Nutricia Metabolics Webinar Series

Biochemistry and Management of Fatty Acid Oxidation Disorders: From Infancy to Adulthood

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Nutritional Management of Fatty Acid Oxidation Disorders

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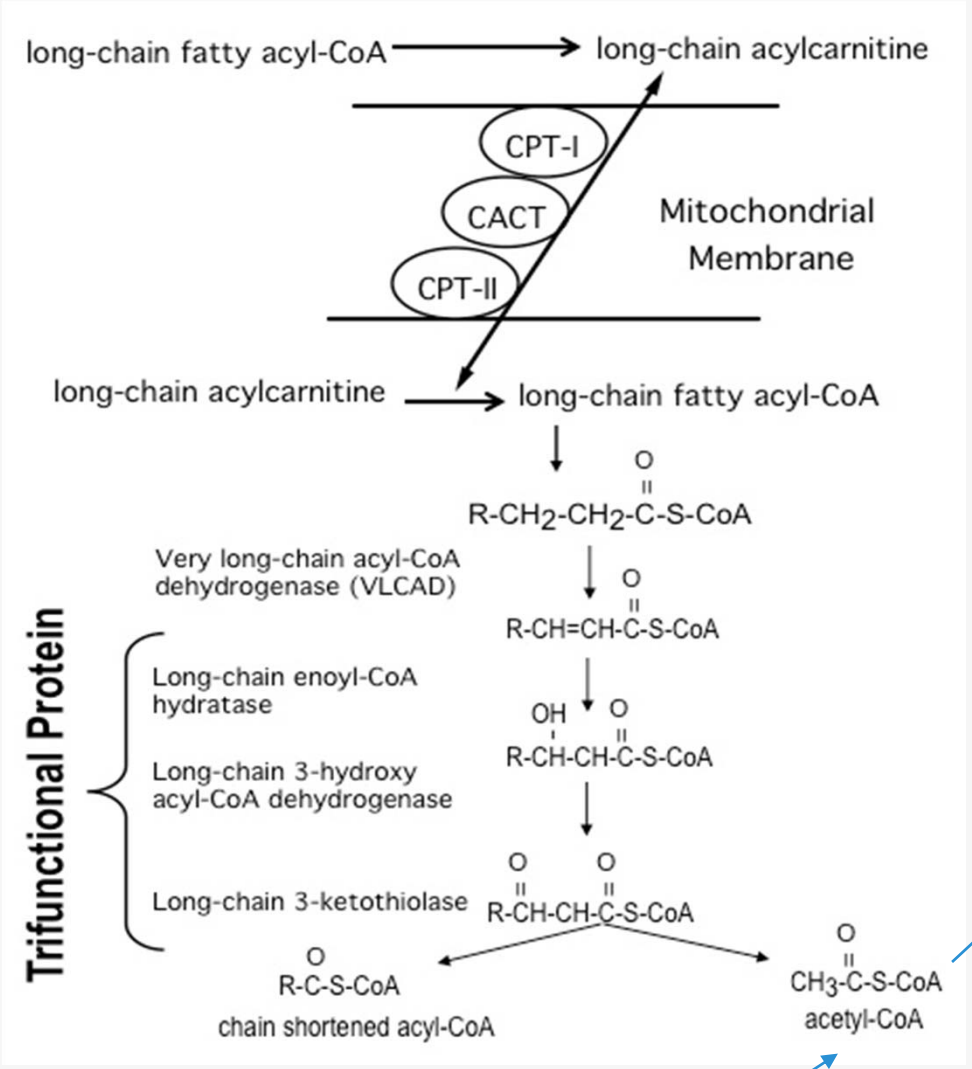
Fatty acid oxidation pathway

- Long Chain: 20 to 12 Carbons
- Medium Chain: 12 to 6 Carbons
- Short Chain: 6 to 4 Carbons



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Treatment Principles: VLCADD, TFP, LCHADD

- Avoid fasting
- Reduce long chain fatty acids in diet
- Supplement with medium chain fats to bypass enzymatic block
- Assure adequate essential fatty acid intake
- Prevent hypoglycemia
- Aggressive illness management
- Carnitine supplementation?

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LC-FAOD Treatment varies:
Enzyme defect and severity of defect

- LCHADD and TFP: Always consider severe
- VLCADD:
  - Severe infantile presentation with cardiomyopathy
  - Infantile/childhood presentation with episodes of hypoketotic hypoglycemia
  - Late onset: Rhabdomyolysis later in life
- **Last two groups, often asymptomatic with NBS diagnosis.**

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So, what are fasting limits?

Consider:

- Diagnosis
- Severity of disease
- Health status
- Anxiety of parents

Age	# of hours
0 to 1 month	3 to 6
1 to 3 months	4 to 6
4 months	4 to 8
5 months	4 to 8
6 months	4 to 8
7 months	6 to 8
8 months	6 to 10
9 months	6 to 10
10 months	6 to 10
11 months	6 to 10
≥ 12 months	10 to 12
≥ 24 months	10 to 12

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Diet composition for neonates with LC-FAOD

Asymptomatic

Continuing breastfeeding - with or without formula - may be possible for some

Fat: *40 to 50% of total kcals*

- 20 – 25%E as LCT
- 20 – 25%E as MCT
  - →50% of fat as LCT
  - →50% of fat as MCT

Symptomatic/Severe

Change to low fat-MCT supplemented formula

Fat: *40 to 50% of total kcals*

- 10 – 15%E as LCT
- 30 – 40%E as MCT
  - →20 – 30% of fat as LCT
  - →60 – 80% of fat as MCT

At this time, we are not good at predicting the degree of treatment required for Asymptomatic infants

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Fat content of medical foods used to treat long-chain FAOD in the USA

Formula	Total Fat % kcal	LCF % fat	MCT % fat	LA mg/100g	ALA mg/100g	Ratio N6:N3	DHA/ARA
Enfaport	48	16	84	350	50	7:1	Yes
Lipistart	40	20	78	1767	246	6:1	Yes
Monogen	25	10	90	473	101	4.7:1	No
Portagen	42	13	87	1620	ND	20:1	No
Pregestimil	50	45	55	4700	480	10:1	Yes

Recommended N6:N3 ratio = 5 to 10 : 1

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MCT supplementation

- Percent of total kcals needs:
  - Use DRI estimate for kcals
  - 10 to 30% of total kcals as MCT, depending on LCF restriction and age
- Based on weight and age:
  - 2 to 3 g/kg in infancy
  - 1 to 1.25 g/kg after first year

(Saudubrey et al, J Inher Metab Dis, 22: 488-502, 1999)

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MCT Supplements

MCT Procal

- 92% of kcal as MCT
- 10 g per 16 g powder (16 g = 1 packet or 2 scoops)
- 105 kcal

MCT Oil

- 100% of kcal as MCT
- 14 g per 15 ml (1 Tbsp)
- 116 kcal

Liquigen

- 96% of kcal as MCT
- 13.5 g per 30 mL (2 Tbsp)
- 135 kcal

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Considerations for MCT

- How long to continue formula?
- “MCT Milk”
  - Add MCT to low fat/skim milk
  - Can include additional protein or CHO source if needed
- Add MCT to different foods

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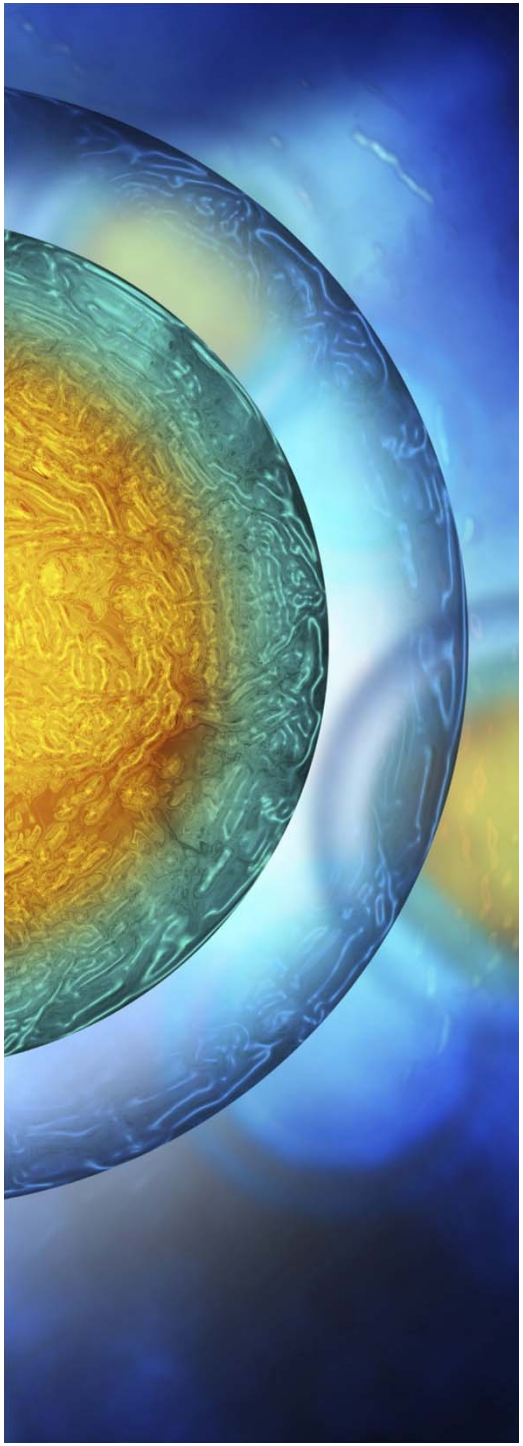

MCT Recipe Resources

- MCT Oil
  - Louisville.edu/medschool/pediatrics/wcec/mctfoods
  - FOoD Kitchen = New cookbook from OHSU out in July
- MCT Powder
  - iMaginative reCipes Tools from VitaFlo

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LC-FAOD: Total fat does not need to be reduced

- Total fat can be equivalent to recommendations for age:
  Based on AI:
  45 to 50% of kcals @ 1 month
  35% of kcals @ 6 months
  30% of kcals @ 1 year

- Counting dietary fat:
  - Mild FAOD: Can use labels
  - Severe FAOD: Count grams of fat to 0.5 g increments

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Diet Considerations for older individuals

- Energy:
  - Those with severe LC-FAOD may have reduced LBM and lower activity reducing energy needs
    - Consider EER for overweight individuals
    - (Gillingham et al,, Mol Genet Metab 2003)
- Protein: Minimum DRI
- Fat:
  - Need at least 10% of total kcals as MCT
  - Minimum 10% of kcals (? down to 8%) from LCF, otherwise will not meet DRI for fat and meet essential fatty acid needs

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LCFA: Monitoring

- Metabolic labs
  - Plasma acylcarnitine profile
  - CK
  - Glucose
  - Liver function
  - Carnitine (total, free, esters)
- Nutrition labs
  - Essential fatty acids
  - Fat soluble vitamins: Consider D, E, A

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Monitoring: Acylcarnitine Profiles

Normalization of acylcarnitines is possible, especially with mild forms of VLCADD

"Adding up acylcarnitines"

VLCADD:

C14:0 + C14:1 + C16:0 + C16:1 + C18:0 + C18:1 + C18:2

LCHADD/TFP:

C16:0-OH + C16:1-OH + C18:0-OH + C18:1-OH + C18:2-OH

Good control = total < 2 umol/L

Best evidence for relationship between acylcarnitine levels and clinical status is for LCHADD

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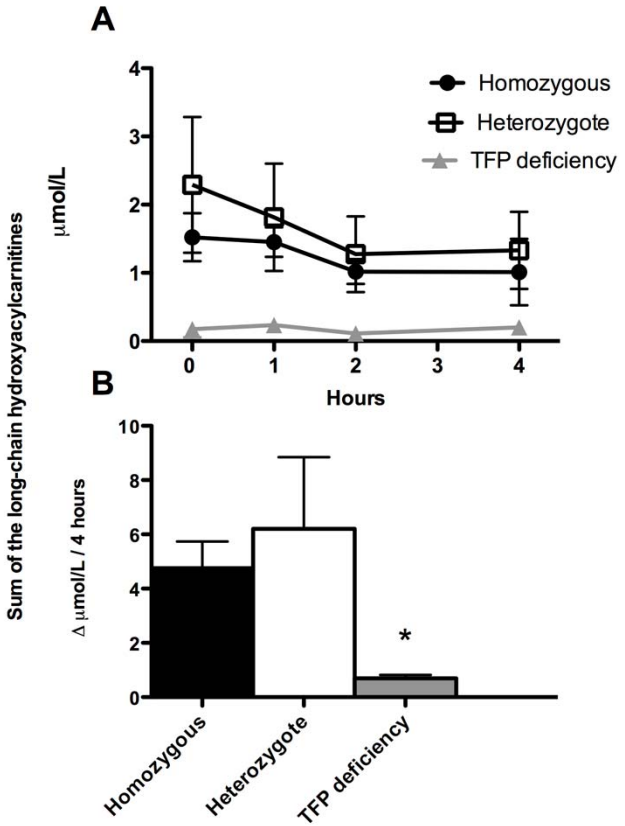
Hydroxyacylcarnitines & Genotype

- Common mutation in TFP of European origin; c.1528G>C
- US population accounts for 80% mutant alleles
  - homozygous or compound heterozygous for c.1528G>C



Gillingham et al, Topics in Clinical Nutrition 2009; vol 24: pp 353-359

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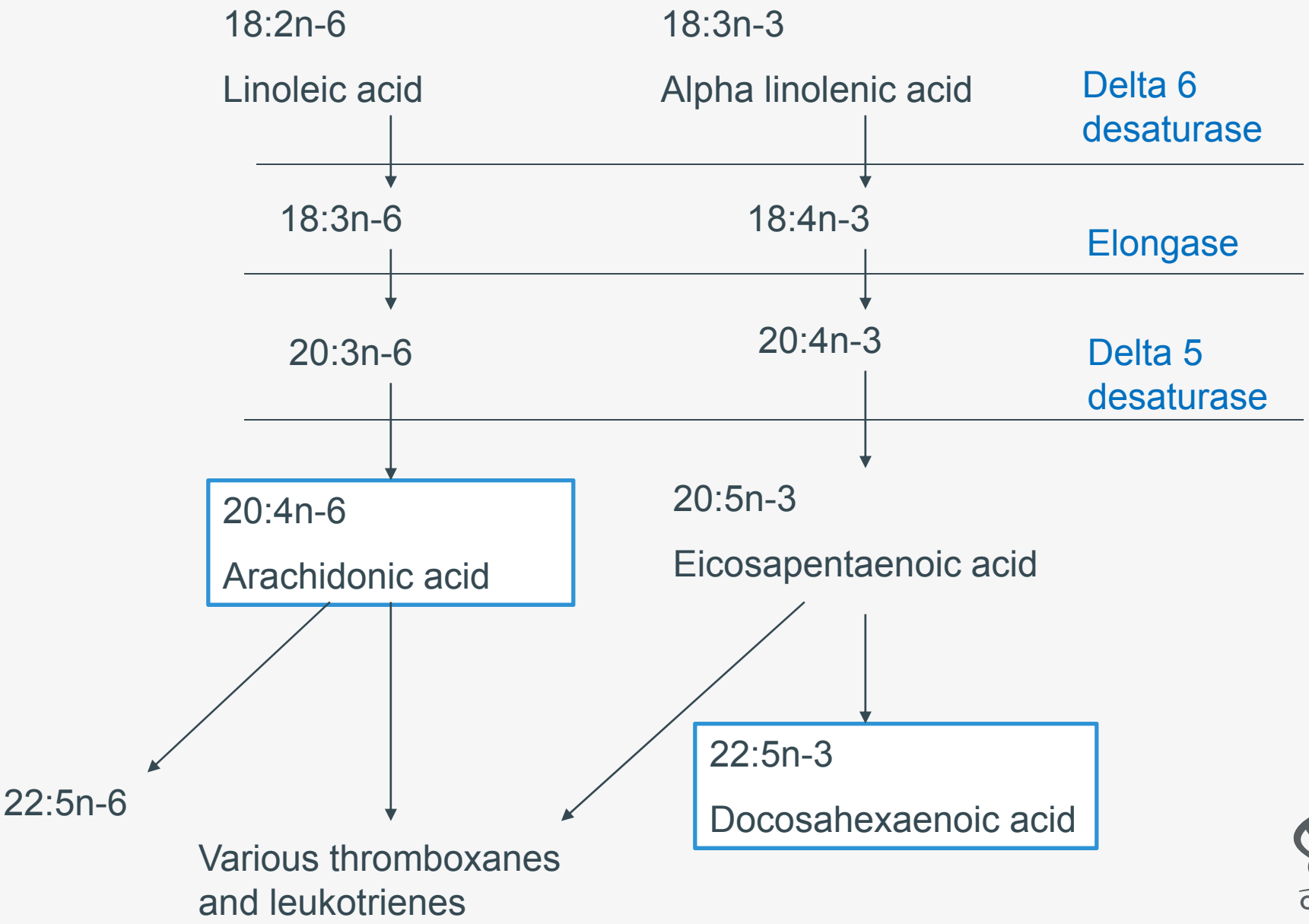
Essential Fatty Acid Pathways



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Fatty acid profiles: Assessing essential fatty acid status

- ARA/DHA supplementation in formulas improves status

Interpreting fatty acid profiles

  - Medium chain fatty acids: C8 to C12
    - Expect elevations with MCT supplement
  - Saturated fatty acids: C16:0, C18:0, C20:0
    - Can expect low levels with fat restriction
    - No clinical concern

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Fatty acid profiles: Assessing essential fatty acid status

- Interpreting fatty acid profiles
  - N-6 metabolites
    - Linoleic acid = C18:2n-6
    - Arachidonic acid = C20:4n-6
    - Holman ratio: Normal 0.01 – 0.04; not a sensitive marker
  - Solutions if low
    - Add vegetable oils (safflower, walnut, canola)
    - Lean meats = preformed arachidonic acid

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Fatty acid profiles: Assessing essential fatty acid status

Interpreting fatty acid profiles

- N-3 metabolites
  - α-linolenic acid = C18:3n-3
  - Low levels are not of concern
  - EPA = C20:5n-3
  - DHA = C22:6n-3
  - ARA: DHA ratio. Goal < 4; Higher # suggests low n-3 compared to n-6
- Solutions
  - Adding sources of α-LA may not correct low DHA
  - Consider DHA supplementation

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LC-FAOD and Illness: At Home Management

- Symptoms develop from FAO metabolites before hypoglycemia develops:
  - Do not use glucose meters
- Avoidance of fasting essential
  - 4 hours max for most ages
- Calories, calories, calories
  - Simple carbohydrate needed
  - Provide intake goal to caregivers

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A diagnosis of “mild” VLCADD doesn’t mean there isn’t a risk of decompensation

J Inherit Metab Dis
DOI 10.1007/s10545-009-9041-6

CASE REPORT

Genotype–phenotype correlations: sudden death in an infant with very-long-chain acyl-CoA dehydrogenase deficiency

Curtis R. Coughlin II · Can Ficicioglu

This child died at age 38 hours (prior to NBS) with hypoglycemia. No cardiac involvement. Had genotype associated with mild disease, V283A.

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Glucose Polymer Protocol for Acute Management

Age	Glucose polymer (%)	Dose mL/kg/h	Fluid requirement mL/kg/day	Energy
0–6 months	15	7.7	183	110
6–12 months	15	7.0	168	100
1–3 years	20	4.5	110	90
3–6 years	25	3.3	80	80
6–12 years	25	2.6	65	65
or 6–12 years	30	2.25	54	65
12–15 years	30	1.8	42	50
>15 years	30	1.6	38	45

Table 2
American household measures for glucose polymer solutions and caloric densities.

15% solution	15 g in 100 mL	8 tsp in 4 fl oz.	60 kcal/dL, 16.8 kcal/fl oz
20% solution	20 g in 100 mL	11 tsp in 4 fl oz.	80 kcal/dL, 22.4 kcal/fl oz
25% solution	25 g in 100 mL	4½ tb in 4 fl oz.	100 kcal/dL, 28 kcal/fl oz
30% solution	30 g in 100 mL	5½ tb in 4 fl oz.	120 kcal/dL, 33.6 kcal/fl oz

Legend: tsp, teaspoon (5 mL); tb, tablespoon (15 mL); fl oz, fluid ounce (30 mL).

Van Hove JLK et al. Molecular Genetics and Metabolism 97 (2009) 1-3

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Carbohydrate Solutions for FAOD Illness

Concentration	Rehydration Soln (Pedialyte) 4 kcal/oz	Juice/Gatorade 15 kcal/oz	PolyCal®
15% (17 kcal/oz)	8 oz 240 ml		4 Tbsp + 2 tsp 30 g
20% (22 kcal/oz)	8 oz 240 ml		6 Tbsp + 2 tsp 40 g
20% (22 kcal/oz)		8 oz 240 ml	2 Tbsp +2 tsp 18 g
25% (28 kcal/oz)		8 oz 240 ml	4 Tbsp + 2 tsp 30 g
30% (34 kcal/oz)		8 oz 240 ml	6 Tbsp + 2 tsp 40 g

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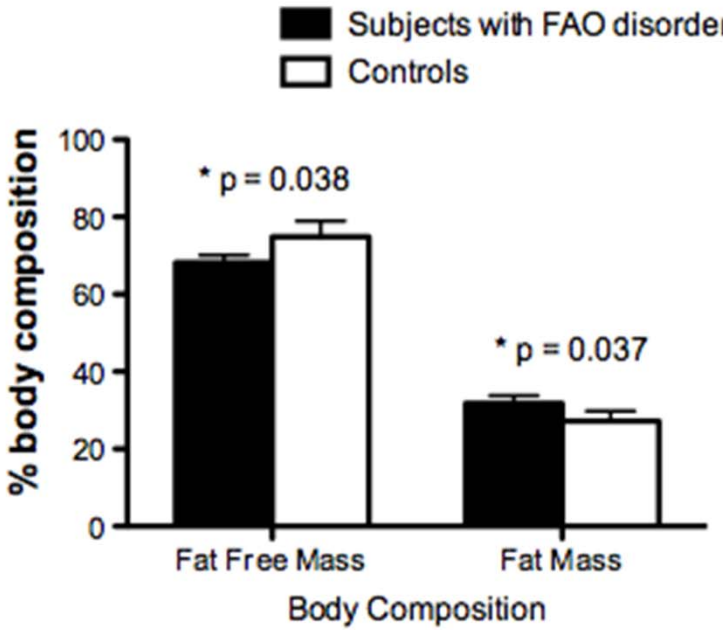
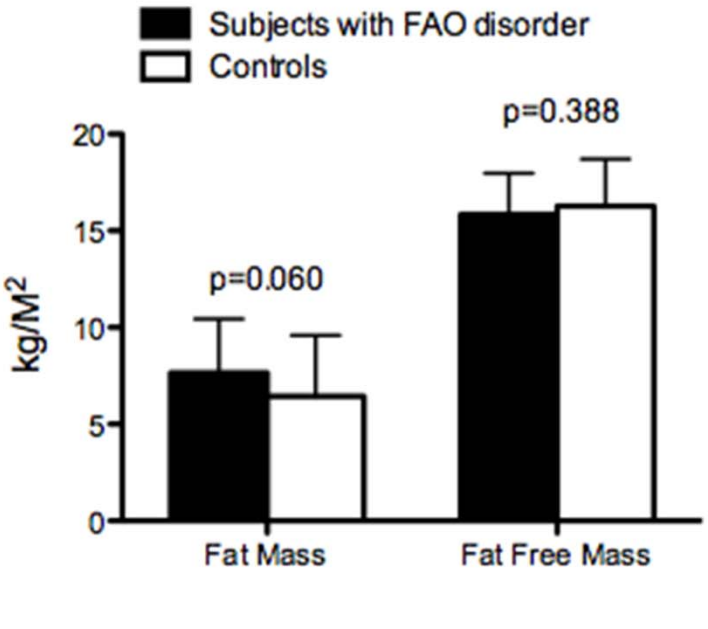
Altered Body Composition





- Lower lean mass; higher fat mass in subjects with same BMI compared to controls
- Due to increase in fat mass

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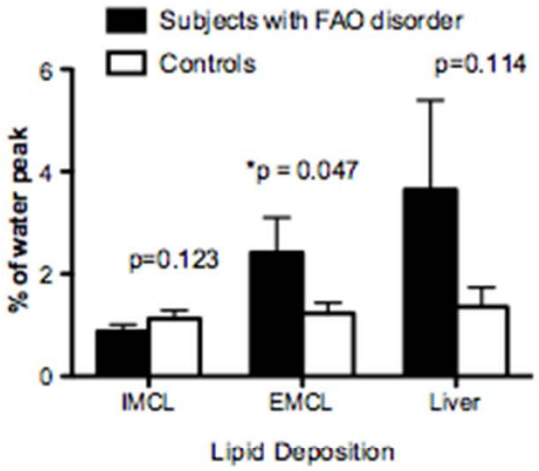
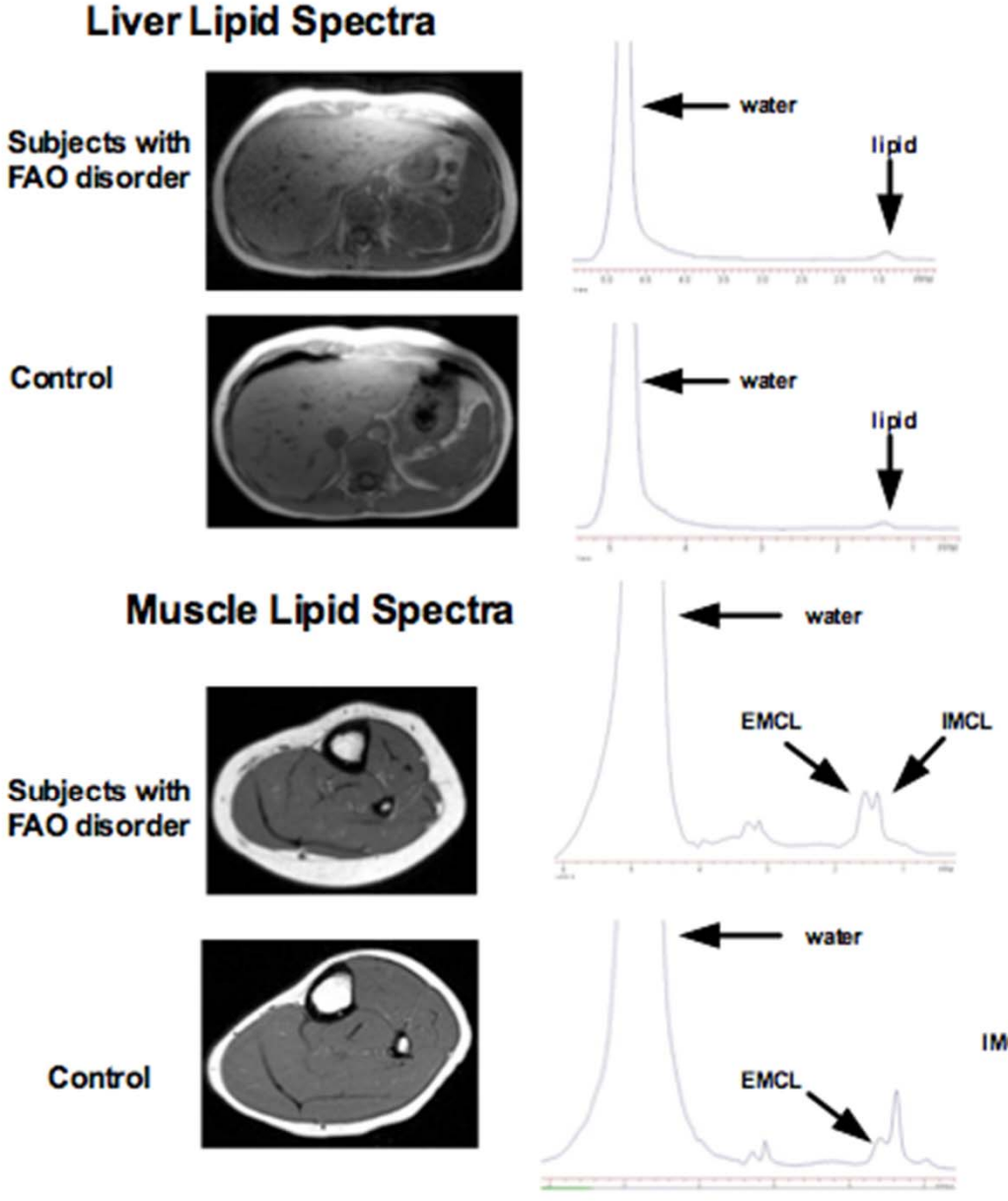
Liver and Muscle Lipid Deposition



- Increased liver & EMCL lipid



Nutrition Therapy for adolescents & adults

Chronic complications

- Muscle pain/fatigue
- Recurrent rhabdomyolysis
- LCHAD: retinopathy/peripheral neuropathy

Nutrition Therapy

- Promote normal body composition
  - ↑ Lean body mass
  - Normal fat mass
- Provide appropriate energy
- Prevent or decrease episodes of rhabdomyolysis

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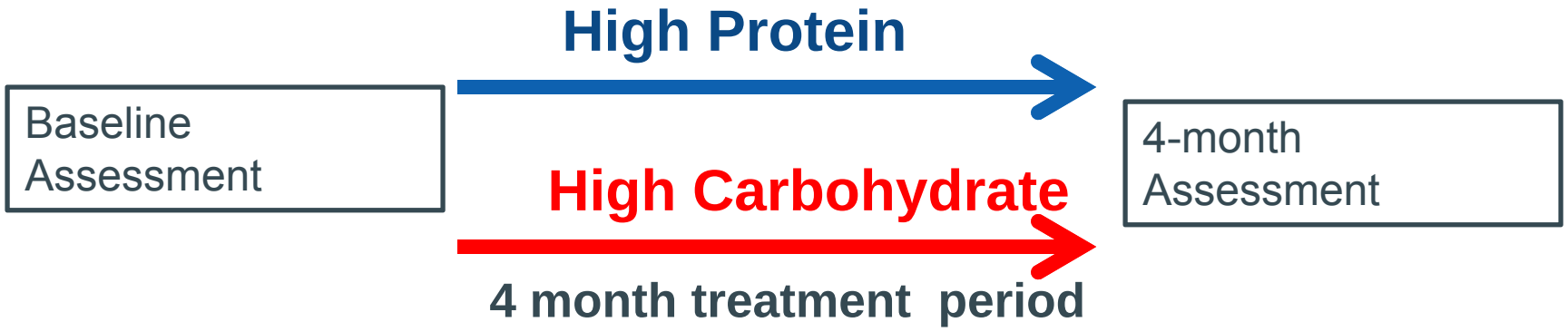
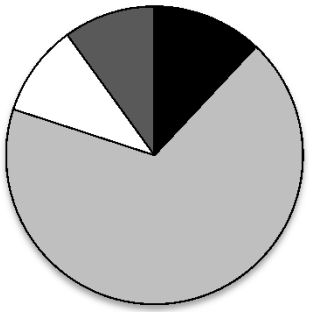
Increased Protein

- Randomized 13 subjects with long-chain FAO disorder to high carbohydrate diet or high protein diet for 4 months



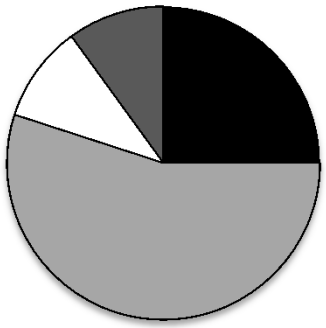
Standard Diet

Protein
12% energy
0.8-1.6 g/kg



protein carbohydrate LCFA MCT

High Protein



Protein
25% energy
1.2-2.6 g/kg

protein carbohydrate LCFA MCT

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Increased Protein Intake

What did they really eat at home?
Based on 3-day diet records….

Standard Diet	High Protein Diet
Protein	Protein
14% energy	19% energy
0.70-1.5 g/kg	0.8-2.0 g/kg

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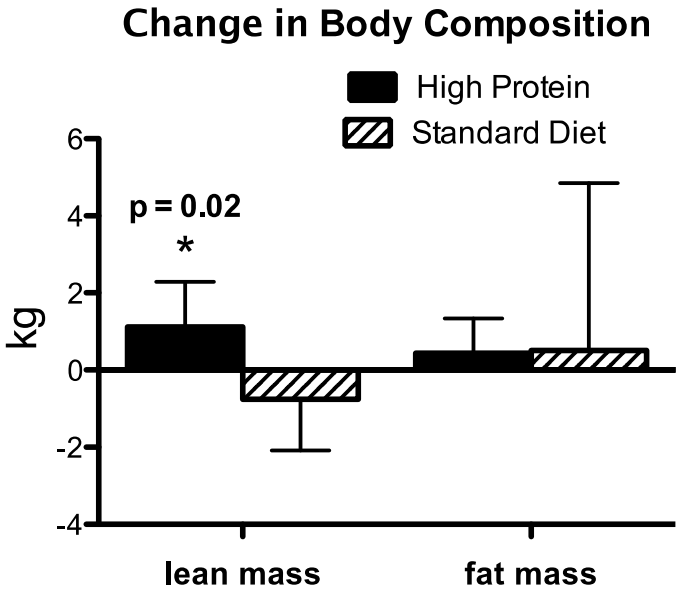
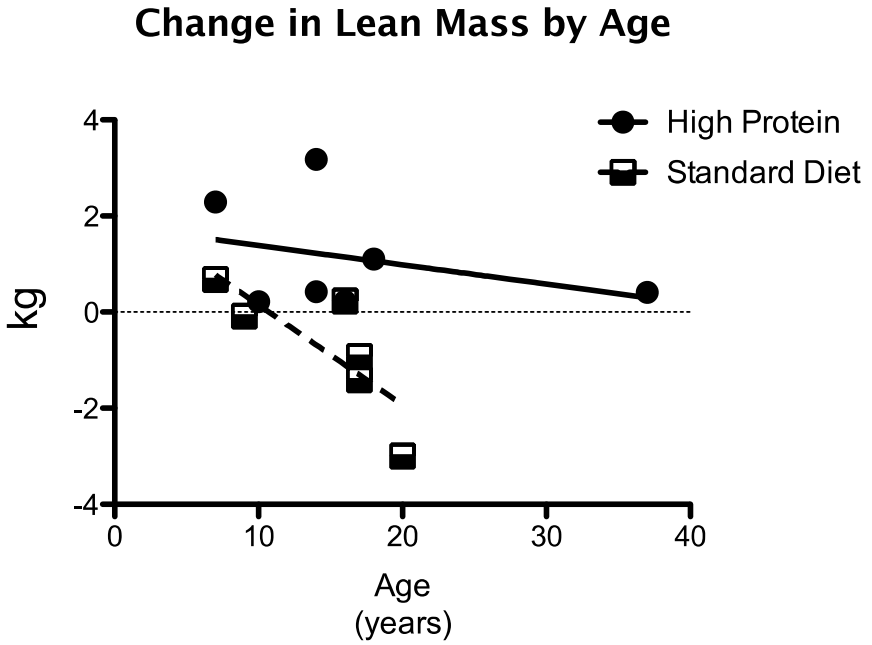
High Protein Diet Increased Lean Mass



High protein increased lean mass.



Lean mass loss in older subjects on standard diet.

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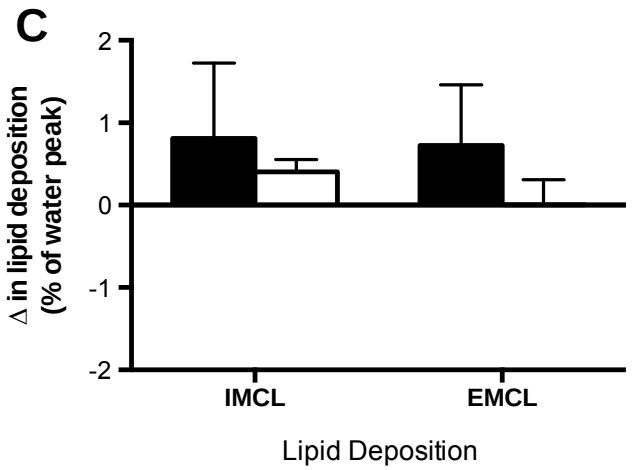
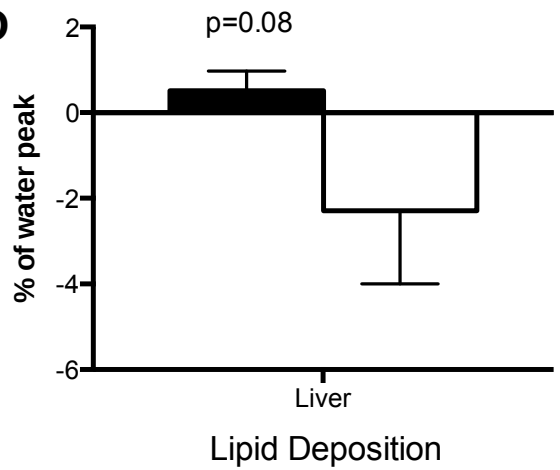
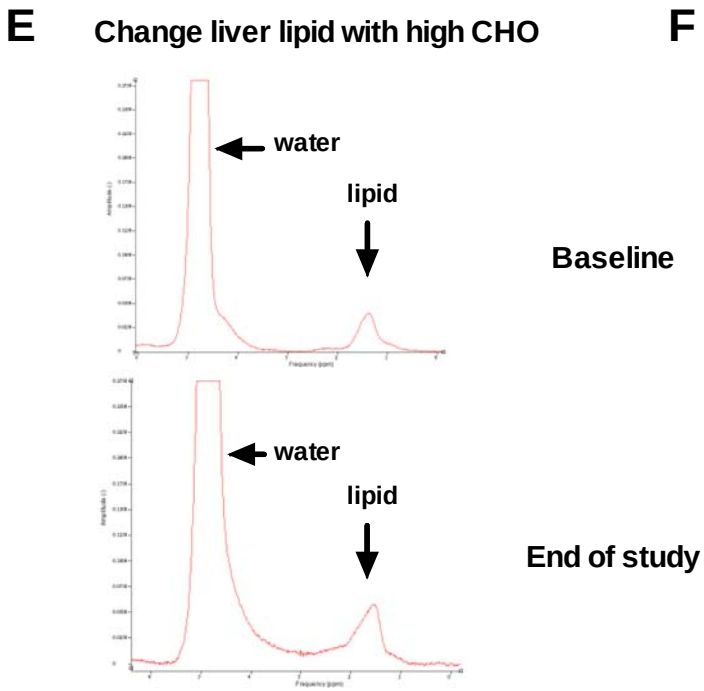
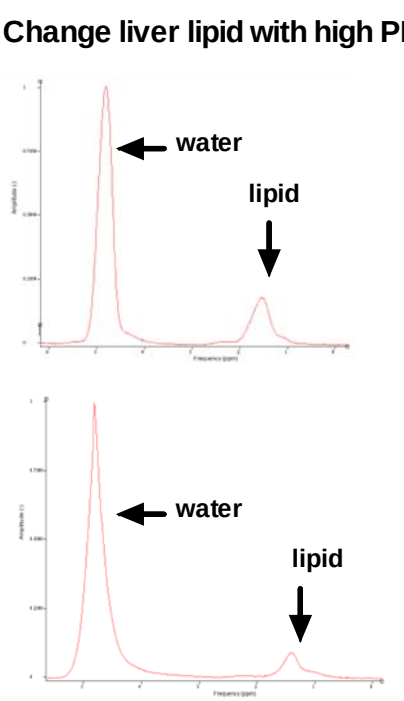
High Protein Diet lowered Liver Lipid









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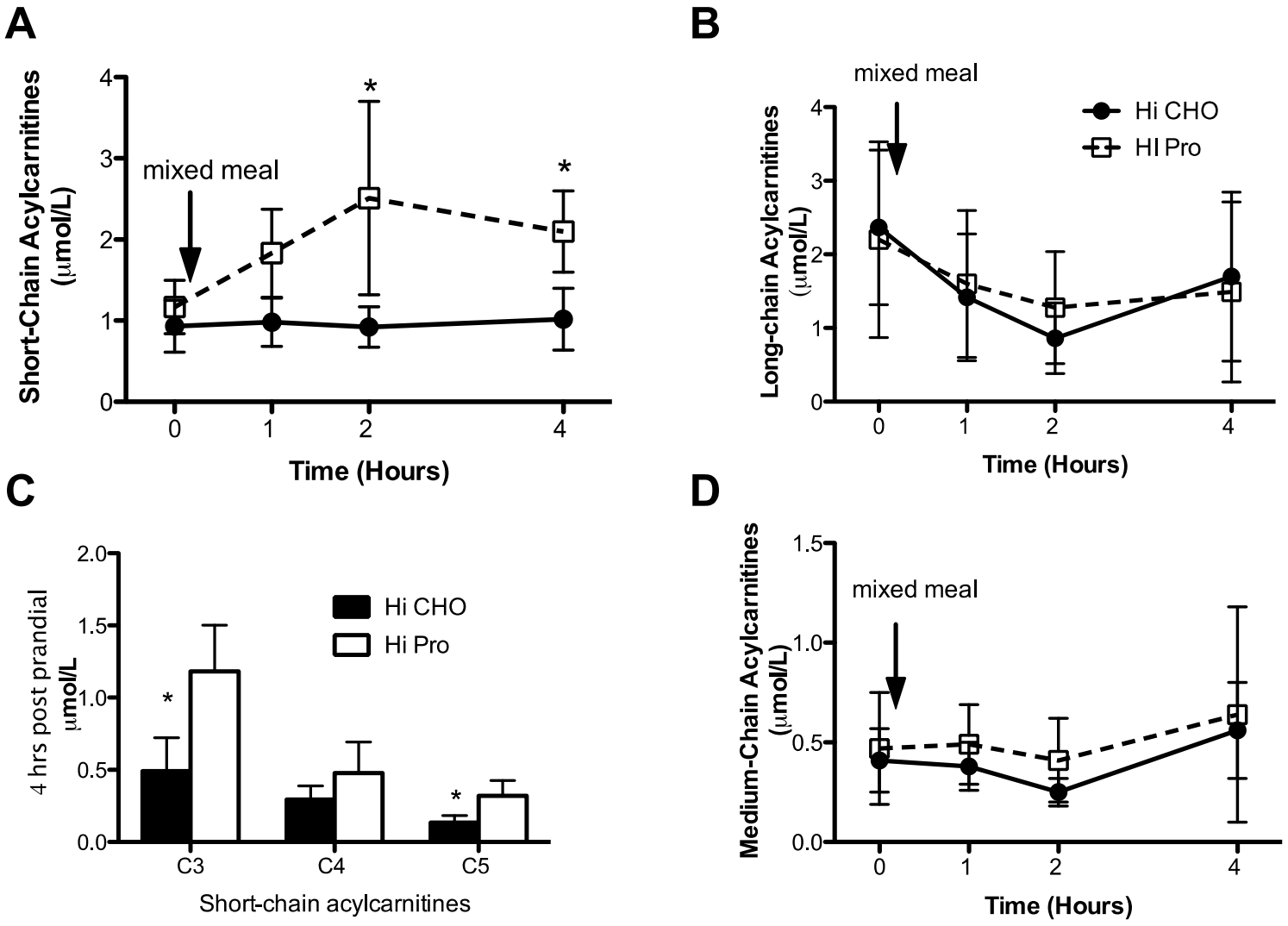
Acylcarnitines



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Increased Protein Intake

- **Maintain lean body mass**
  - Larger reserves against muscle loss with rhabdomyolysis?
- Lower liver lipid content
- Maintain metabolic control
- No hypoglycemia with decreased carbohydrate intake

Note: Included children >7 yr of age and older. May not be appropriate for infants and toddlers

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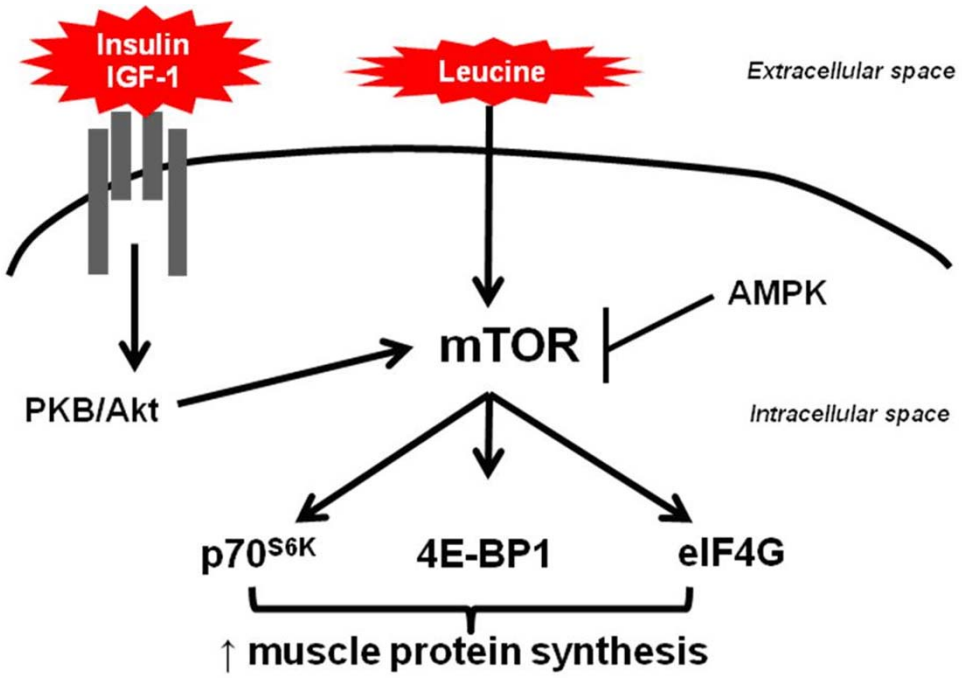
Benefits of Whey Protein?

- High in branched-chain amino acids
- Leucine stimulator of muscle protein synthesis via mTOR signaling
- 20% of protein in cow's milk is whey



http://www.efdeportes.com/efd131/leucine-stimulates-mtor-and-muscle-protein-synthesis.htm

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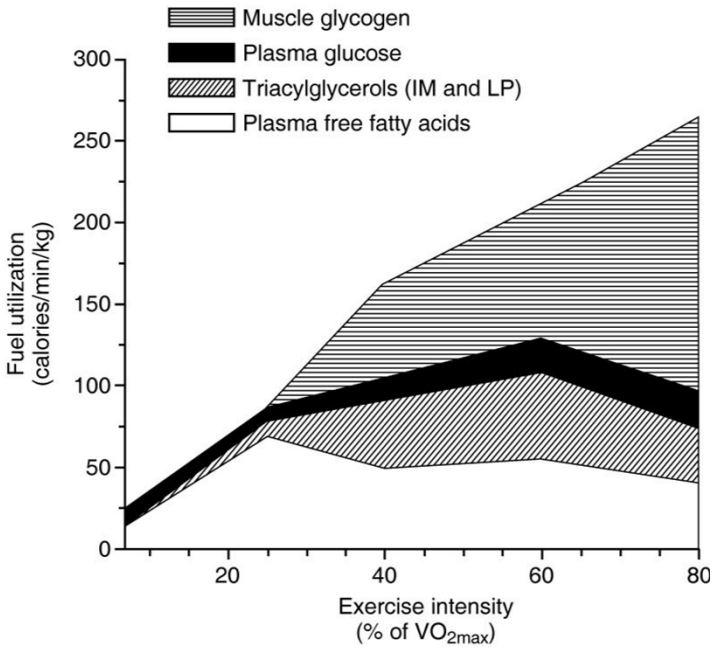
Optimizing exercise

Pre-exercise

- Simple carbohydrates
- MCT



(Data from Romijn JA, Coyle EF, Sidossis LS, Gastaldelli A, Horowitz JF, Endert E, Wolfe RR [1993] Regulation of endogenous fat and carbohydrate metabolism in relation to exercise intensity and duration. Am J Physiol 265:E380–E391; and van Loon LJC, Greenhaff PL, Constantin-Teodosiu D, Saris WHM, Wagenmakers AJM [2001] The effects of increasing exercise intensity on muscle fuel utilization in humans. J Physiol 536:295.)

Post-exercise

- Carbohydrates
- Protein

Patients with FAO disorders depend on muscle glycogen & plasma glucose during exercise.

- MCT spares glycogen during exercise.
- CHO:pro mix stimulates glycogen resynthesis post-exercise

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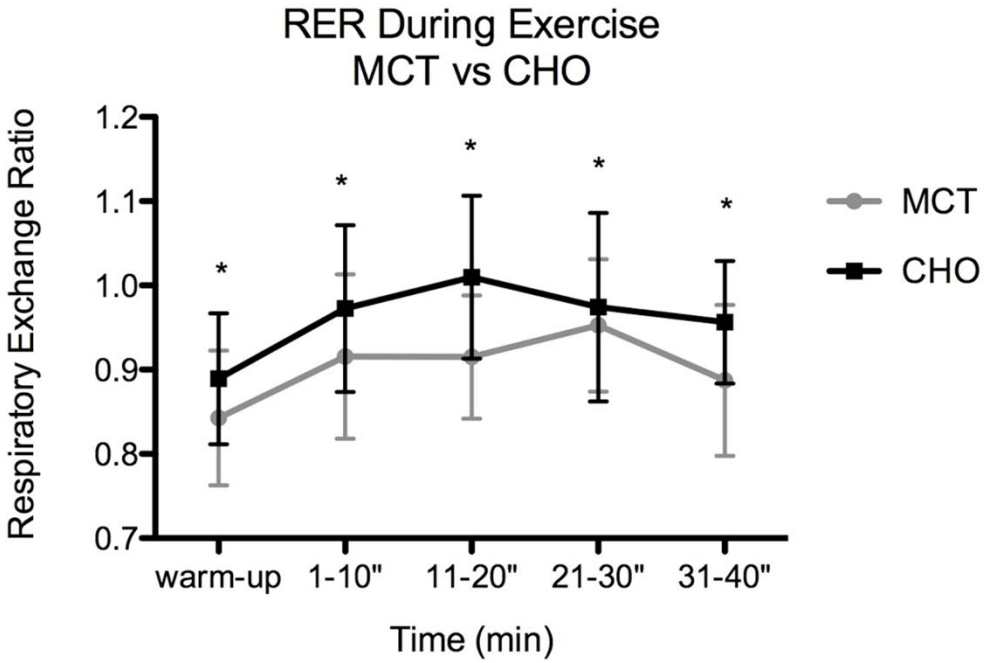
Moderate Intensity Exercise

- Randomized cross-over
  - 1 gm CHO per kg lean mass
  - 0.5 gm MCT per kg lean mass
- Warm-up at 1.5 mile/hr X 3 min
- Speed and grade @ 60% max HR X 40 min
  - 220-age (yrs) = estimated max HR
- Repeat same speed and grade

MCT lowers RQ



- MCT ↓ RQ during warm-up
- Lower RQ throughout exercise
- Oxidized more fat during that bout of exercise

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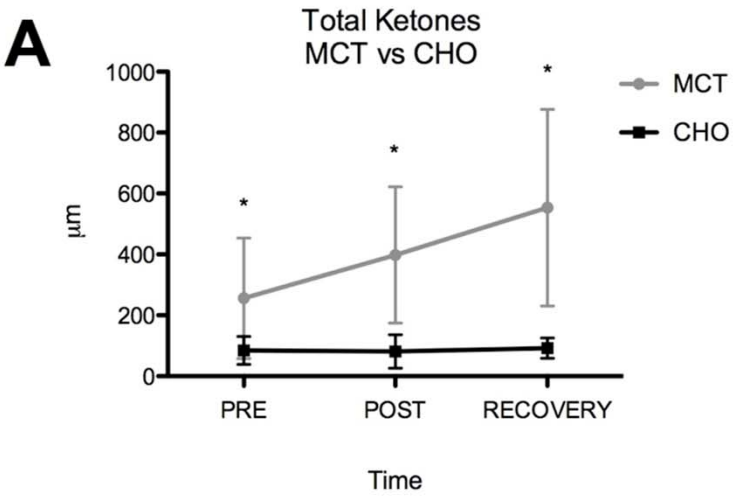
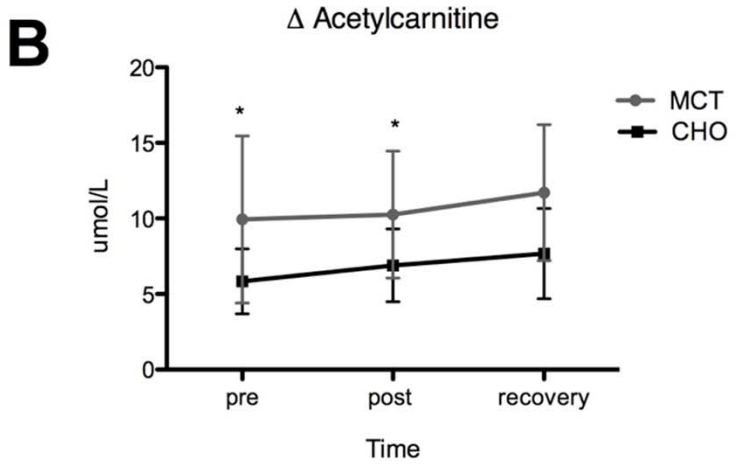
MCT increases Ketones





- Ketones increased
  - prior to exercise
  - further with exercise

- Acetylcarnitine increased
  - prior to exercise
  - enhanced acetyl-CoA synthesis

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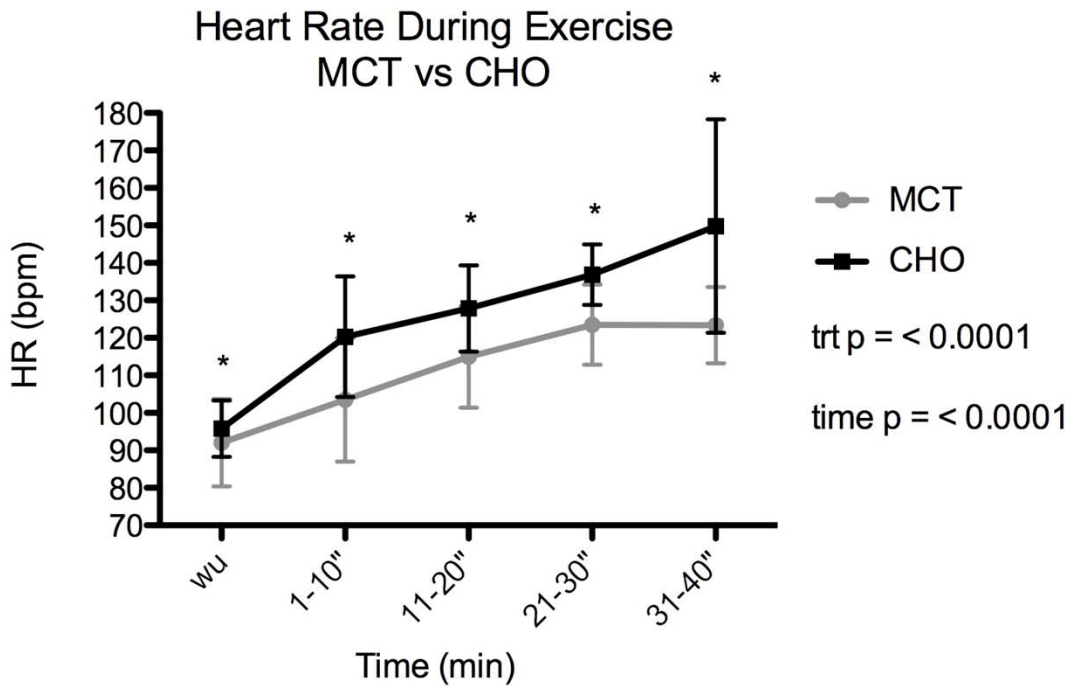
Lower Heart Rate



- Lower heart rate during exercise for same work

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MCT prior to exercise

- Exercised ≈ 40 subjects with long-chain FAOD @ 60% estimated max heart rate
  - No episodes of rhabdomyolysis
  - No ↑ CPK; even when elevated at baseline
- MCT improves biochemical & physiological parameters
- Lowers incidence of rhabdomyolysis?

- Routine exercise prescription might be best rhabdomyolysis prevention.

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Optimizing exercise

Pre-exercise

- 6-8% glucose solution such as Gatorade, apple juice
- Mix with 0.1-0.2 gm MCT per kg body weight
- Consume 20-45 min before exercise

Examples:

- 70 kg man consume
  - 7-14 gm MCT oil mixed with 8 oz Gatorade
  - 1-2 TBSP Liquigen with 8oz apple juice

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Optimizing exercise

Post-exercise

- 3:1 ratio of carbohydrate to protein snack
- Consume in first 45 min post exercise to maximize glycogen resynthesis
- 100-200 kcal for adults

Examples:

- Chocolate milk
- Apple or pretzels with 1oz. low-fat cheese
- Berries & fat-free Greek yogurt
- Fruit smoothie
- ½ slice whole wheat toast & egg white

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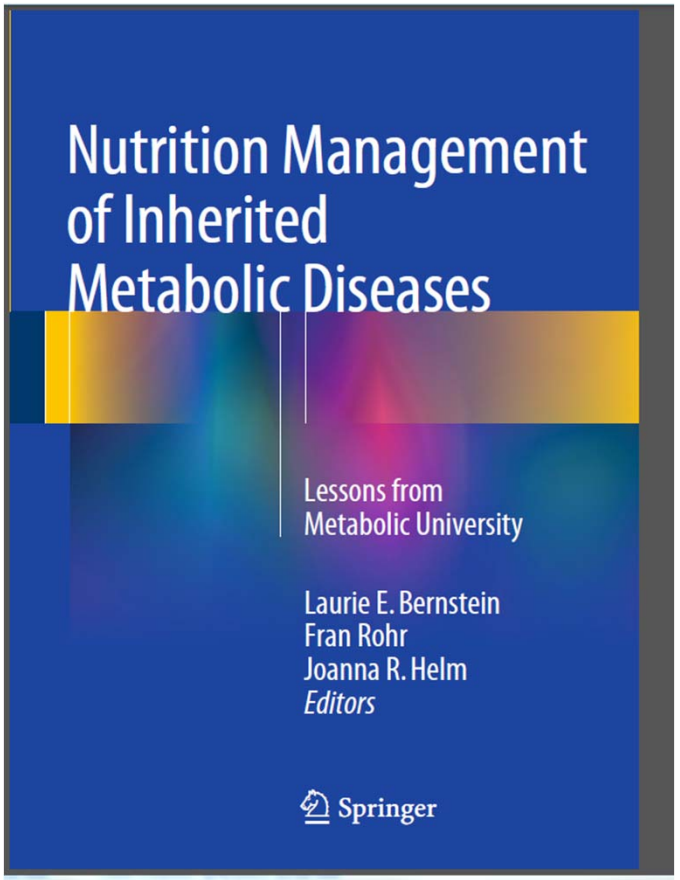
An Excellent Reference



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