Long-chain fatty acid oxidation disorders: Pathophysiology, diagnosis and management

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How are LC-FAOD currently managed and how may this change in the future?

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LC-FAOD, long-chain fatty acid oxidation disorders.

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Nutritional management for FAOD[1–3]

Restrict LCTs and provide alternative energy sources

- Provide adequate nutrition for growth and development
- Supplement with MCT to replace LCT (extent dependent on severity of FAOD)
- Protein supplementation

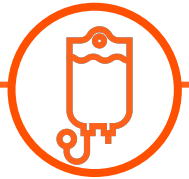
Avoid fasting

- 4 hours maximum fast until age 4 months, with 1 additional hour/month up to 8 hours maximum until age 1 year
- Up to 10-hour overnight fast after infancy

FAOD, fatty acid oxidation disorders; LCT, long-chain triglycerides; MCT, medium-chain triglycerides; OCTN 2, organic cation transporter 2.

1. Merritt JL II, et al. *Ann Transl Med.* 2018;6:473. 2. Knottnerus SJG, et al. *Rev Endocr Metab Disord.* 2018;19:93–106. 3. Spiekerkoetter U, et al. *J Inherit Metab Dis*. 2009;32:498–505.

Nutritional management for FAOD[1–3]



Increased caloric need during illness

- Carbohydrate-rich enteral fluids
- IV dextrose if necessary

Carnitine supplementation

- Low-dose supplementation may ameliorate myopathic symptoms
- Controversial due to theoretical risk of cardiac arrhythmias

FAOD, fatty acid oxidation disorders; IV, intravenous.

1. Merritt JL II, et al. *Ann Transl Med.* 2018;6:473. 2. Knottnerus SJG, et al. *Rev Endocr Metab Disord.* 2018;19:93–106. 3. El-Gharbawy A and Vockley J. *Pediatr Clin North Am*. 2018;65:317–35.

Unmet needs and patient risks despite nutritional therapy[1,2]

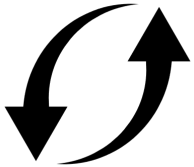
Older patients

Muscle symptoms, myopathy and rhabdomyolysis

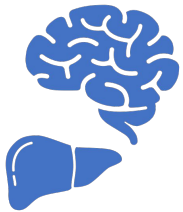
Recurrent rhabdomyolysis leads to accumulation of blood CPK and myoglobin, causing kidney damage/failure

Younger patients

Low blood sugar



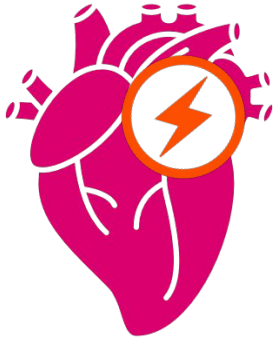
Increased blood ammonia



Loss of consciousness and coma

Liver damage (usually reversible)

Patients at any age



Acute or chronic cardiomyopathy

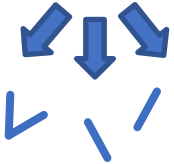
CPK, creatinine phosphokinase.

1. Knottnerus SJG, et al. *Rev Endocr Metab Disord.* 2018;19:93–106. 2. Moniz MS, et al. *Rev Bras Ter Intensiva*. 2017;29:111–4.

Future approaches: Triheptanoin

Highly purified, synthetic medium odd-chain (C7) triglyceride, which is catabolized to heptanoate and crosses the mitochondrial membrane without carnitine, bypassing faulty LC metabolic mechanisms[1]

Metabolized by medium-chain fatty acid oxidation enzymes



Metabolic products contribute to energy metabolism and glycogen sparing

78-week single-arm Phase II study in 29 patients with severe LC-FAOD (mean age 12 years)[1,2]

- Triheptanoin titrated to 25–35% of calorie intake

Significant reduction in rate of major clinical events and hospitalizations at 78 weeks compared with 78 weeks before study

- Majority of subjects on MCT in the pre-study period

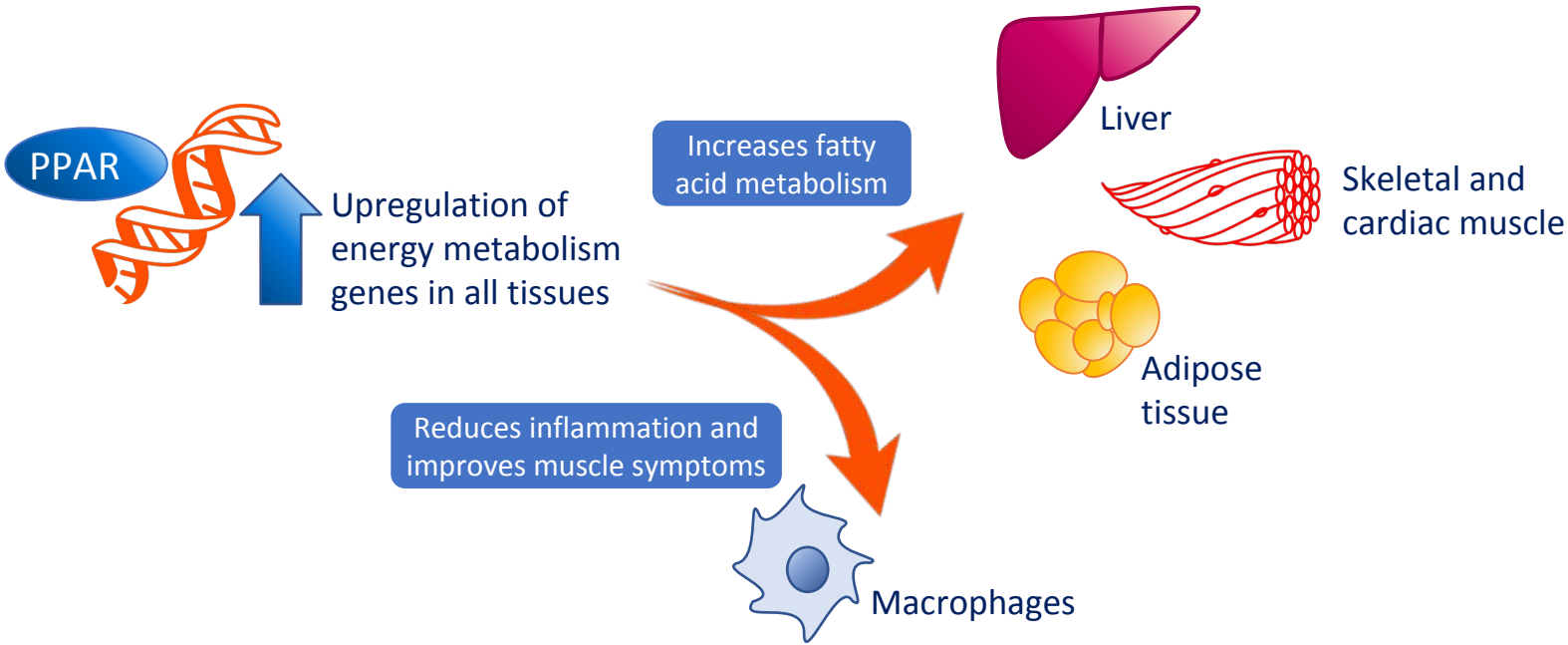
Improved exercise endurance and tolerance at interim analysis and week 60

Significant improvements in physical health composite scores of SF-12v2 after 24 weeks, maintained to 78 weeks

LC, long-chain; LC-FAOD, long-chain fatty acid oxidation disorders; MCT, medium-chain triglycerides; SF-12v2, Medical Outcomes Study Short Form version 2.

1. Vockley J, et al. *Molec Genet Metab.* 2017:120:370–7. 2. Vockley J, et al. *J Inherit Metab Dis*. 2019;42:169–77.

Future approaches: PPARδ agonists[1]



Phase 1 safety study with REN001 is underway in patients with fatty acid oxidation disorders[2]

PPAR, peroxisome proliferator–activated receptor.

1. Reilly SM, Lee C-H. *FEBS Lett.* 2008;582:26–31. 2. Clinicaltrials.gov. February 2019. [Cited 27 February 2020]. Available from: https://clinicaltrials.gov/ct2/show/NCT03833128.