20.2	-0.16 (-2.2 to 1.8)	0.87

Zenith L et al. Clin Gastroenterol Hepatol (in press)

Results - 2

Table 2. Baseline and Study End measurements – Quality of life, liver function and liver enzymes

	Exercise Group		Control Group		Difference between mean changes (95% CI)	ANCOVA p value
	Baseline	Study End	Baseline	Study End		
CLDQ						
Total	5.72 ± 0.63	6.01 ± 0.63	5.42 ± 0.81	5.39 ± 0.96	0.35 (-0.14 to 0.84)	0.15
Fatigue	4.64 ± 1.52	5.62 ± 0.71	4.88 ± 1.12	4.93 ± 0.93	0.80 (0.22 to 1.38)	0.01
EQ-VAS	73.9 ± 9.2	83.6 ± 11.1	78.2 ± 13.3	66.2 ± 21.0	20.4 (5.1 to 35.8)	0.01
MELD	9.7 ± 2.4	10.3 ± 2.60	10.2 ± 1.9	10.8 ± 2.70	0.08 (-1.36 to 1.52)	0.91
Child Pugh score	6.2 ± 1.4	6.3 ± 1.4	6.3 ± 1.4	6.3 ± 1.06	0.08 (-0.78 to 0.94)	0.84
ALT	36.2 ± 16.6	40.4 ± 21.5	66.7 ± 75.9	68.0 ± 67.3	-0.92 (-9.8 to 8.0)	0.83
AST	50.9 ± 33.6	54.1 ± 37.4	72.6 ± 62.2	66.7 ± 75.9	5.05 (-6.1 to 16.2)	0.35
Bilirubin	20.7 ± 10.9	25.7 ± 8.8	27.0 ± 13.7	31.9 ± 11.8	-1.7 (-7.3 to 4.0)	0.54
Albumin	38.0 ± 5.2	37.9 ± 5.1	36.8 ± 4.0	36.4 ± 3.3	0.48 (-1.4 to 2.4)	0.59

Zenith L et al. Clin Gastroenterol Hepatol (in press)

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?