All About Ketones

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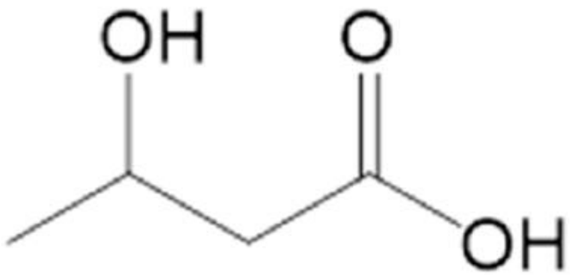
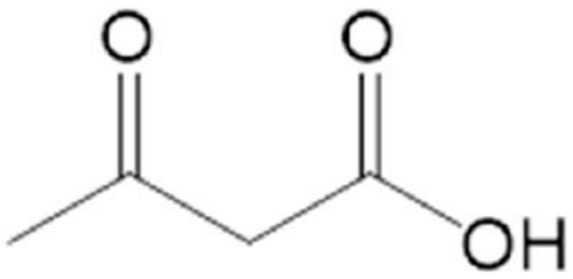
Oregon Health & Science University

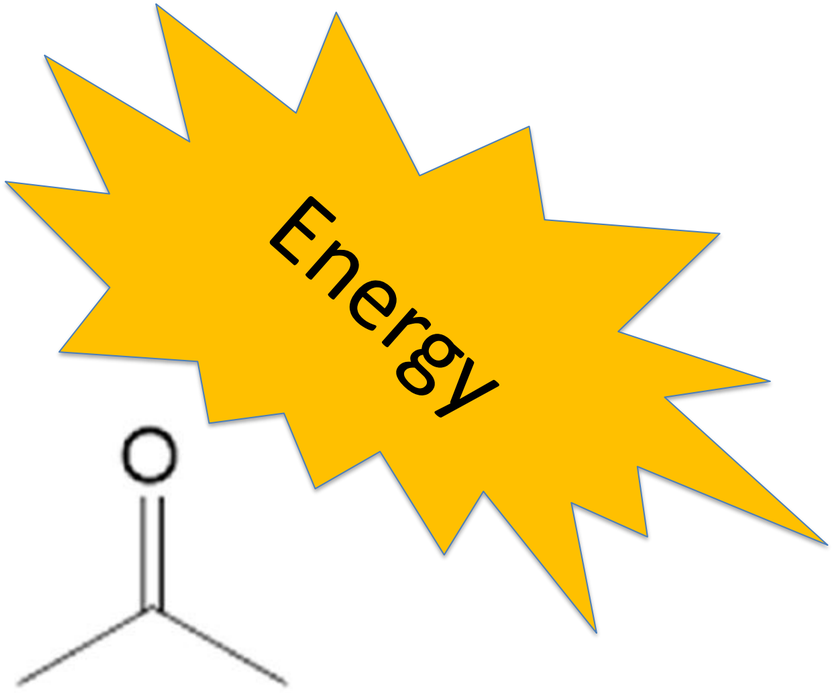
What are Ketones?



Beta-hydroxybutyrate



Acetoacetate



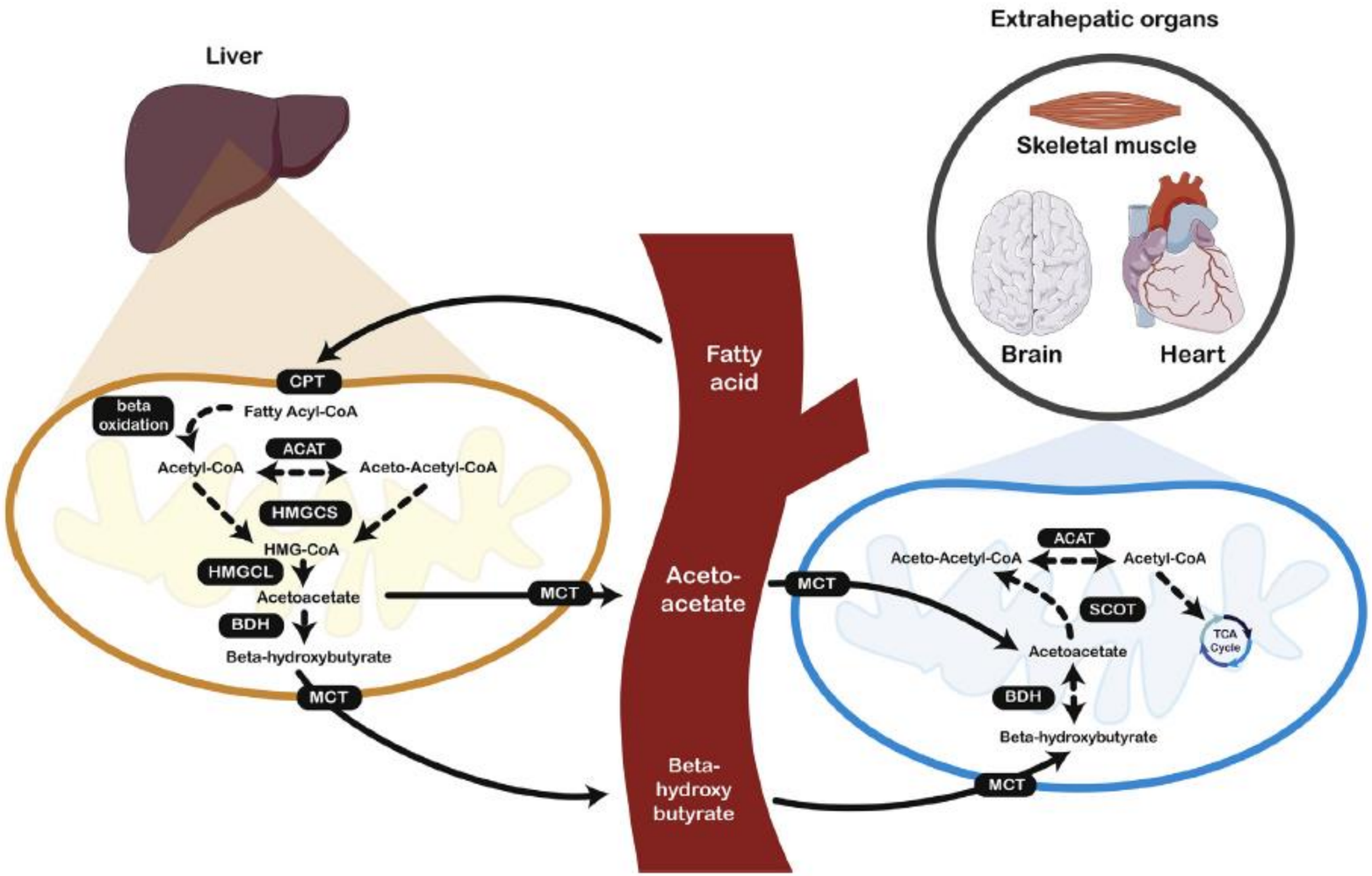
Acetone

Figure 1. The chemical structures of the three ketone bodies.

Liu, H. et al. The role of ketone bodies Endocrines 2023; 4:236-249

How are ketones made?

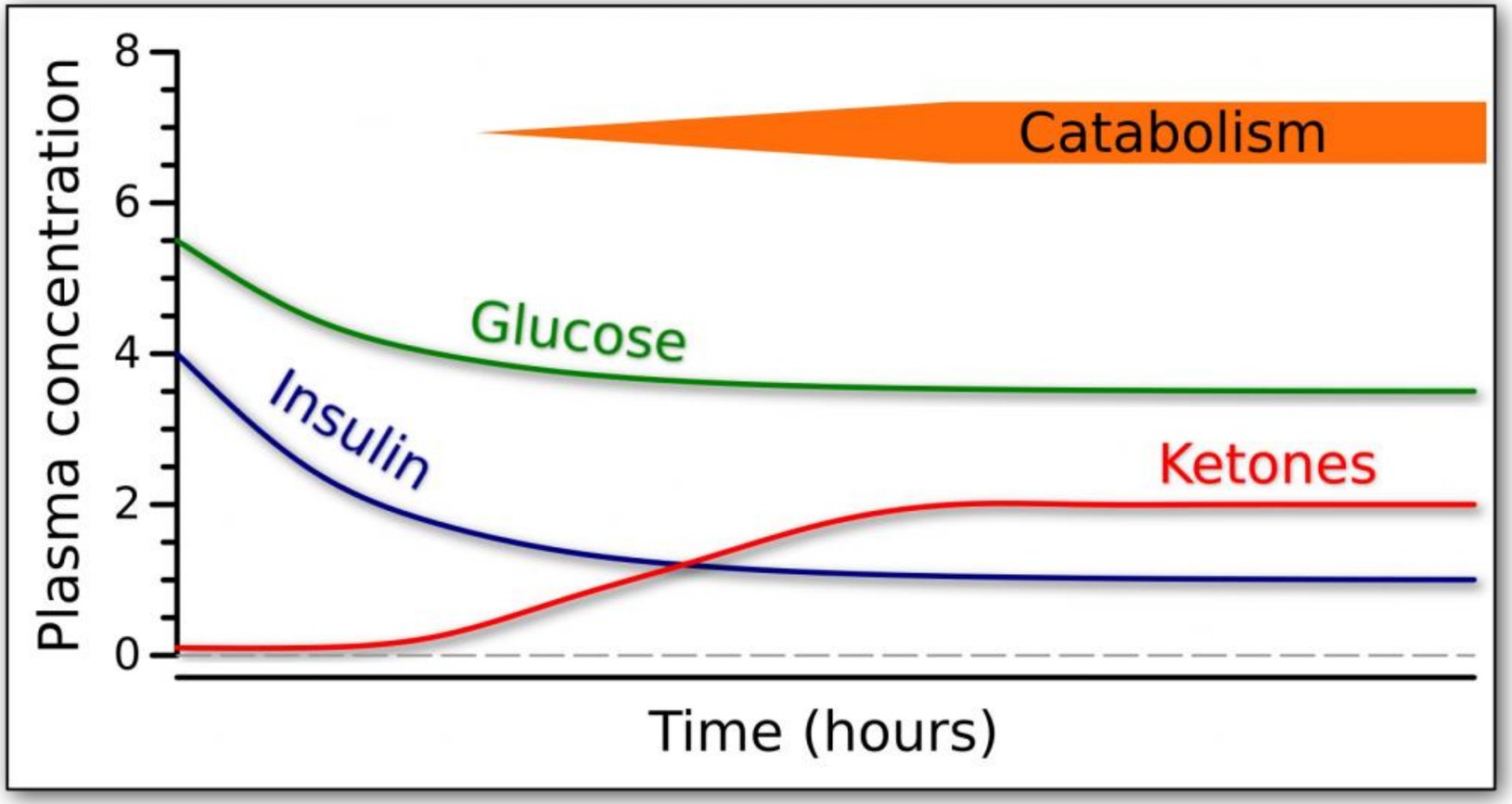
FAO



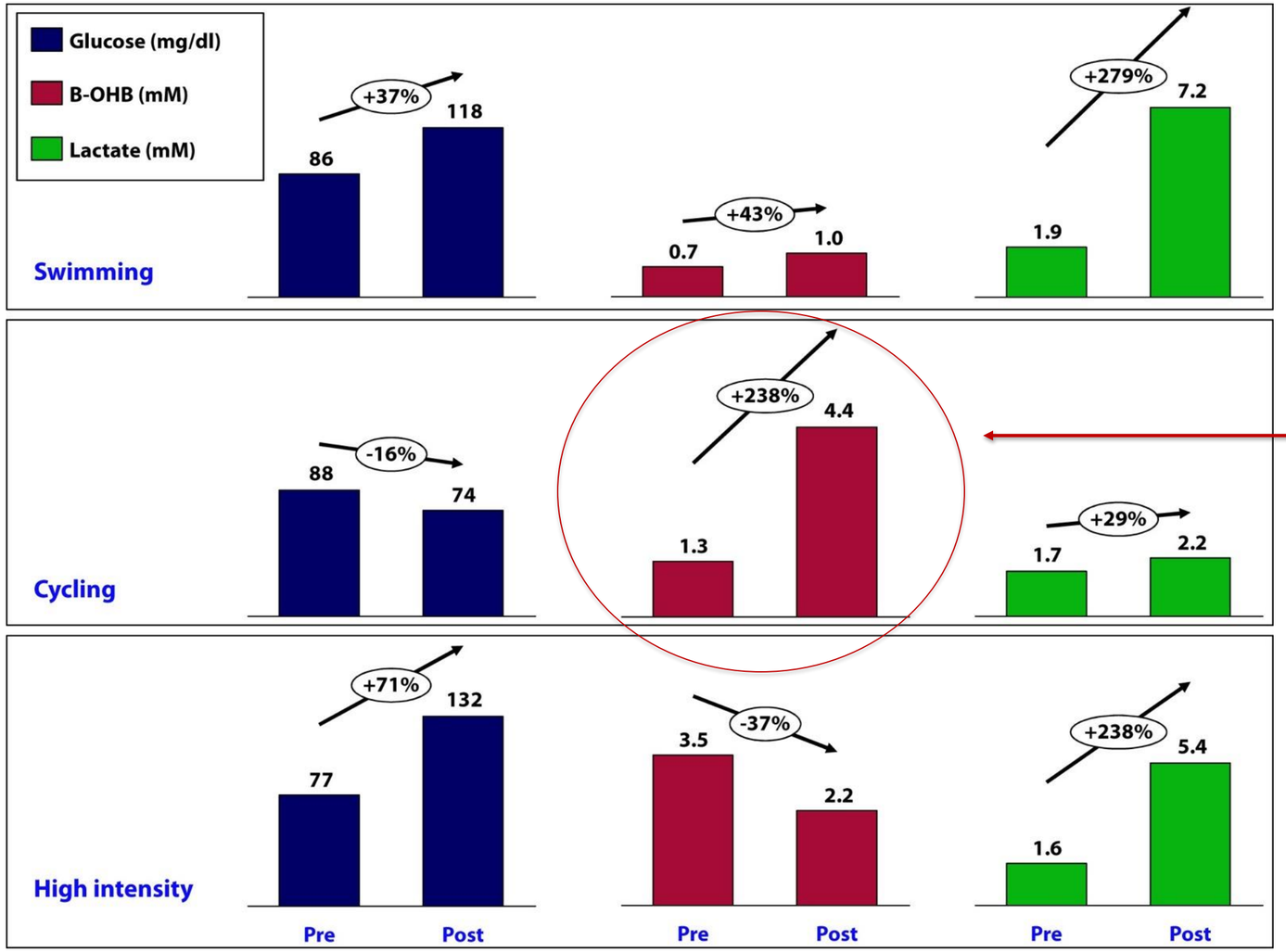
Yurista SR et al Therapeutic Potential of Ketone bodies J Am Coll Cardiol 2021; 77:1160-9

When are ketones made?

FASTING

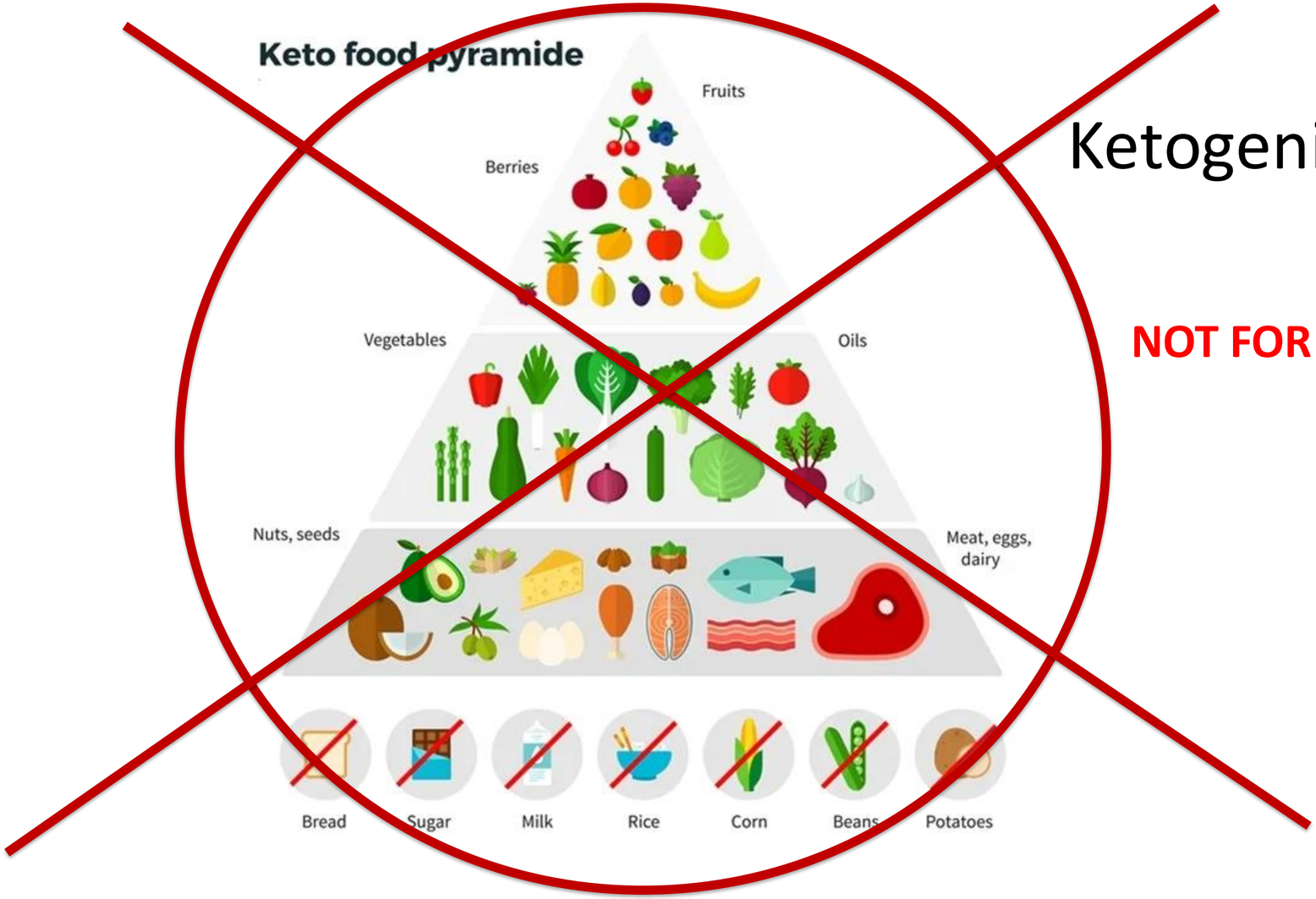


When are ketones made?



Moderate intensity exercise

When are ketones made?



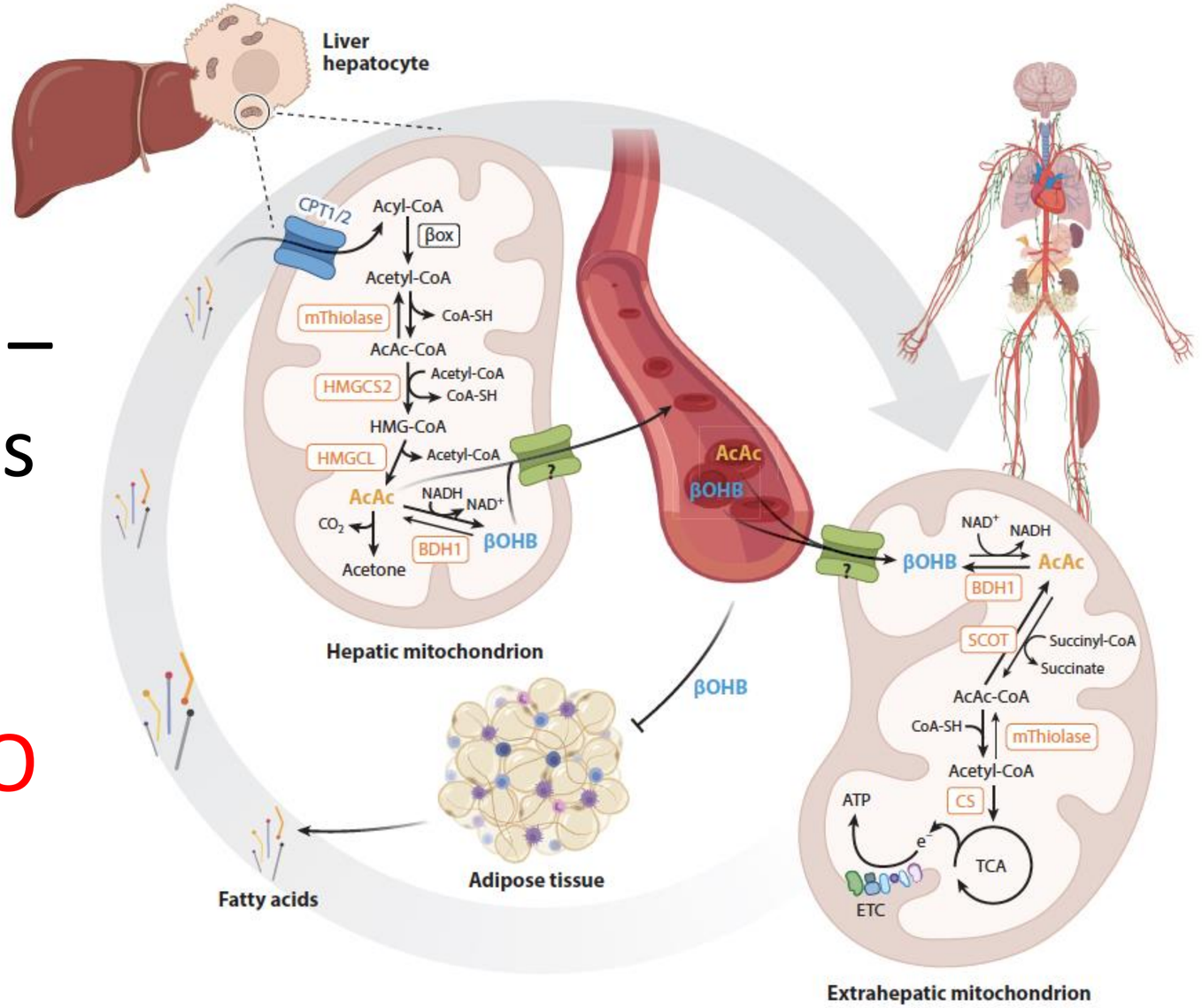
Ketogenic Diet

NOT FOR People with a FAOD

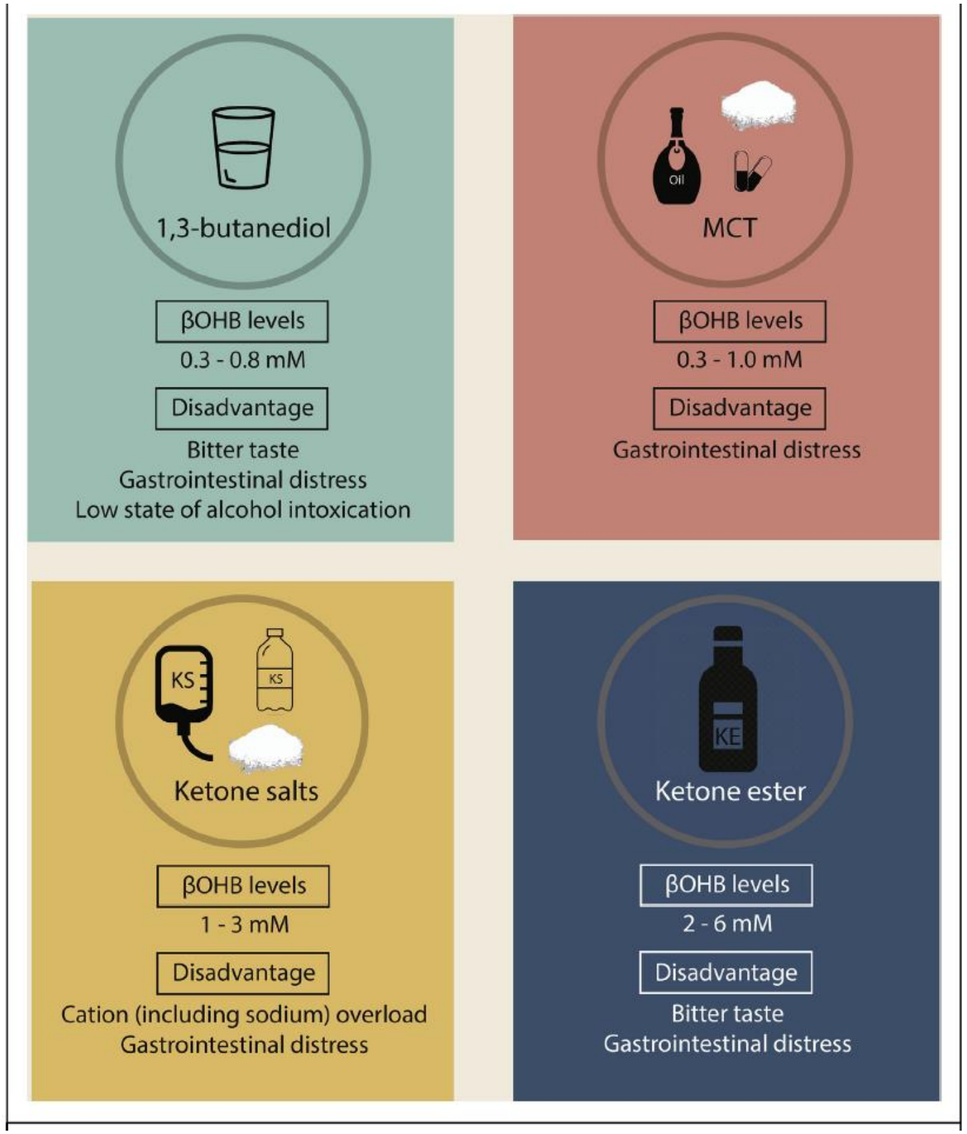
People with FAODs are hypoketotic

No liver FAOD –
No ketogenesis

Ketones- end product of FAO



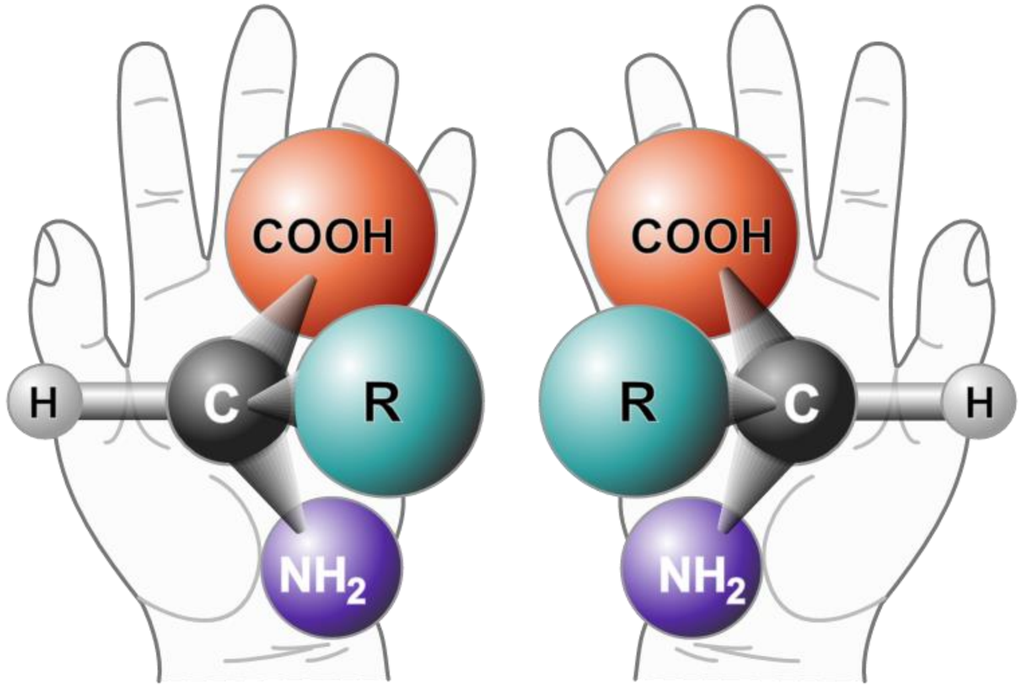
Supplemental Ketones



Yurista SR et al Therapeutic Potential of Ketone bodies J Am Coll Cardiol 2021; 77:1160-9

D, L forms of ketones

- Enantiomers or optical isomers are the exact same molecule but with different 3D structure around a chiral or central carbon atom
- B-hydroxybutyrate has 2 enantiomers
  - D b-hydroxybutyrate
  - L b-hydroxybutyrate



D, L forms of ketones

- Endogenously produced ketones from the liver are only D beta hydroxybutyrate
- Commercial salt products are a mix of 50% D and 50% L beta hydroxybutyrate
- We call this a Racemic mix or both enantiomers in the mixture
- Ketone esters like delta G are D beta hydroxybutyrate on a glycerol backbone
- The salt ketone product by Nestle Health Science is D beta hydroxybutyrate

Is there a difference in D,L BHB metabolism?

Enantiomer-specific pharmacokinetics of D,L-3-hydroxybutyrate: Implications for the treatment of multiple acyl-CoA dehydrogenase deficiency

Willemijn J. van Rijt[1] | Johan L. K. Van Hove[2] | Frédéric M. Vaz[3,4] | Rick Havinga[5] | Derk P. Allersma[6] | Tanja R. Zijp[6] | Jirair K. Bedoyan[7] | M. R. Heiner-Fokkema[8] | Dirk-Jan Reijngoud[5] | Michael T. Geraghty[9] | Ronald J. A. Wanders[3] | Maaike H. Oosterveer[5] | Terry G. J. Derks[1]

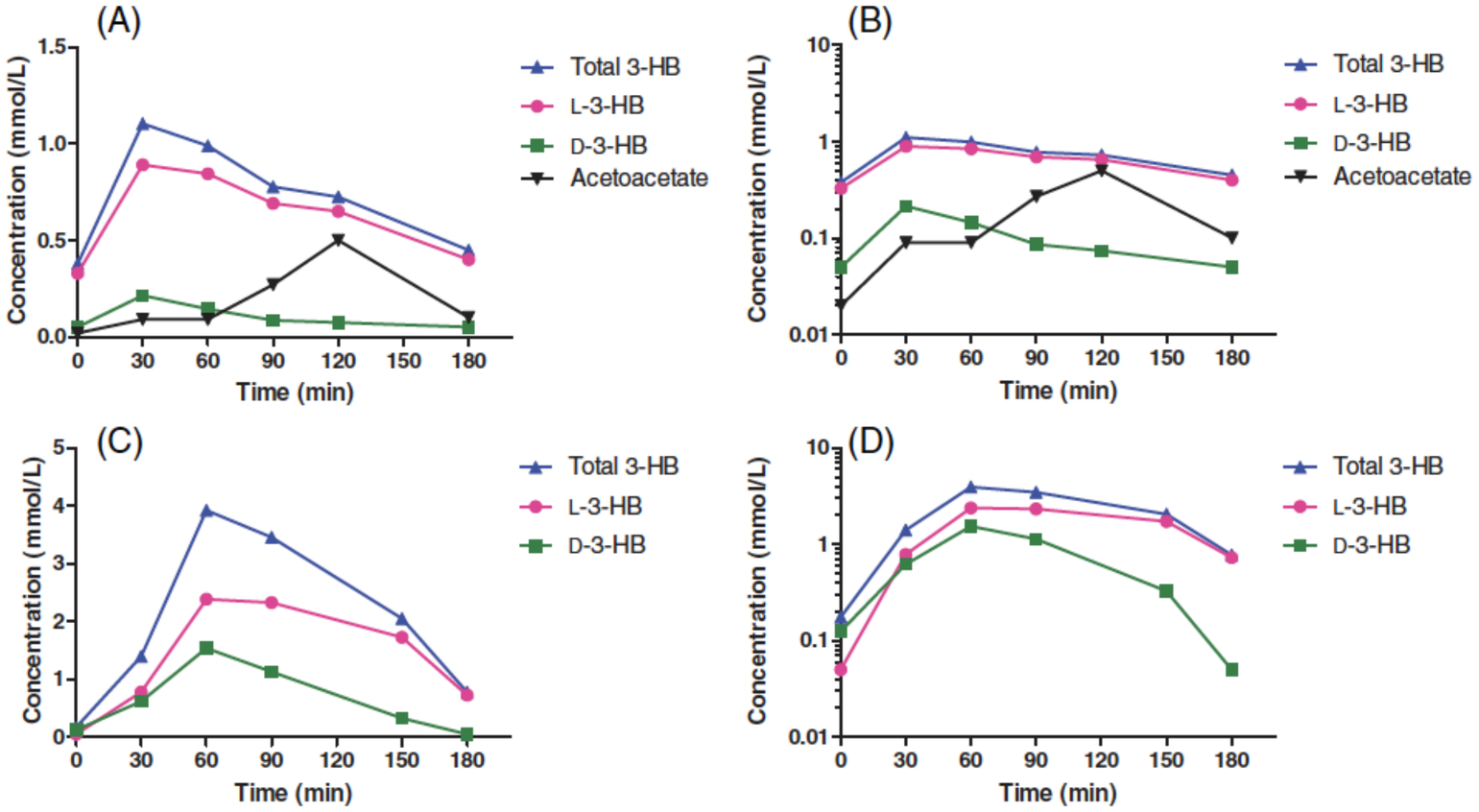
J Inherit Metab Dis. 2021;44:926–938.

Oral D, L racemic mix of BHB

- Measured D, L BHB in blood after oral dose in 2 patients with MADD
- L-BHB higher than D-BHB in blood
- Peaked within 30-60 min
- Returned toward baseline at 3 hours

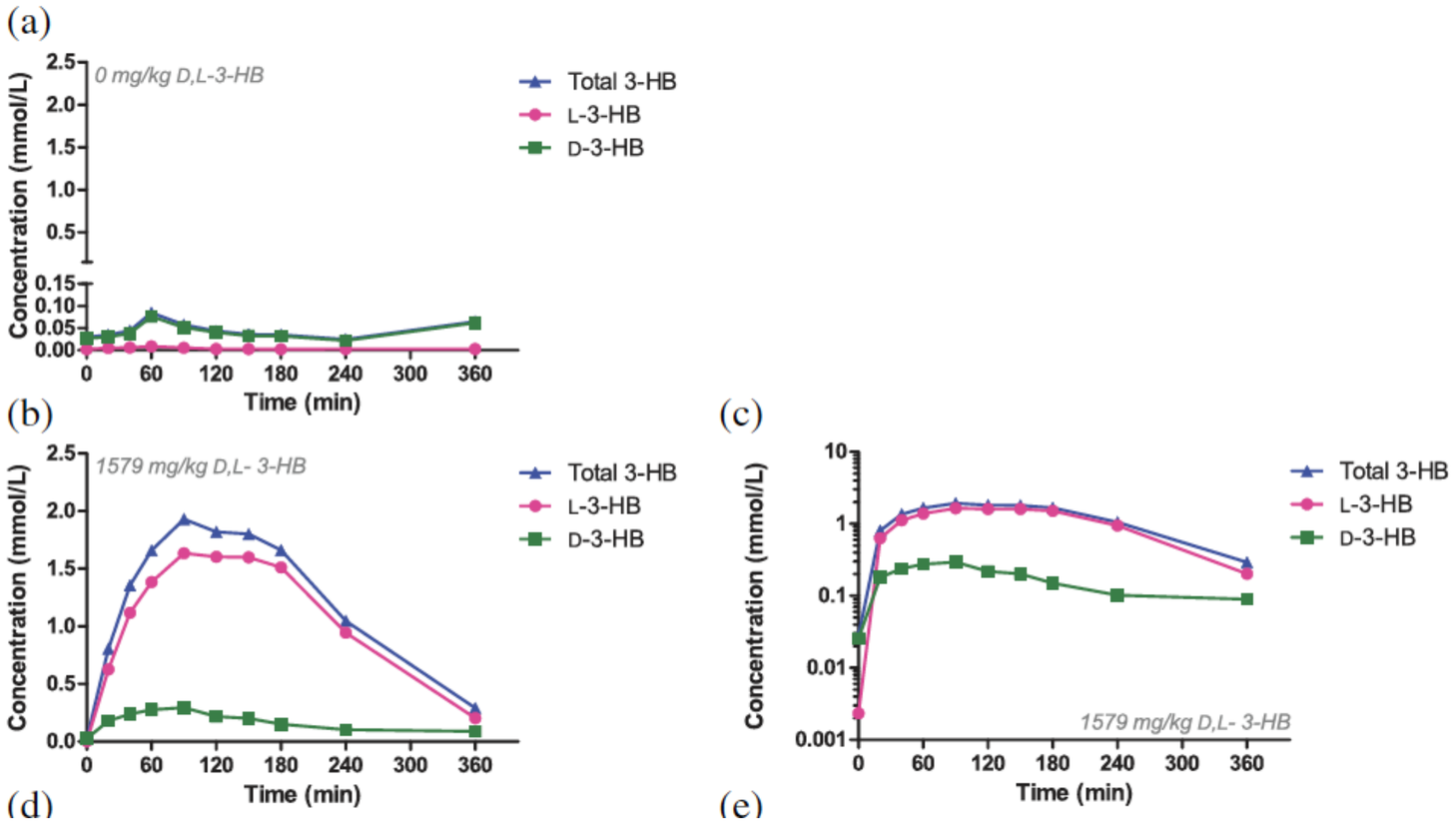
Absolute Amount

Log fold change

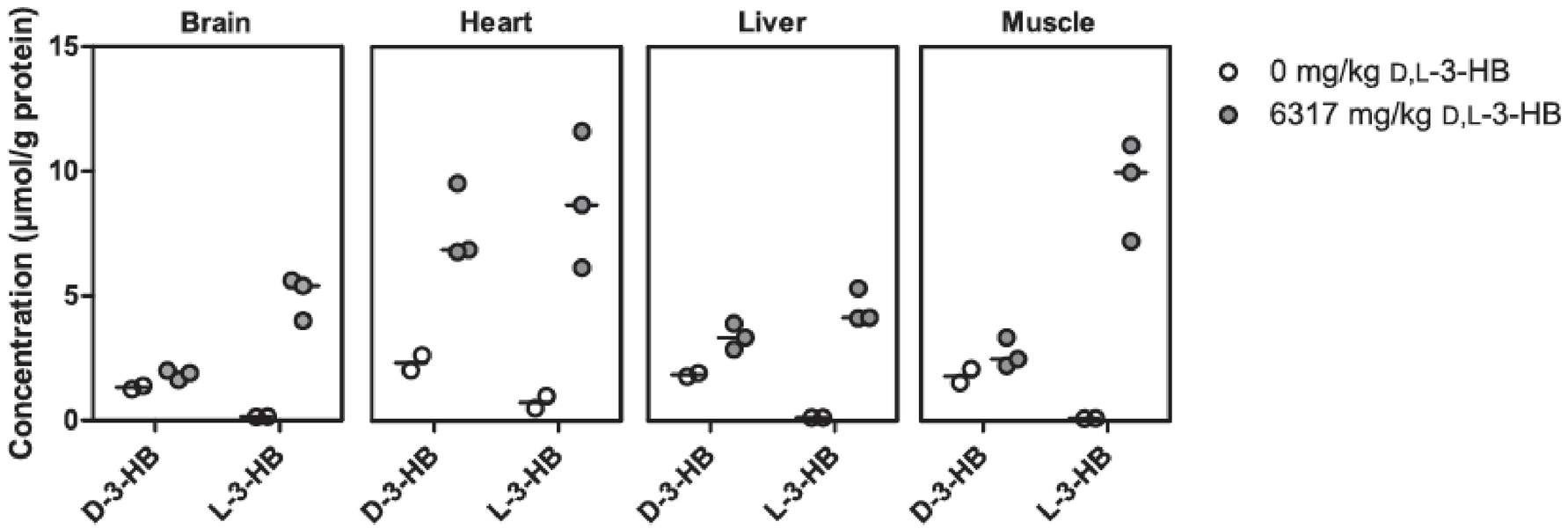


Oral D, L racemic mix of BHB

- Fed control salt load or D,L BHB to rats; measured blood concentrations
- L BHB higher than D BHB
- Peaked at 60 min
- Returning to baseline at 6 hours

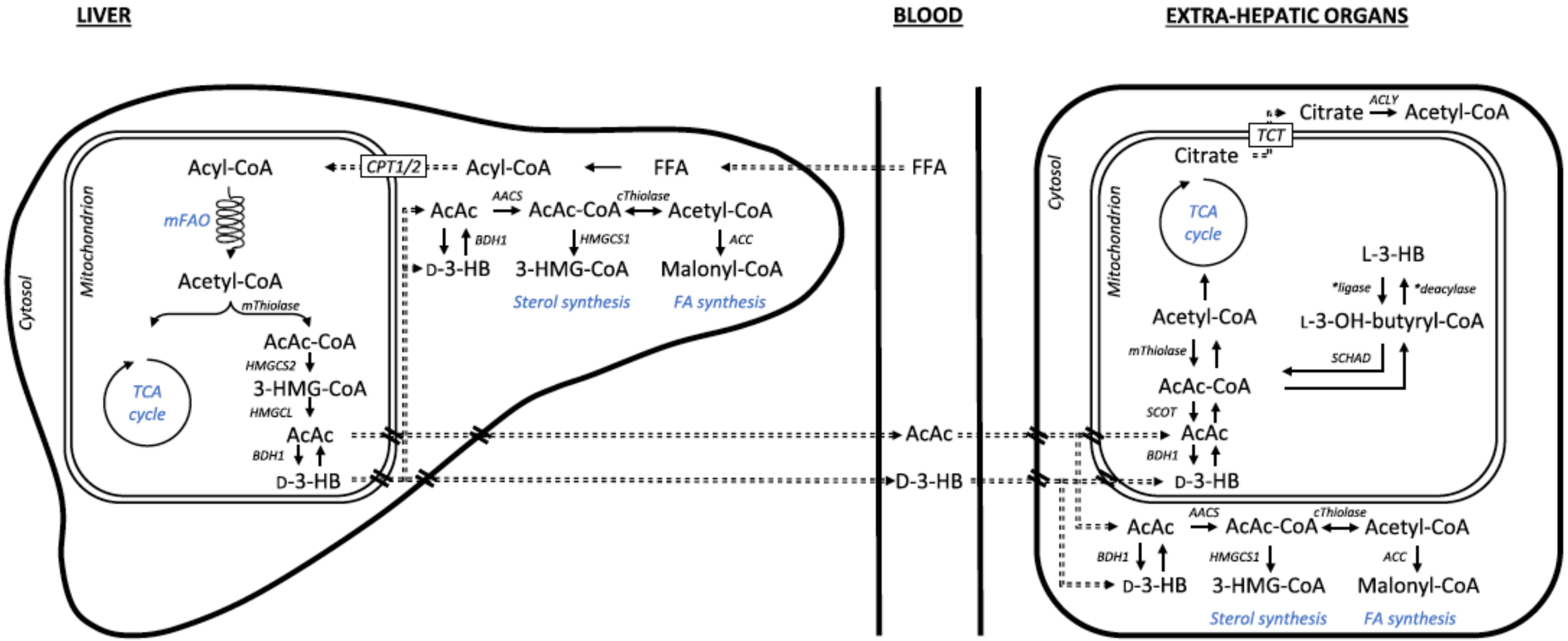


Tissue concentrations of D, L BHB



- Looked at tissue concentrations in the rats
- L BHB higher in the brain; muscle
- D BHB high in heart

What does high blood L BHB mean?



- High L BHB – slower uptake into tissue or slower metabolism?
- L BHB predominately used to make cholesterol/fatty acids in the brain?
- D BHB for energy tissues like the heart; L BHB for brain symptoms like leukodystrophy

D,L racemic mix vs D only in controls

Metabolism of Exogenous D-Beta-Hydroxybutyrate, an Energy Substrate Avidly Consumed by the Heart and Kidney

Bernard Cuenoud[1], Mickaël Hartweg[2], Jean-Philippe Godin[3], Etienne Croteau[4], Mathieu Maltais[5,6], Christian-Alexandre Castellano[6], André C. Carpentier[5,7,8] and Stephen C. Cunnane[5,6,8]*

frontiers in Nutrition

February 2020 | Volume 7 | Article 13

Compare MCT, D,L BHB salt and D BHB salt

- Healthy volunteers
- Consumed 3 different meals
  - MCT
  - D,L BHB racemic mix
  - D BHB only

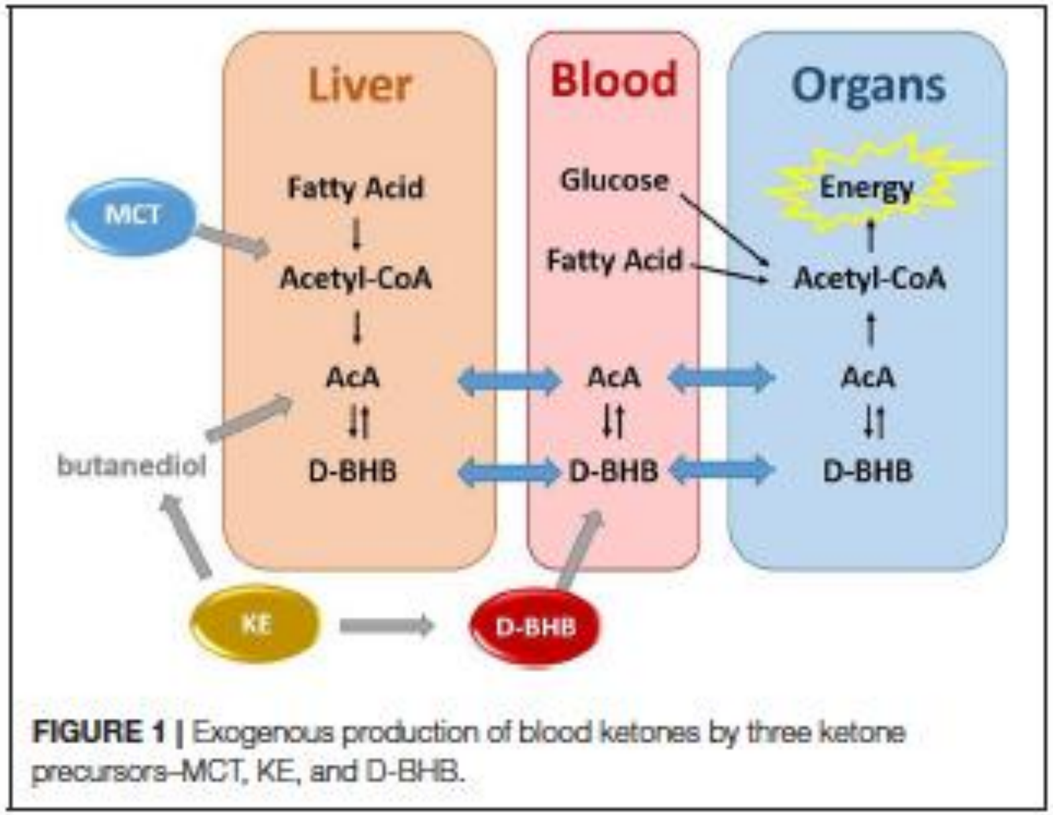


FIGURE 1 | Exogenous production of blood ketones by three ketone precursors–MCT, KE, and D-BHB.

D BHB raised plasma ketones most

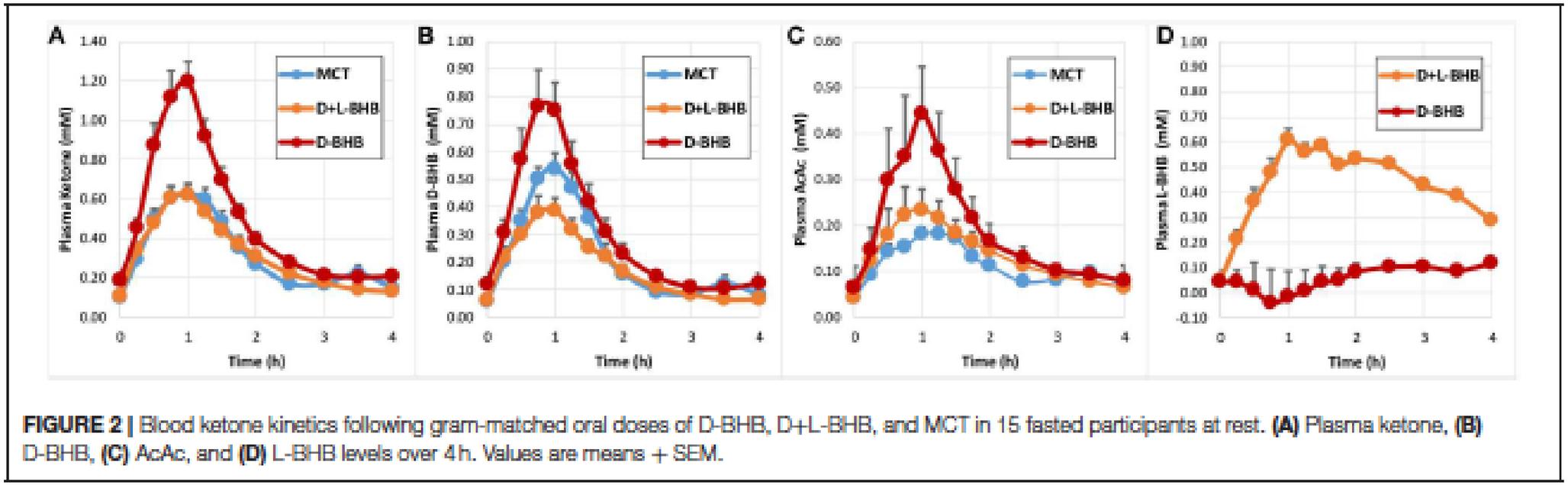


FIGURE 2 | Blood ketone kinetics following gram-matched oral doses of D-BHB, D+L-BHB, and MCT in 15 fasted participants at rest. **(A)** Plasma ketone, **(B)** D-BHB, **(C)** AcAc, and **(D)** L-BHB levels over 4 h. Values are means + SEM.

- Plasma D BHB peaked at 1 hour; highest with D BHB only
- L BHB only observed with D,L mix as expected

D BHB oxidized for energy in heart, kidney

- Participant consumed tracer D-BHB
- Used PET imaging; pink indicates presence of tracer
- Uptake visible in heart and kidney

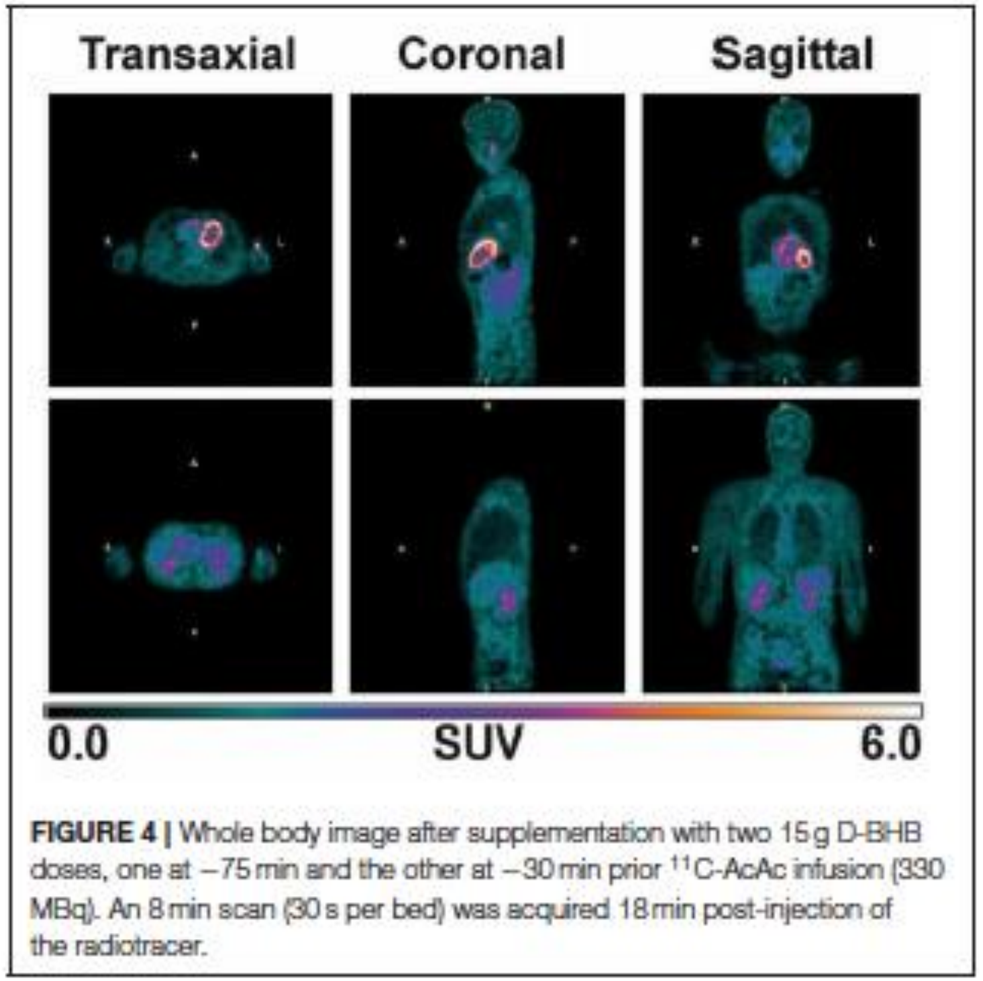


FIGURE 4 | Whole body image after supplementation with two 15 g D-BHB doses, one at −75 min and the other at −30 min prior ^{11}C-AcAc infusion (330 MBq). An 8 min scan (30 s per bed) was acquired 18 min post-injection of the radiotracer.

Genetics inMedicine | ARTICLE

Open

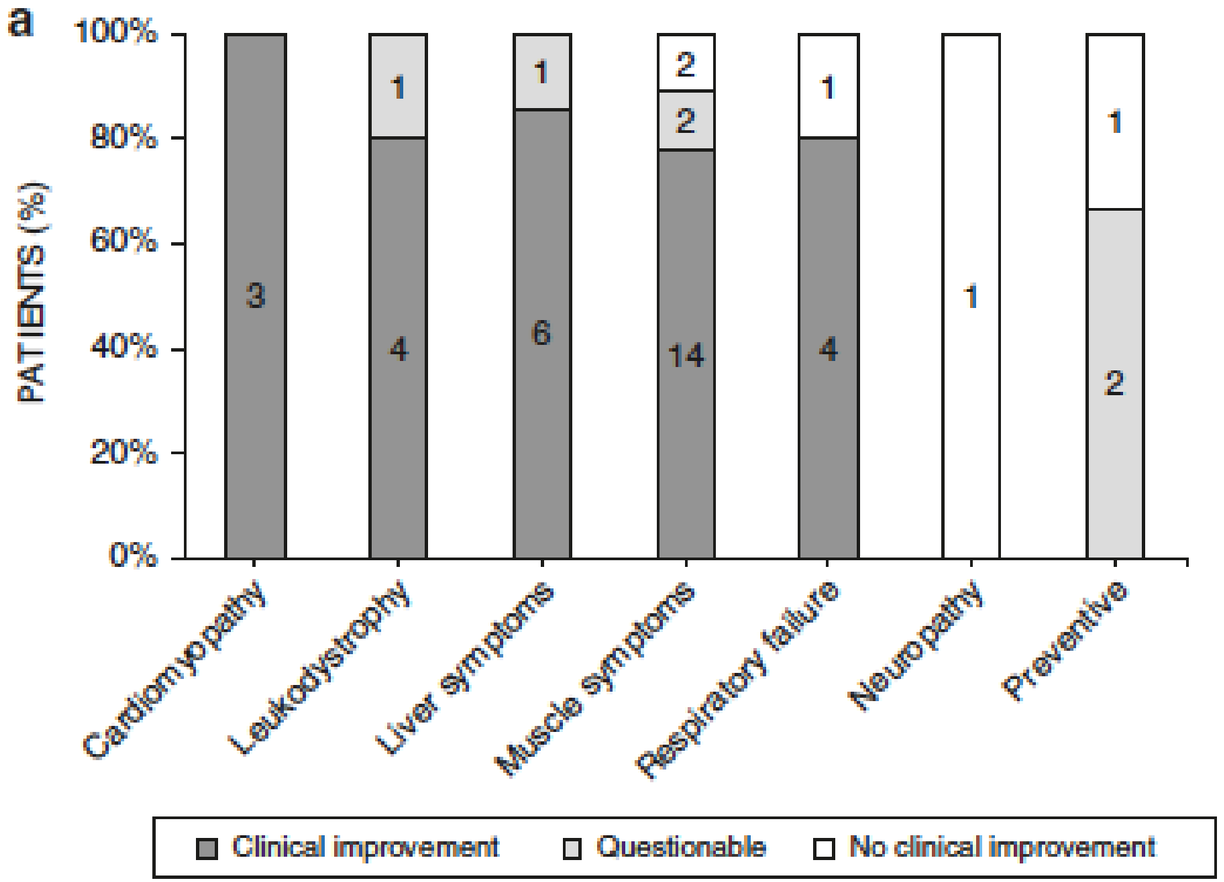
Efficacy and safety of D,L-3-hydroxybutyrate (D,L-3-HB) treatment in multiple acyl-CoA dehydrogenase deficiency

Table 2 Summarized patient and D,L-3-hydroxybutyrate treatment characteristics according to outcome.

	Clinical improvement upon D,L-3-HB treatment		
	Yes (*n* = 16; 70%)	**Questionable (*n* = 3; 13%)**	**No (*n* = 4; 17%)**
Gender	M:F = 9:7	M:F = 1:2	M:F = 0:4
Alive	12 (75%)	2 (67%)	3 (75%)
Current age	13 years (6.5 years)	3 years (1.5 years)	13.5 years (10.5 years)
Age at death	1.5 years (8 years)	8 months	10 days
Age at onset	3 months (8 months)	3 days (5 months)	3 months (5 years)
Congenital anomalies	-	-	-
Positive NBS results	8 (50%)	3 (100%)	2 (50%)

van Rijt et al Genetics in Medicine 2020

Clinical improvement



Improvement: cardiomyopathy, brain leukodystrophy, liver, muscle symptoms

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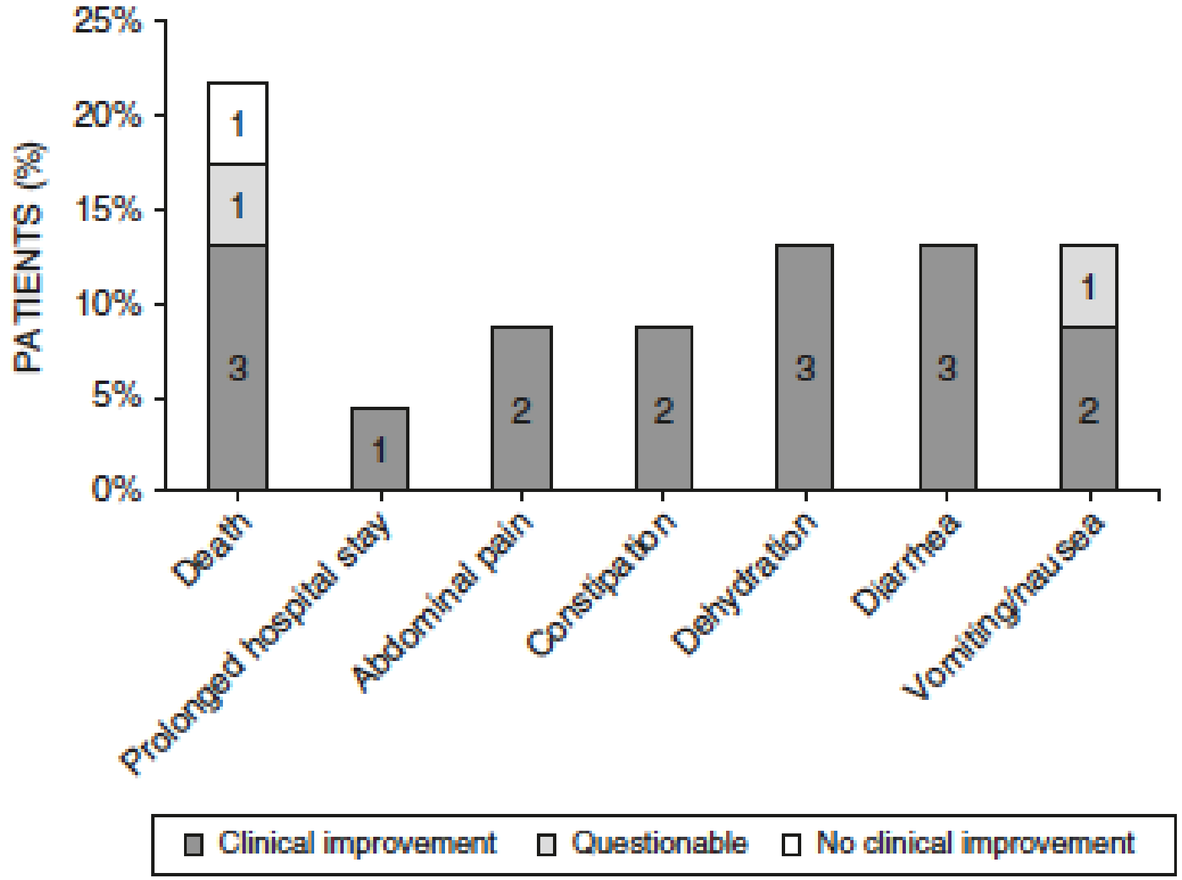
Adverse Effects



Adverse effects: mostly GI related; can include dehydration

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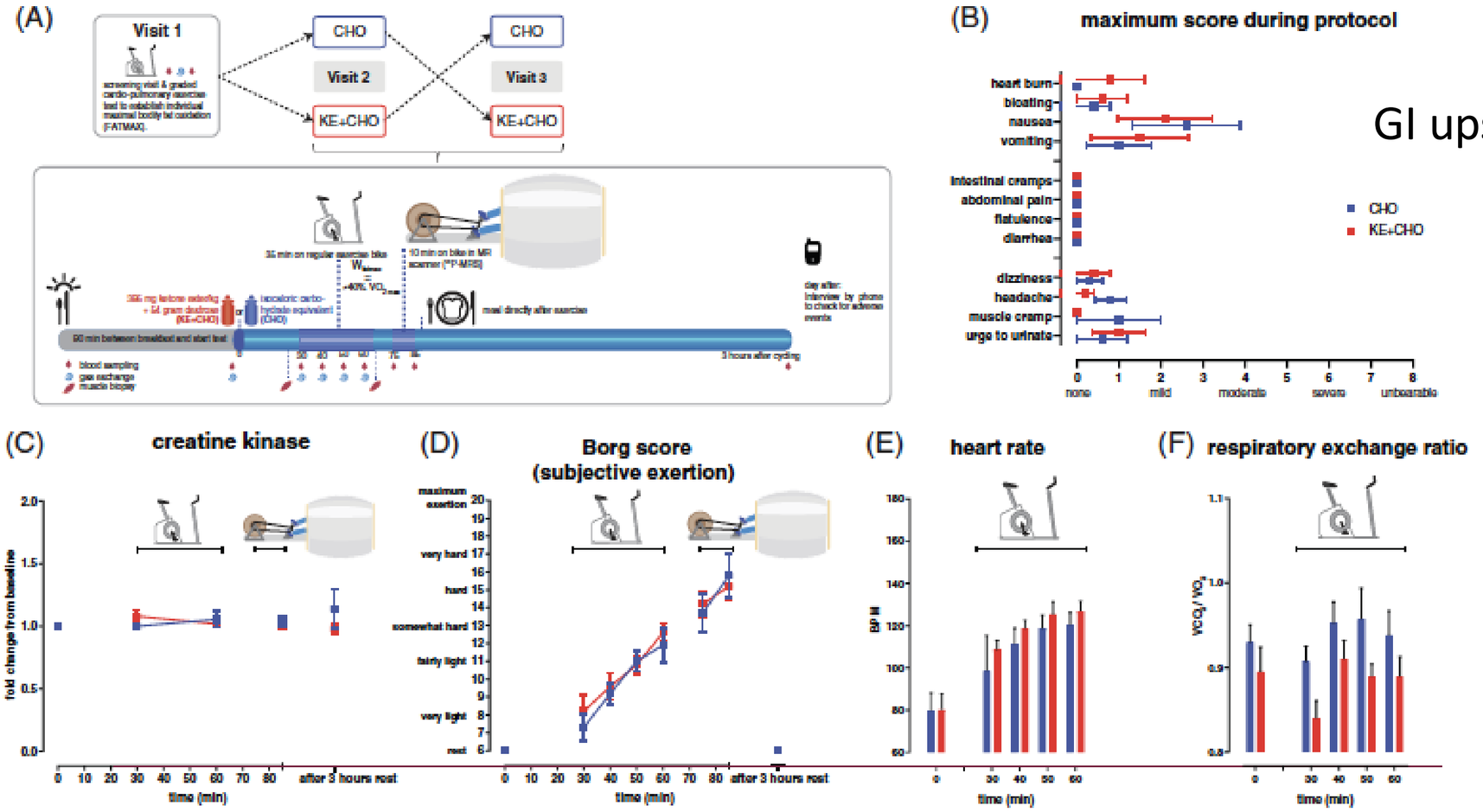
Nutritional ketosis improves exercise metabolism in patients with very long-chain acyl-CoA dehydrogenase deficiency

Ketone Ester

Similar exercise outcomes



GI upset

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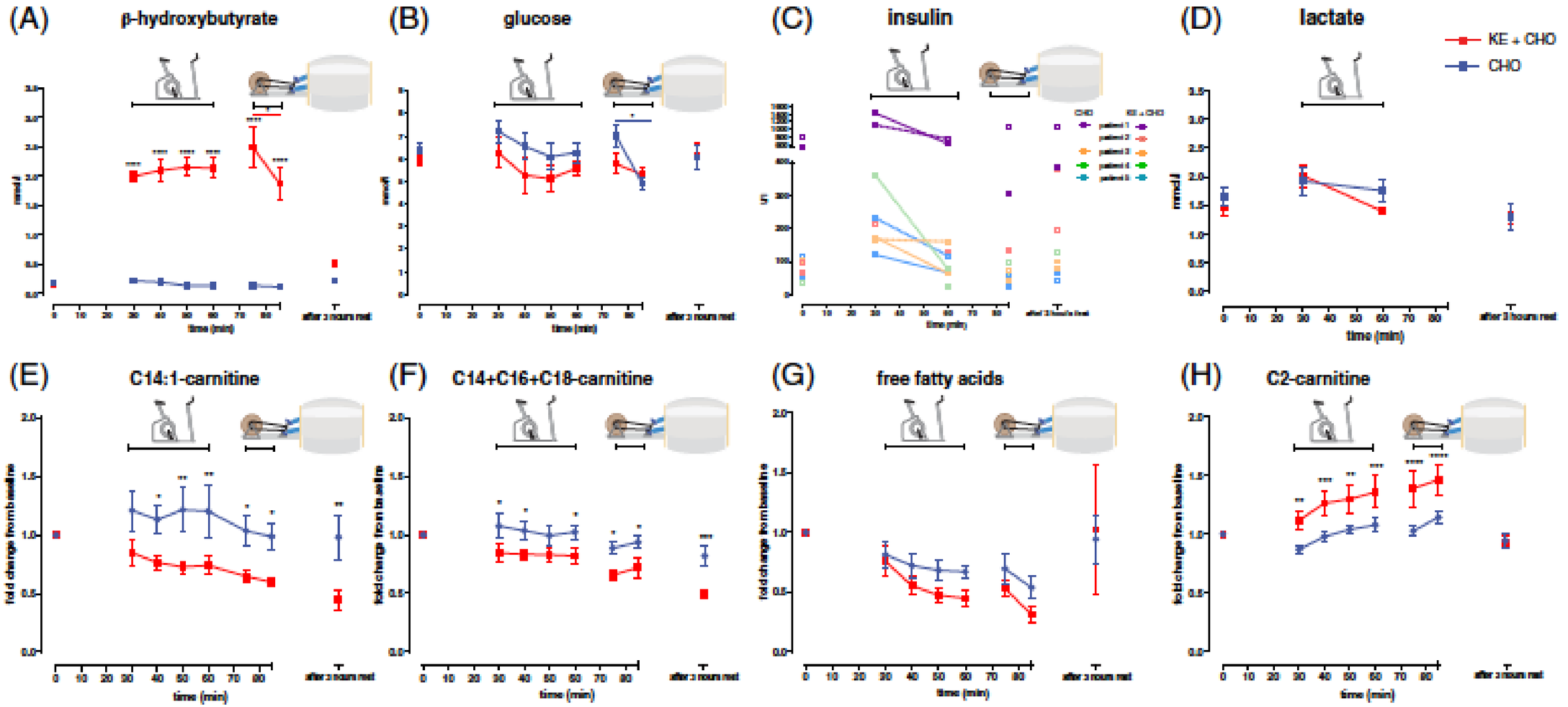
Ketone Ester



Raised ketones and acetyl-carnitine

Lowered free fatty acids and long-chain acylcarnitines

Bleeker et al JIMD 2019

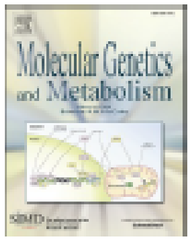
D BHB salt

Molecular Genetics and Metabolism 144 (2025) 109070

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

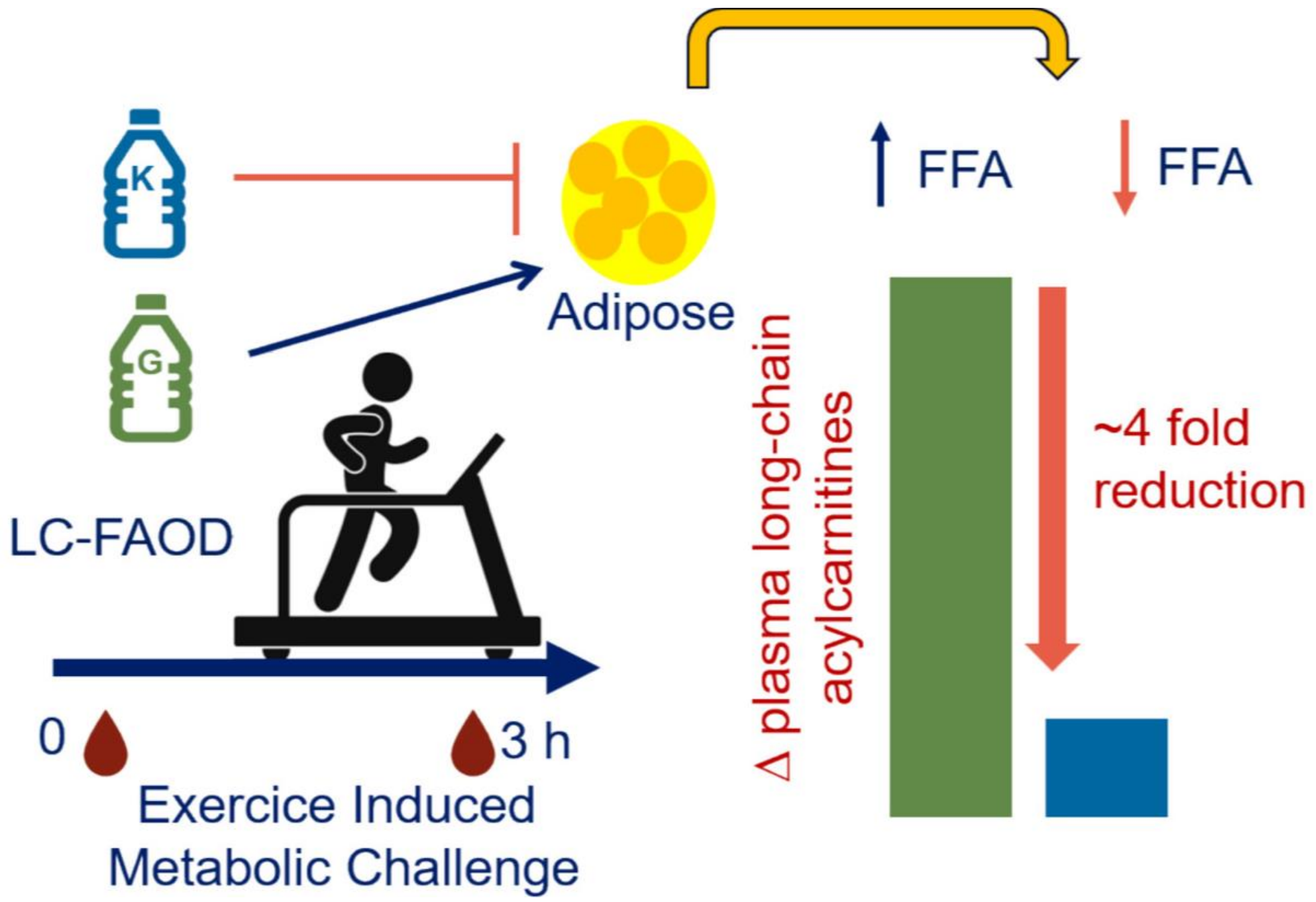


D-BHB supplementation before moderate-intensity exercise suppresses lipolysis and selectively blunts exercise-induced long-chain acylcarnitine increase in pilot study of patients with long-chain fatty acid oxidation disorders

Ashley N. Gregor [a], Philippe Delerive [b], Bernard Cuenoud [b,d], Irina Monnard [c], Karine Redeuil [c], Cary O. Harding [a], Melanie B. Gillingham [a,*]

[a] Department of Molecular & Medical Genetics, Oregon Health & Science University, Portland, OR, USA
[b] Nestlé Health Science, Research and Clinical Development, Lausanne, Switzerland
[c] Nestlé Research, Lausanne, Switzerland
[d] Department of Medicine, Faculty of Medicine and Health Sciences, Université de Sherbrooke, Sherbrooke, Canada

Ketones suppressed FAO with exercise



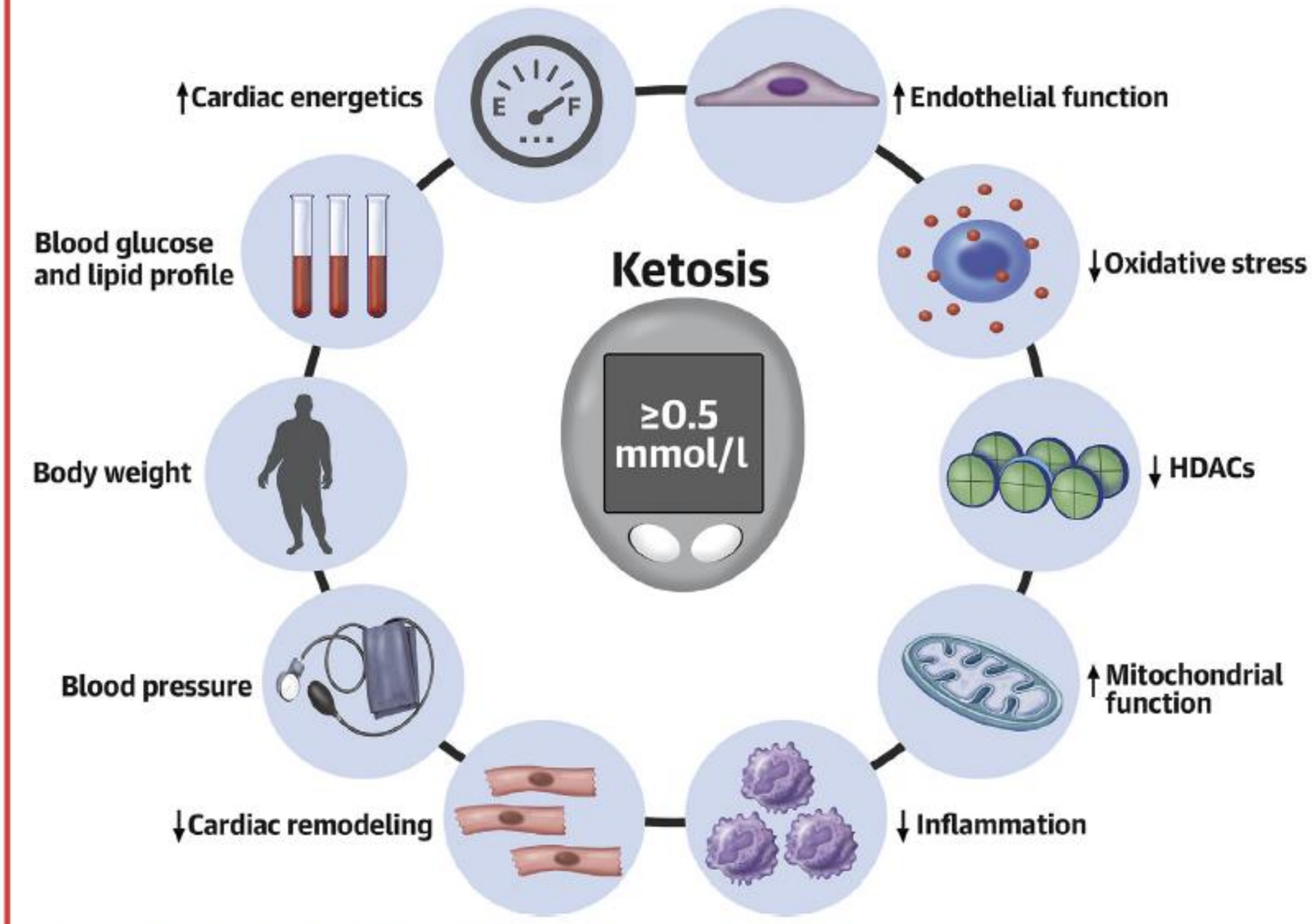
What we know

- D BHB endogenously synthesized
- D BHB used for energy; particularly in the heart and muscle
- D BHB suppresses adipose release of fatty acids and lowers acylcarnitines
- L BHB high in blood after D, L BHB consumption
- L BHB not used for energy
- L BHB high in the brain tissue

What we do not know

- Does L BHB have other benefits? Particularly in the brain?
- Should we focus on D BHB only or is there an advantage of a D, L mix?

CENTRAL ILLUSTRATION Bioenergetic and Pleiotropic Effects of Ketone Bodies



Yurista, S.R. et al. J Am Coll Cardiol. 2021;77(13):1660–9.