

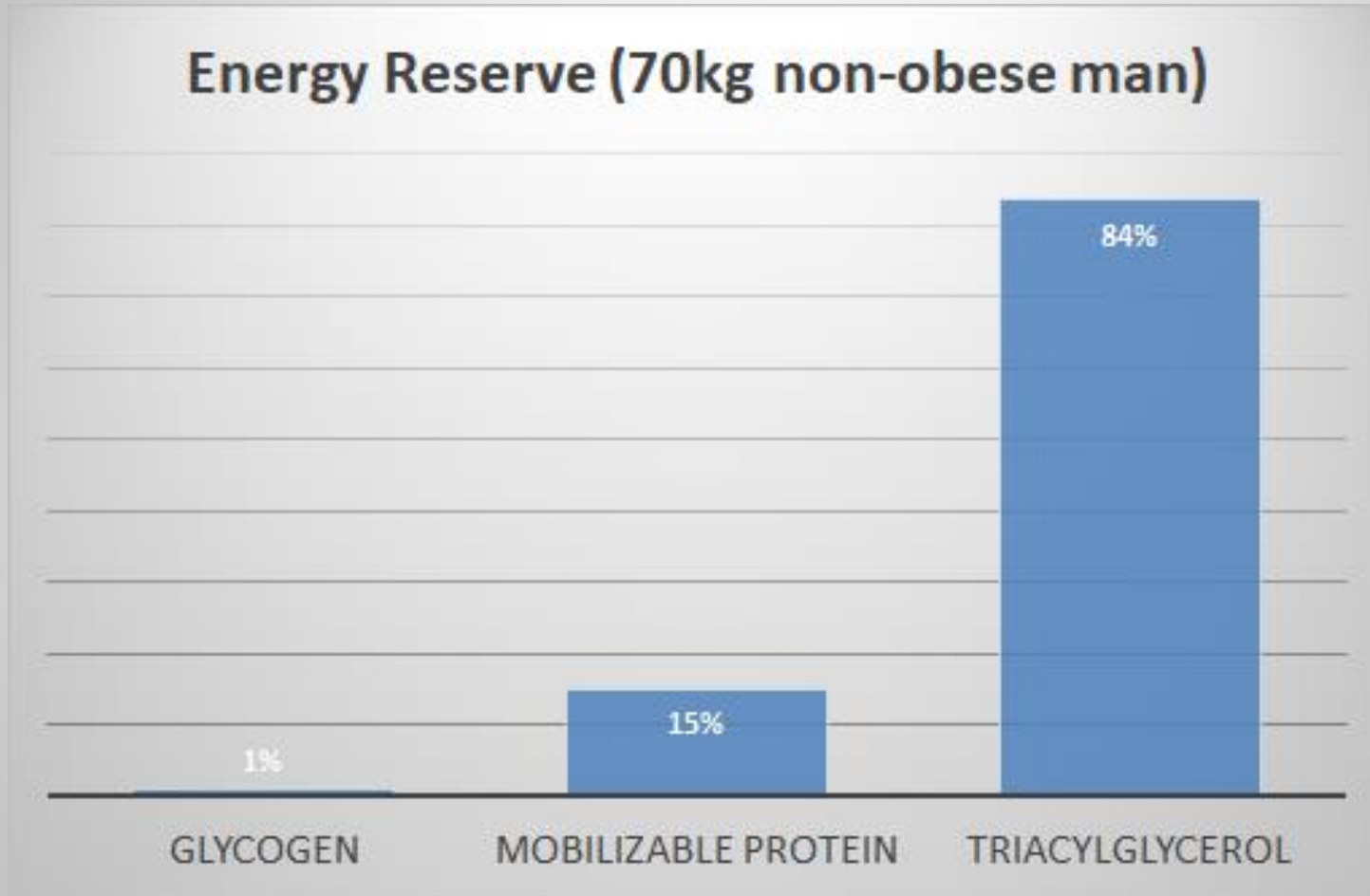
The Ketogenic Diet

Content

- Introduction – Why ketosis occur
- Macronutrient formula for a Keto Diet
- Ketone Synthesis
- Health and Longevity (Life span study in mice)
- Training – Strength and Mass gains on Keto
- Protein Mass Balance
- Aspartame and Keto
- TMAO and Resistant Starch on High Fat Diet
- How to Measure Ketones (home use)
- Advanced Troubleshooting

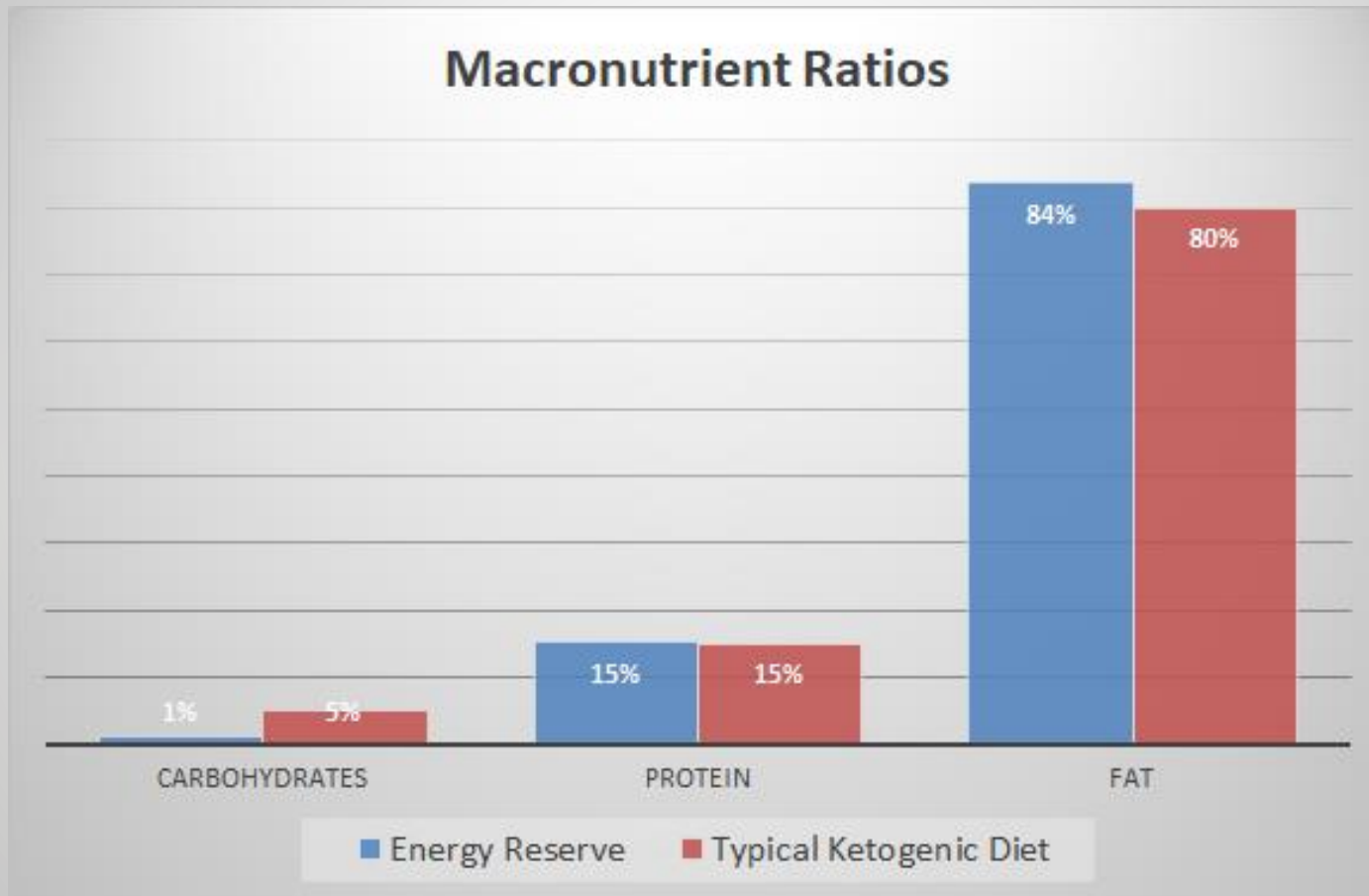
Why Ketosis Occur

Energy Reserve in the Human Body



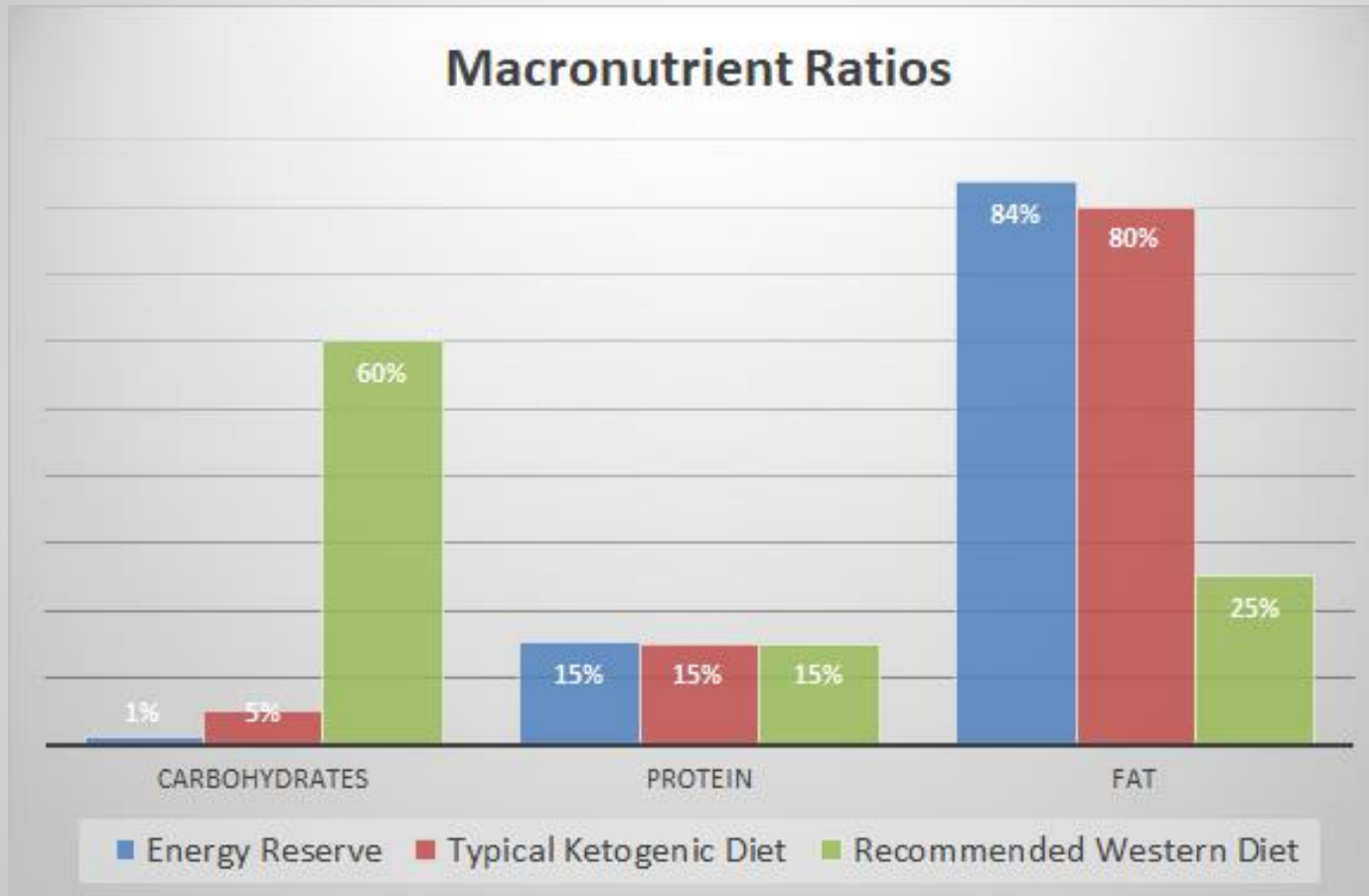
Why Ketosis Occur

Macronutrient Profile



Why Ketosis Occur

Macronutrient Profile



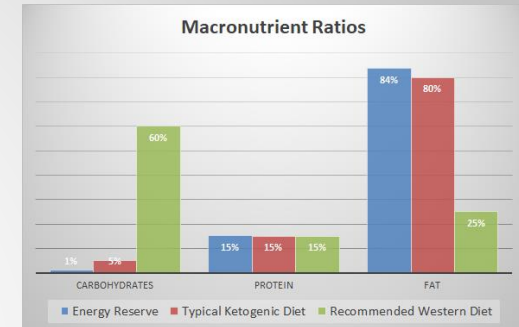
Why Ketosis Occur

Implication of High Carb Diet

- Western Diet has a poor match with preferred energy consumption

- Carbohydrate has to be burned first since they cannot be stored

Consequently fat is stored in the adipose tissue in the presence of carbohydrate.



- Excessive carbohydrates are also converted to fat for storage

- Capability to burn fat is decreased. The body becomes dependent on a high meal frequency since carbohydrates storage is limited

- Between meals protein can be used to synthesize carbohydrates. However, the body will protect its muscle tissue by decreasing the metabolism and signal extreme cravings to eat more.

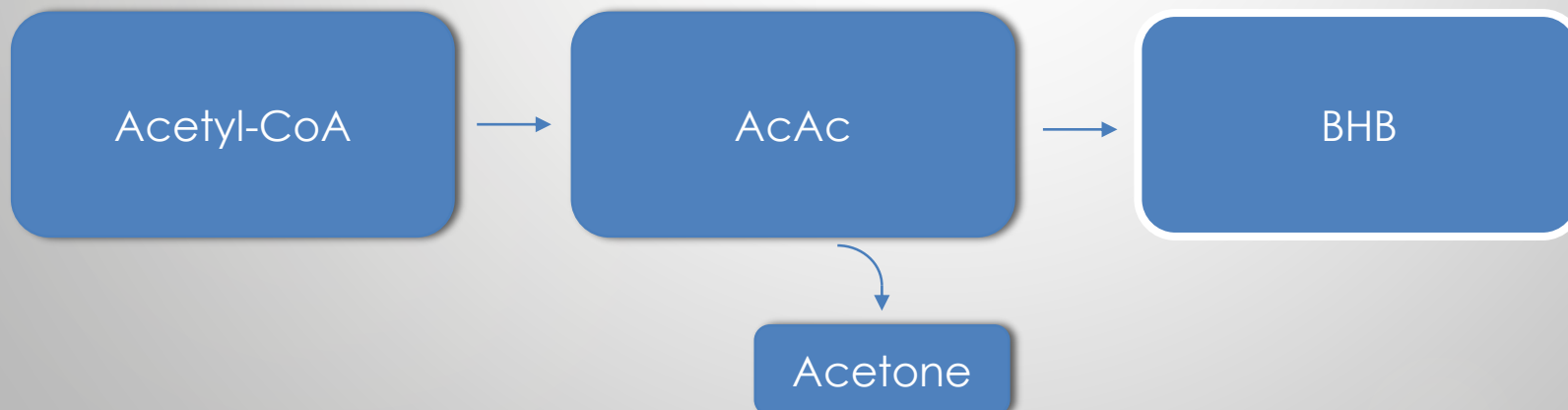
Ketone Synthesis

The Primary and Secondary Ketone

Acetoacetate (AcAc)

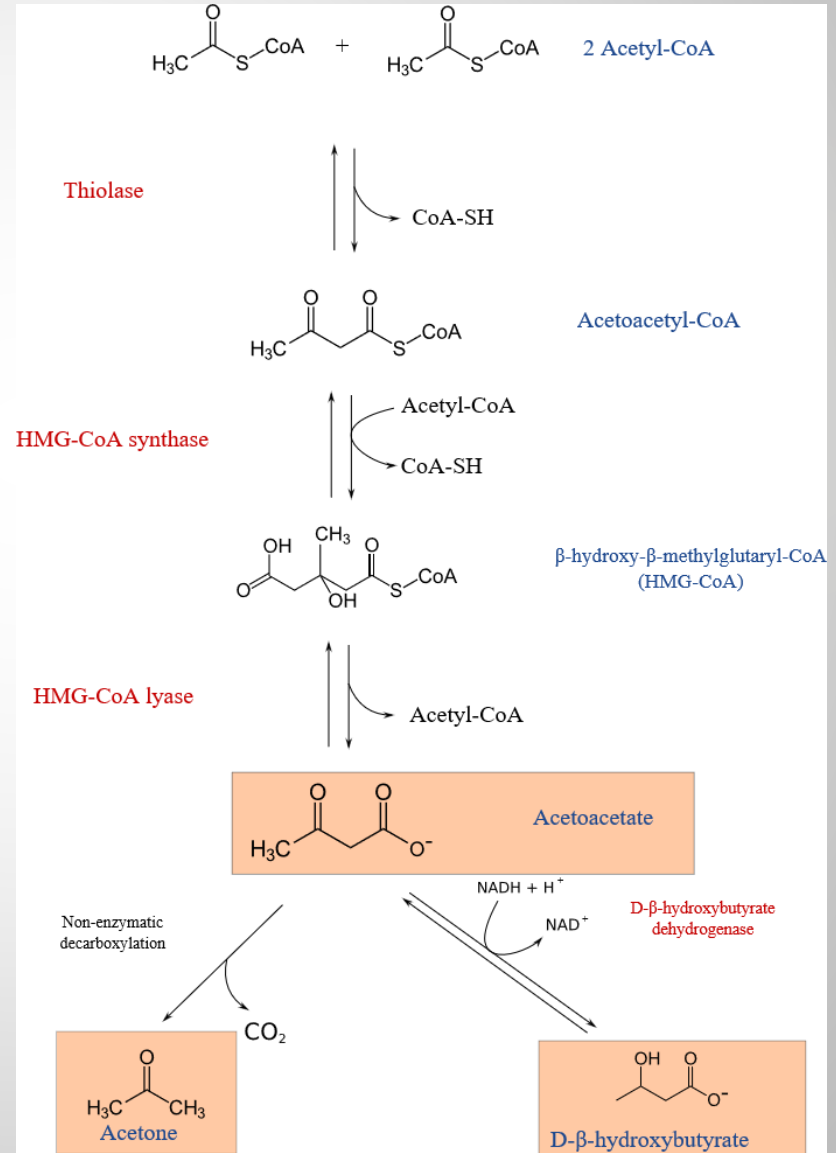
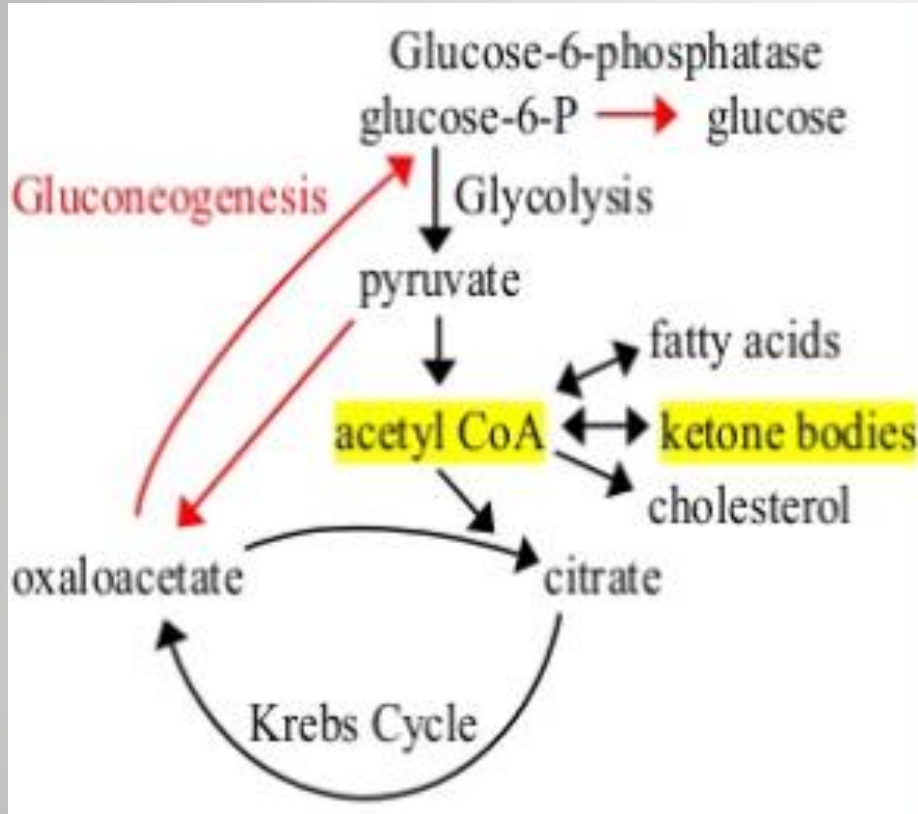
Acetone

Beta-HydroxyButyrate (BHB)



Why Ketosis Occur

Geeking out on Biochemistry



When Ketosis Occur

The Macronutrient Formula for Ketosis

Brain Energy → 120g/day of Glucose

Glucogenic substrates < 120g → Ketone production starts

Macro nutrient formula (g)

Carbohydrates + $0.5x(\text{Protein} - 50) + 0.1x\text{Fat} < 120 \text{ g}$

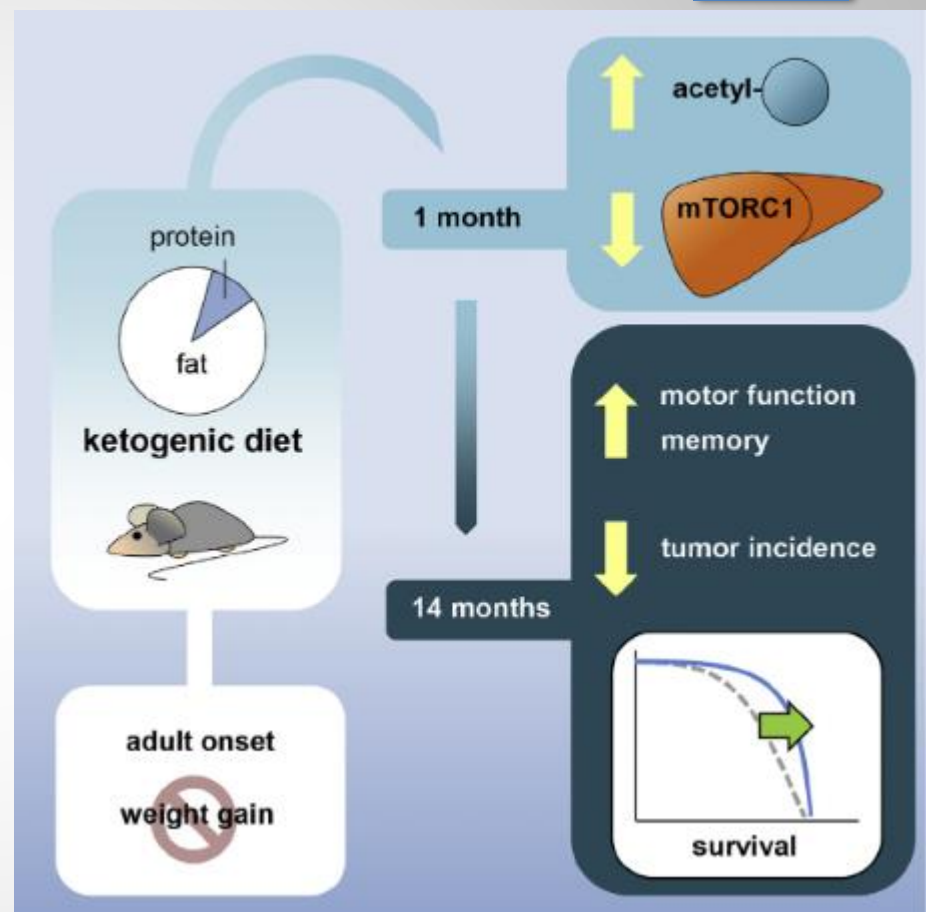
Example

You eat: 50g carbs + 150g Protein + 200g Fat →
 $50\text{g} + 0.5x100 + 20\text{g} = 120\text{g}$ (just on the limit)

Health and Longevity

Lifespan study in mice model

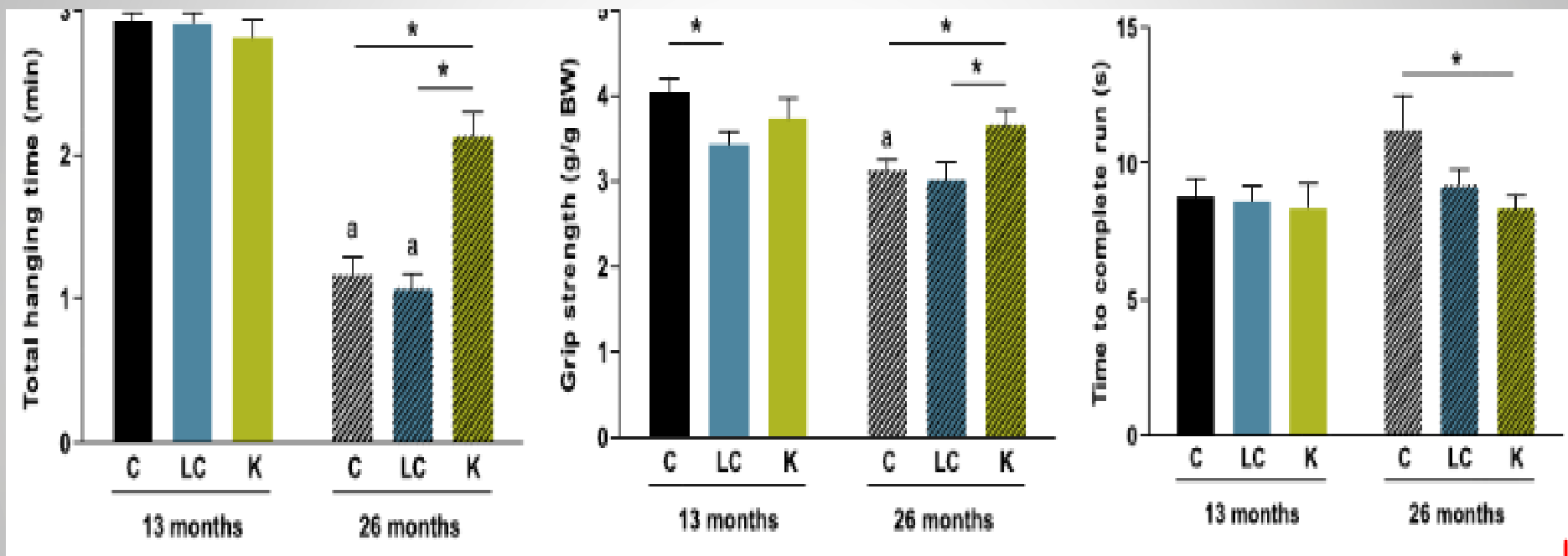
- Ketogenic diet extends longevity in adult male mice
- Motor function, memory, and muscle mass are preserved in aged ketogenic mice
- Protein acetylation is increased in the liver and skeletal muscle of ketogenic mice
- mTOR signaling decreased in liver but increased in skeletal muscle



- ▶ Roberts MN, Wallace MA, Tomilov AA, Zhou Z, Marcotte GR, Tran D, Perez G, Gutierrez-Casado E, Koike S, Knotts TA, Imai DM, Griffey SM, Kim K, Hagopian K, Haj FG4, Baar K, Cortopassi GA, Ramsey JJ, Lopez-Dominguez JA.
- ▶ **A Ketogenic Diet Extends Longevity and Healthspan in Adult Mice.** Cell Metab. 2017 Sep
- ▶ <https://www.ncbi.nlm.nih.gov/pubmed/28877457>

Health an Longevity

Strength and Endurance



- ▶ Roberts MN, Wallace MA, Tomilov AA, Zhou Z, Marcotte GR, Tran D, Perez G, Gutierrez-Casado E, Koike S, Knotts TA, Imai DM, Griffey SM, Kim K, Hagopian K, Haj FG4, Baar K, Cortopassi GA, Ramsey JJ, Lopez-Dominguez JA.
- ▶ **A Ketogenic Diet Extends Longevity and Healthspan in Adult Mice.** Cell Metab. 2017 Sep
- ▶ <https://www.ncbi.nlm.nih.gov/pubmed/28877457>

Health an Longevity

A Cyclic (bi-weekly) KD

Control

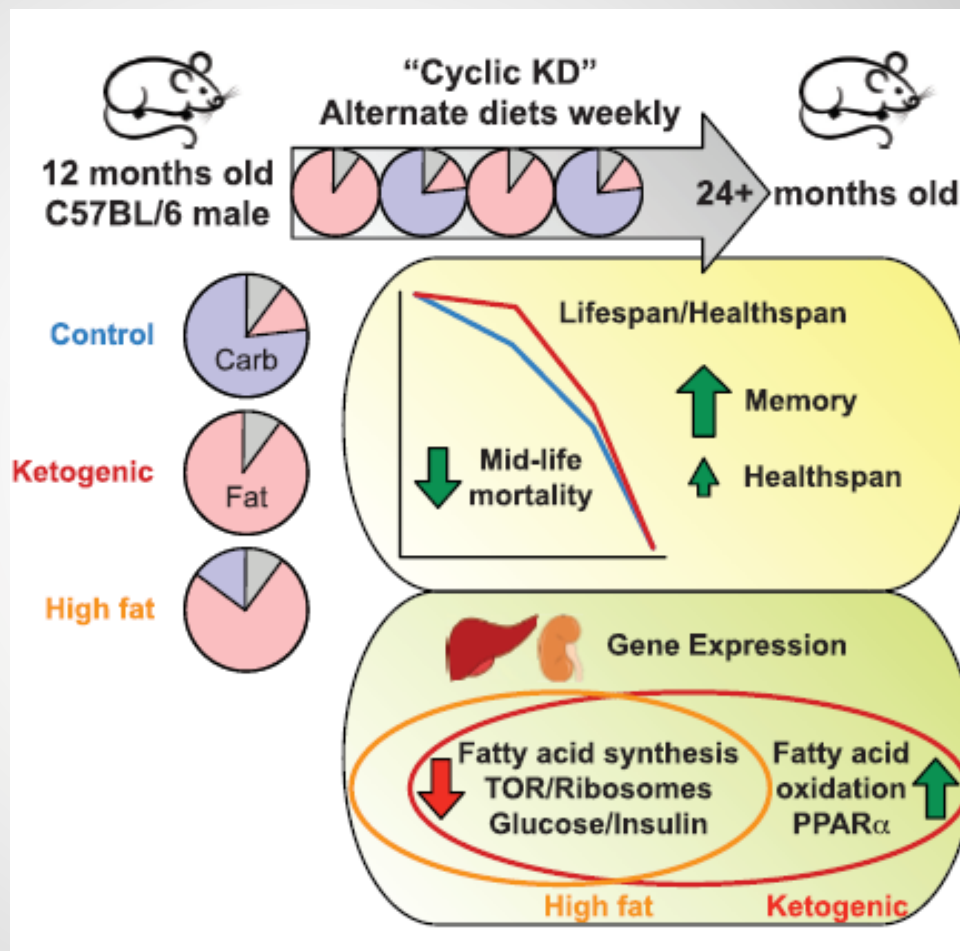
Protein	10%
Fat	13%
Carbs	77%

High Fat (HF)

Protein	10%
Fat	75%
Carbs	15%

Cyclic Ketogenic (KD)

Protein	10%
Fat	90%
Carbs	0%



Newman JC, Covarrubias AJ, Zhao M, Yu X, Gut P, Ng CP, Huang Y, Haldar S, Verdin E.

Ketogenic Diet Reduces Midlife Mortality and Improves Memory in Aging Mice. Cell Metab. 2017 Sep

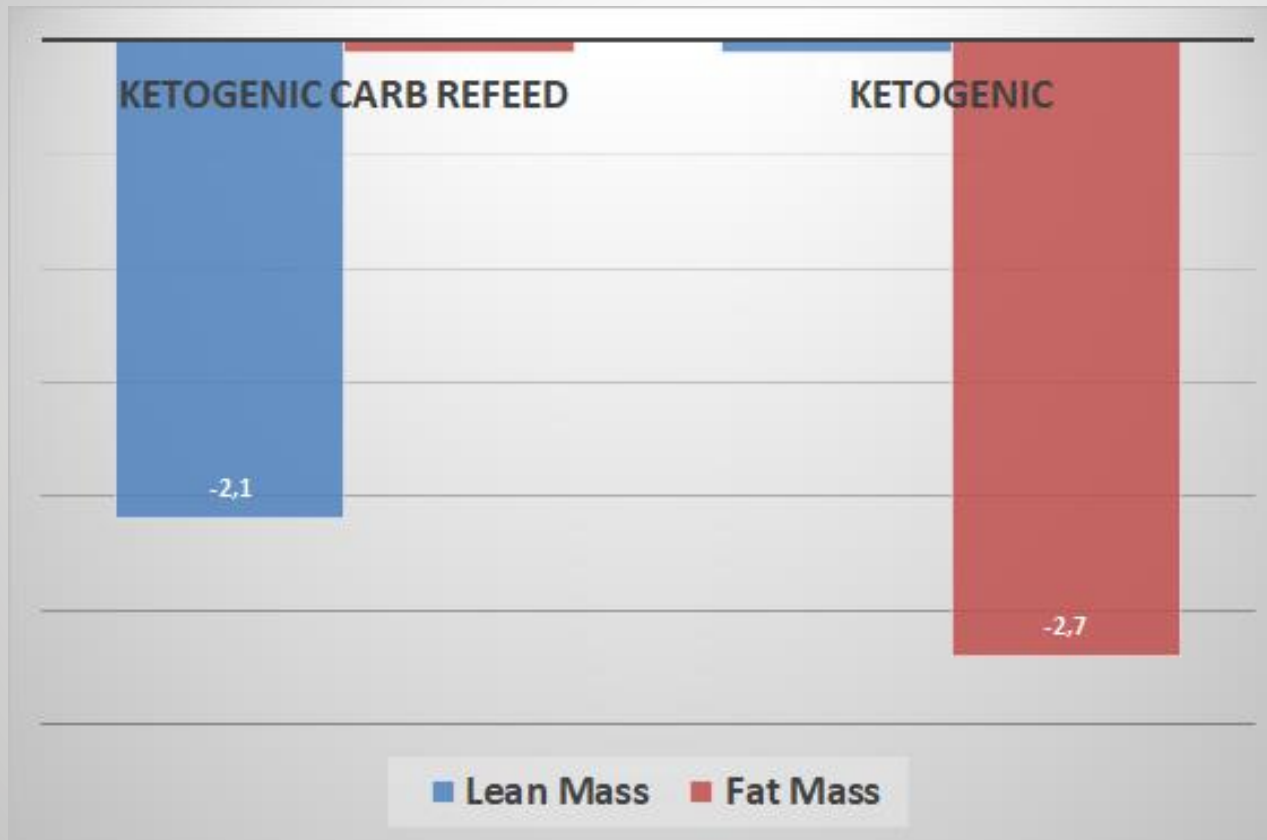
<https://www.ncbi.nlm.nih.gov/pubmed/28877458>

Human Cycle Times Need to be longer

Cyclic Ketogenic Diet

Two groups with resistance trained males put on 500kcal deficit with:

- **Ketogenic Continuous** - 5% CHO, 25% PRO, and 70%
- **Ketogenic Carb Refeed** 2d/week (refeed at 50% CHO, 25% PRO, 25% FAT)



Sharp, M.S., Lowery, R.P., Shields, K.A., Hollmer, C.A., Lane, J.R., Partl, J.M., Wilson, J.M

The 8 Week Effects of Low Carbohydrate Dieting vs. Very Low Carbohydrate Dieting With Refeed on Body Composition. Journal of Strength and Conditioning Research February 2016 Vol. 30 - Issue : p S1–S171

Protein Mass Balance

In Vivo Accessible Protein

Example A – Not in ketosis

Consume: 20g carbs + 100g Protein + 300g Fat

Glucogenic substrates: 20g + 30g = 50g (need is 120g)

70g carb missing → Convert protein to carbs

Protein 100g - 70g = 30 gram "free" protein

Basal metabolism = 50g → 20 g protein missing

Example B – In ketosis

Glucogenic substrates: 20g + 30g = 50g (need is 50g)

0 carb missing (ketones replaces about 70g of glucose)

Protein 100g - 0g = 100g "free" protein

Basal metabolism = 50g → 50g excess protein

Conclusion: Ketones spares at least 70g of protein

Keto and Resistance Training Strength & Power

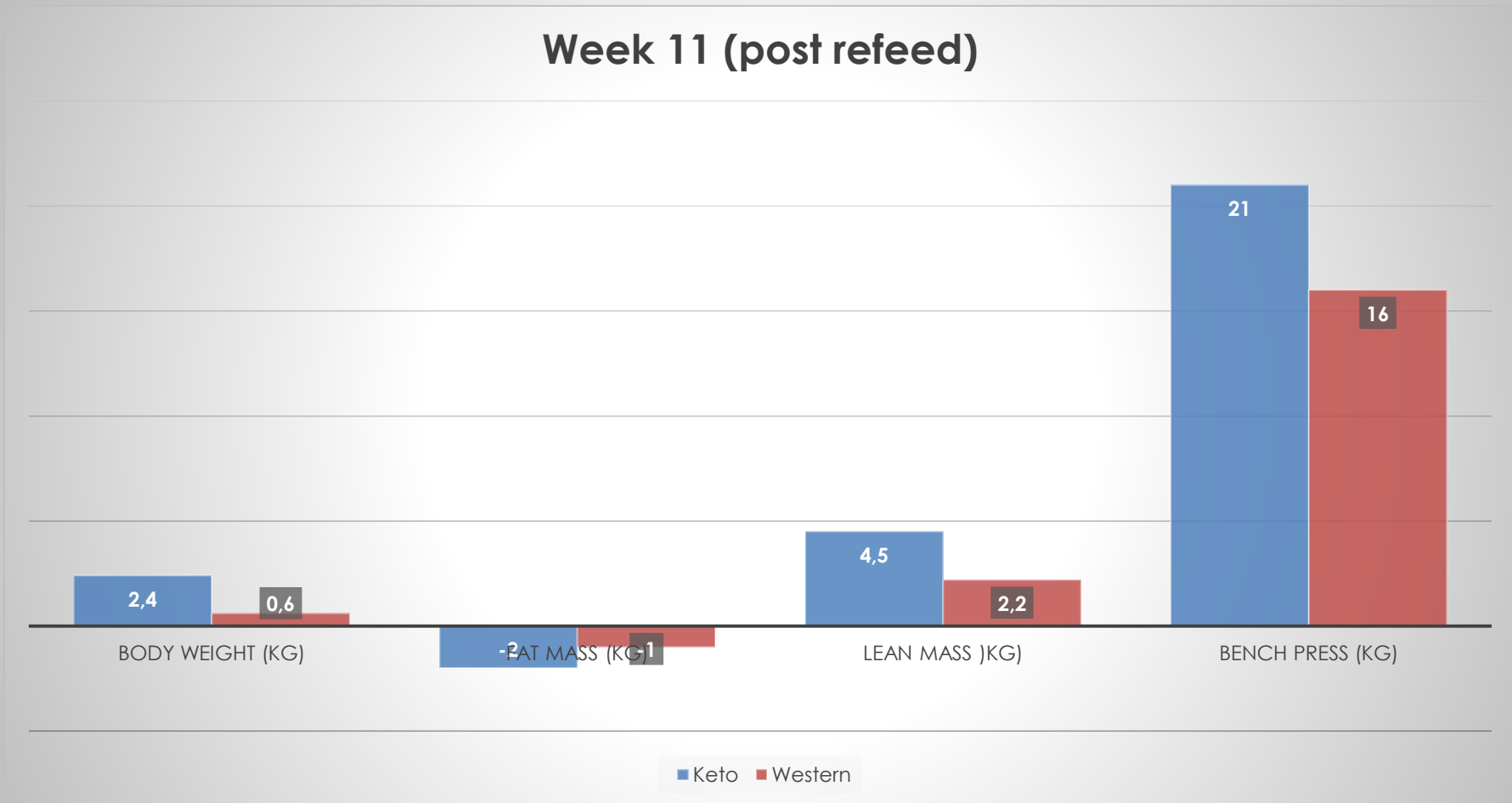
	Week 1-2	Week 3-10	Week 10-11	Week 1-2	Week 3-10	Week 10-11
Energy (kcal)	2652	2608	2619	2528	2549	2619
Protein (g)	139	133	131	129	132	131
Fat (g)	219	217	115	84	83	116
Carbohydrates (g)	31	31	263	314	317	263

Wilson JM, Lowery RP, Roberts MD, Sharp MH, Joy JM, Shields KA, Partl J, Volek JS, D'Agostino D.

The Effects of Ketogenic Dieting on Body Composition, Strength, Power, and Hormonal Profiles in Resistance Training Males. J Strength Cond Res. 2017 Apr.

<https://www.ncbi.nlm.nih.gov/pubmed/28399015>

Keto and Resistance Training Strength & Power



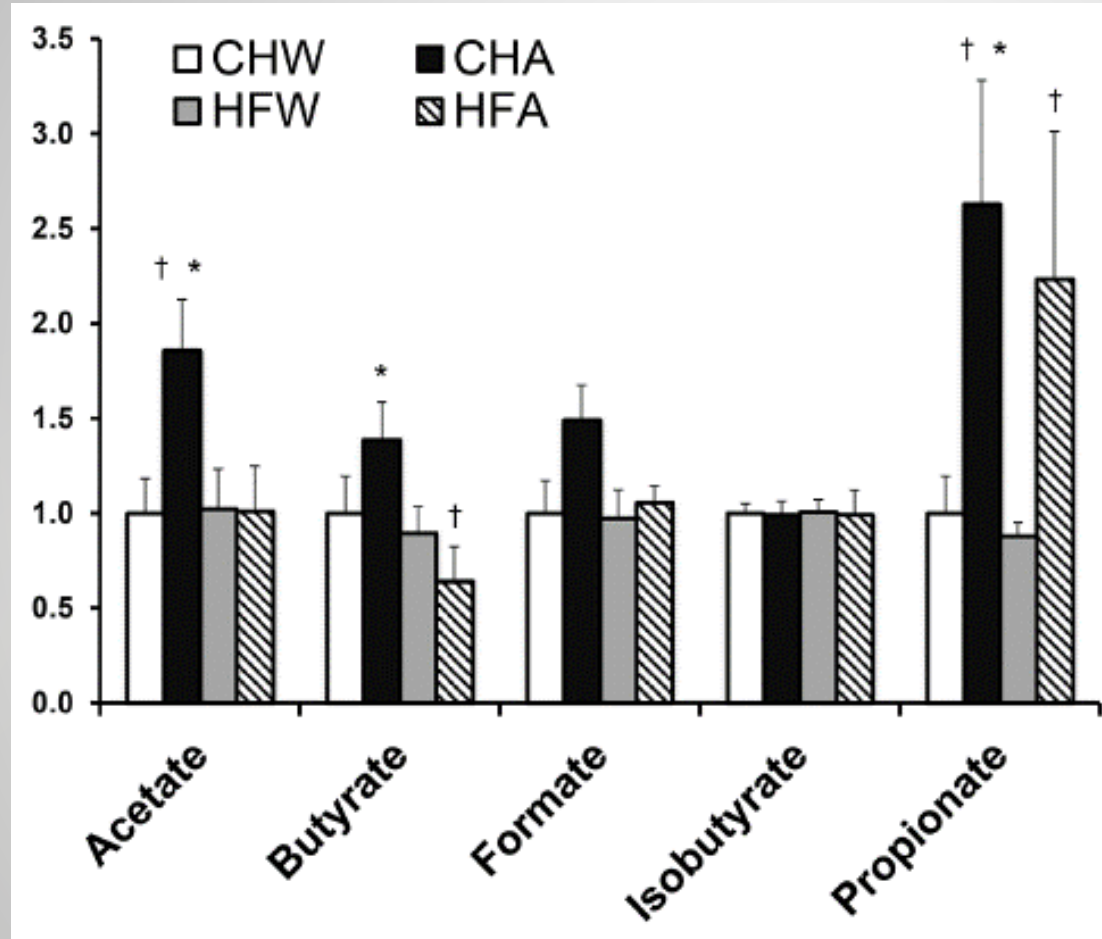
Wilson JM, Lowery RP, Roberts MD, Sharp MH, Joy JM, Shields KA, Partl J, Volek JS, D'Agostino D.

The Effects of Ketogenic Dieting on Body Composition, Strength, Power, and Hormonal Profiles in Resistance Training Males. J Strength Cond Res. 2017 Apr.

<https://www.ncbi.nlm.nih.gov/pubmed/28399015>

Aspartame and Microbe Metabolites

Impact on Short Chain Fatty Acids



Aspartame in the High Fat Diet **decreased Butyrate** and **increased Propionate**

Propionate (C3) can easily be turned into **glucose**

Butyrate (C4) can easily be turned into **ketones**

The change in metabolites can **prevent ketosis**

Palmnäs MS, Cowan TE, Bomhof MR, Su J, Reimer RA, Vogel HJ, Hittel DS, Shearer J.

Low-dose aspartame consumption differentially affects gut microbiota-host metabolic interactions in the diet-induced obese rat. PLoS One. 2014 Oct.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4197030/>

Resistant Starch – A Road to CVD?

TMAO and CVD Risk

- Humans Studies – Risk marker for CVD (correlation)
- Animal Studies – Seems to cause CVD

Maier TV, Lucio M, Lee LH, VerBerkmoes NC, Brislawn CJ, Bernhardt J, Lamendella R, McDermott JE, Bergeron N, Heinzmann SS, Morton JT, González A, Ackermann G, Knight R, Riedel K, Krauss RM, Schmitt-Kopplin P, Jansson JK. **Impact of Dietary Resistant Starch on the Human Gut Microbiome, Metaproteome, and Metabolome.** MBio. 2017 Oct 17. <https://www.ncbi.nlm.nih.gov/pubmed/29042495>

Bergeron N, Williams PT, Lamendella R, Faghihnia N, Grube A, Li X, Wang Z, Knight R, Jansson JK, Hazen SL, Krauss RM. **Diets high in resistant starch increase plasma levels of trimethylamine-N-oxide, a gut microbiome metabolite associated with CVD risk.** Br J Nutr. 2016 Dec

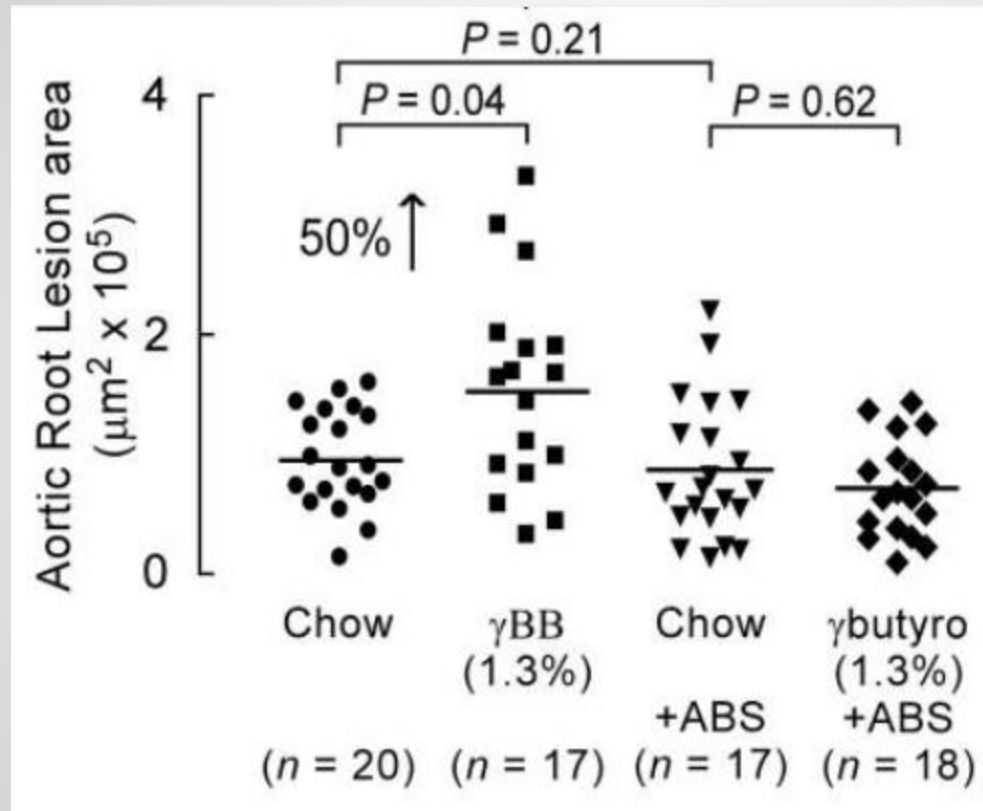
Resistant Starch – A Road to CVD?

Formation of TMAO

- Gut microbe-dependent formation
- Precursor Phosphatidylcholine & L-carnitine (mainly in fish and some in meat)

Resistant Starch – A Road to CVD?

Cause of plaque in Animal model



Koeth RA, Levison BS, Culley MK, et al. **Gamma-Butyrobetaine is a proatherogenic intermediate in gut microbial metabolism of L-carnitine to TMAO.** Cell Metab 2014

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4255476/>

Resistant Starch – A Road to CVD?

Physiological impact of RS

- Postprandial insulin response - Decreased
- Postprandial glucose responses – Decreased
- Fasting insulin – No difference
- Fasting glucose – No difference
- Gut microbiome – Shifted
- Increase in the proportion of Firmicutes to Bacteroides
- Relative increase in Faecalibacterium, Roseburia, and Ruminococcus (low in T2DM)
- Increased plasma levels of **trimethylamine-N-oxide (TMAO)**
- **Profound increase of TMAO with RS on a low carb diet**

Maier TV, Lucio M, Lee LH, VerBerkmoes NC, Brislawn CJ, Bernhardt J, Lamendella R, McDermott JE, Bergeron N, Heinzmann SS, Morton JT, González A, Ackermann G, Knight R, Riedel K, Krauss RM, Schmitt-Kopplin P, Jansson JK. **Impact of Dietary Resistant Starch on the Human Gut Microbiome, Metaproteome, and Metabolome.** MBio. 2017 Oct 17. <https://www.ncbi.nlm.nih.gov/pubmed/29042495>

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Resistant Starch

A Road to Atherosclerosis?

Chen ML, Yi L, Zhang Y, Zhou X, Ran L, Yang J, Zhu JD, Zhang QY, Mi MT.

Resveratrol Attenuates Trimethylamine-N-Oxide (TMAO)-Induced Atherosclerosis by Regulating TMAO Synthesis and Bile Acid Metabolism via Remodeling of the Gut Microbiota. MBio. 2016 Apr

<https://www.ncbi.nlm.nih.gov/pubmed/27048804>

Maier TV, Lucio M, Lee LH, VerBerkmoes NC, Brislawn CJ, Bernhardt J, Lamendella R, McDermott JE, Bergeron N, Heinzmann SS, Morton JT, González A, Ackermann G, Knight R, Riedel K, Krauss RM, Schmitt-Kopplin P, Jansson JK

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Diets high in resistant starch increase plasma levels of trimethylamine-N-oxide, a gut microbiome metabolite associated with CVD risk. Br J Nutr. 2016 Dec

Trøseid M, Hov JR, Nestvold TK, Thoresen H, Berge RK, Svardal A, Lappegård KT

Major Increase in Microbiota-Dependent Proatherogenic Metabolite TMAO One Year After Bariatric Surgery. Metab Syndr Relat Disord. 2016 May.

Ketone Regulation

Hormonal Impact

	Glucagon	Insulin
Aceto Acetate	Minor effect	Minor effect
Beta-Hydroxy butyrate	Increase	Decrease

The effects of insulin and glucagon on ketone-body turnover. Biochem J. 1984 Jul
<http://www.ncbi.nlm.nih.gov/pubmed/6383348>

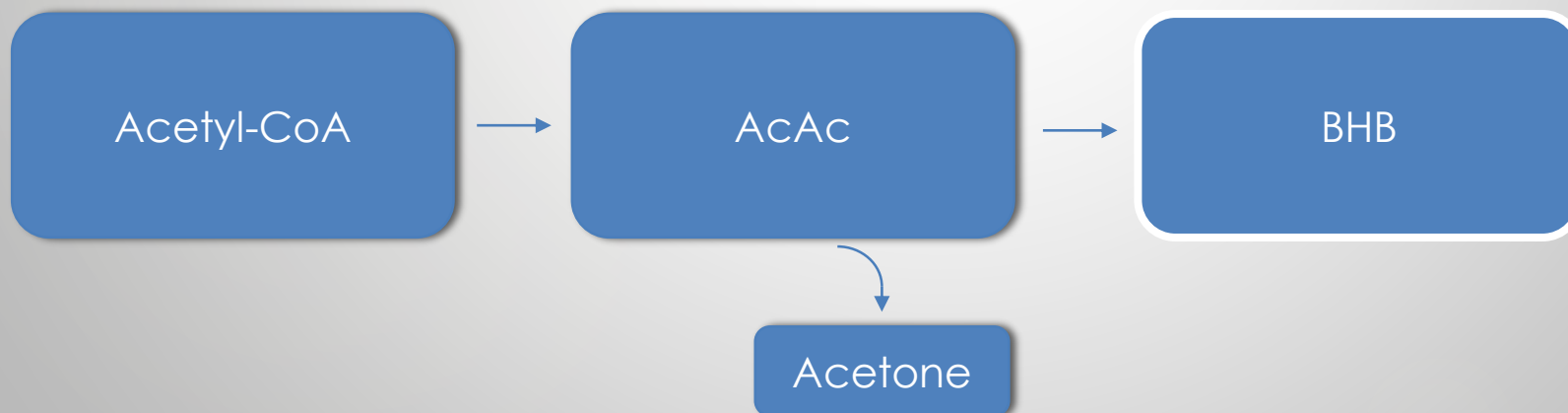
The Hunt for Ketones

How to Measure for Home use

Urine – Acetoacetate (AcAc)

Breath – Acetone (indirect measure of AcAc)

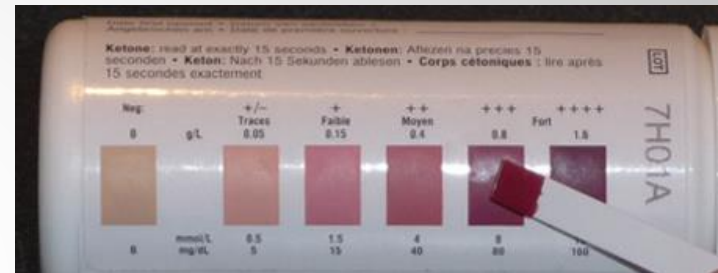
Blood – Beta-HydroxyButyrate (BHB)



The Hunt for Ketones

Urine Test

Sheep
Simple
Time lag



Not always good correlation with blood

AcAc

Shows AcAc in Urine (not in blood)

AcAc only first step into ketosis → (full keto adaptation = BHB)

The Hunt for Ketones

Breath Acetone

One time investment (free tests)
Simple
Real time measure of AcAc
(indirect by Acetone)
Good indication of fat burning
(true for all diets, regardless of if
they are ketogenic or not)
Only shows AcAc, not BHB



Anderson JC

Measuring breath acetone for monitoring fat loss: Review. Obesity (Silver Spring). 2015 Dec

<https://www.ncbi.nlm.nih.gov/pubmed/26524104>

The Hunt for Ketones

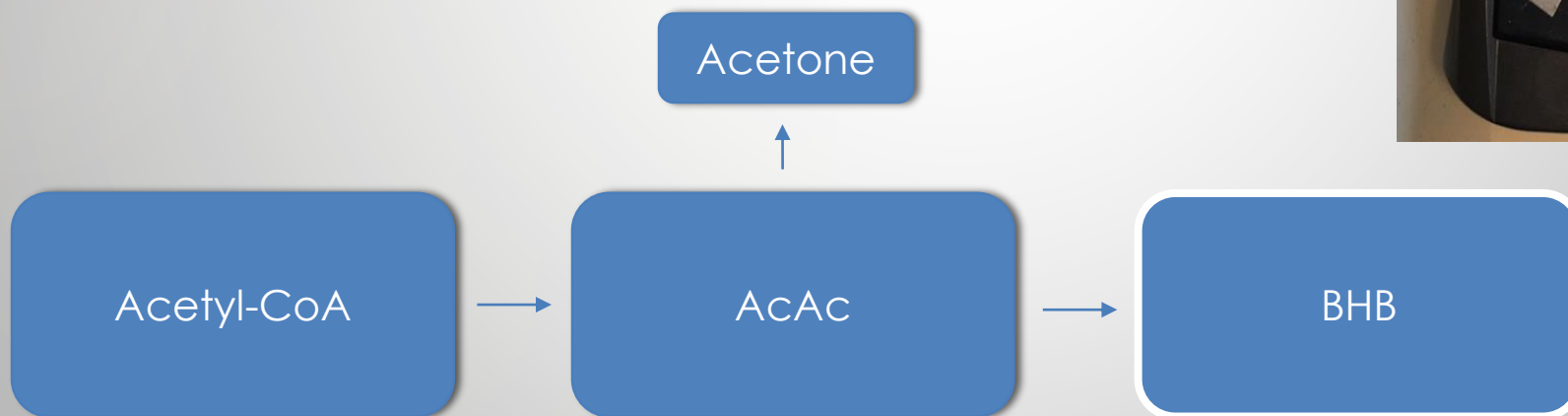
Blood beta-Hydroxybutyrate (BHB)

Expensive (3-5 USD/test)

Shows the primary ketone

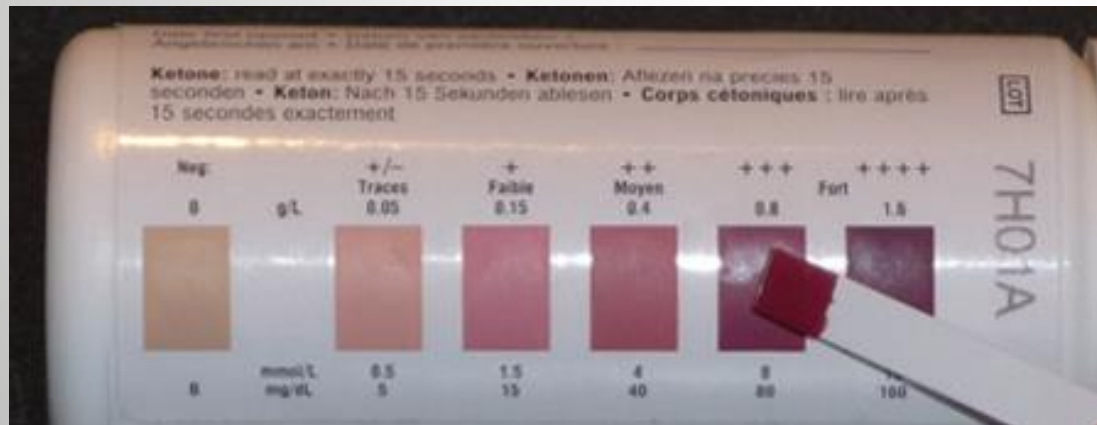
Best way to assess full ketosis

Indicates all pathways are set to burn fat



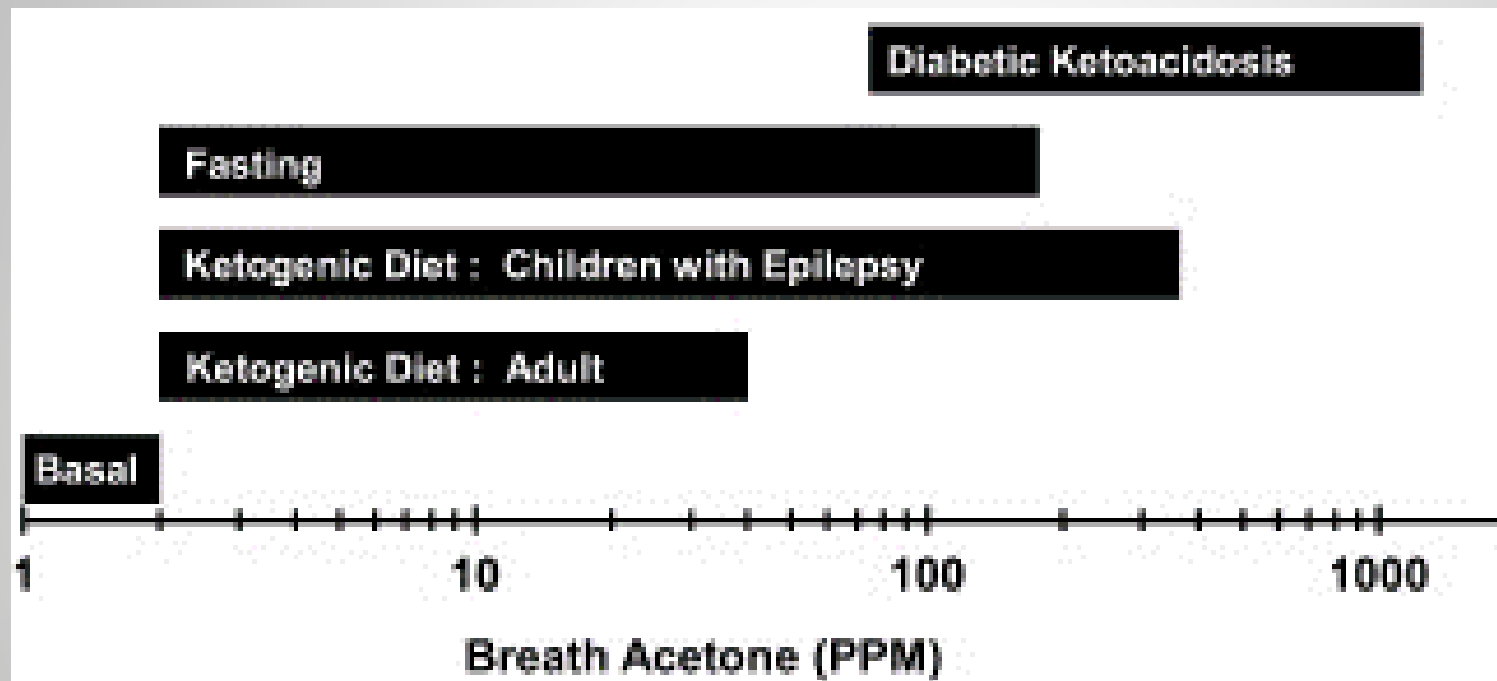
The Hunt for Ketones

Typical Ranges for Urine AcAc



The Hunt for Ketones

Typical Ranges for Breath Acetone



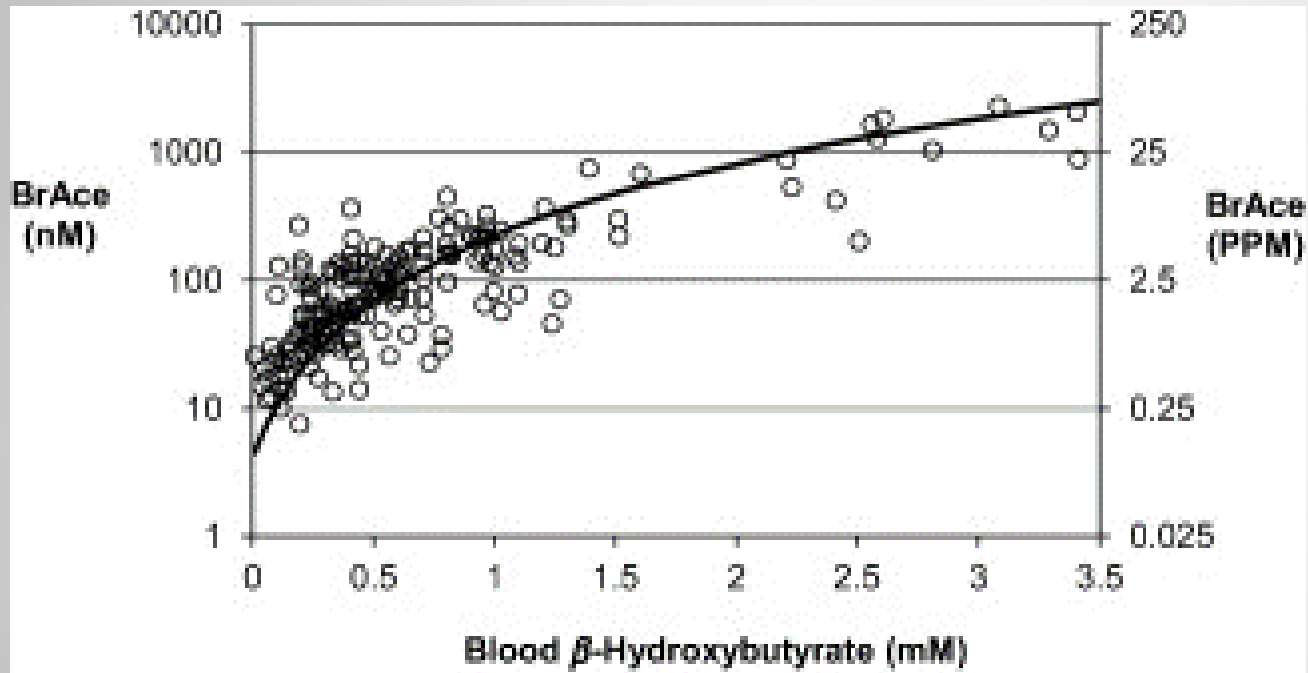
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The Hunt for Ketones

Relationship of AcAc and BHB



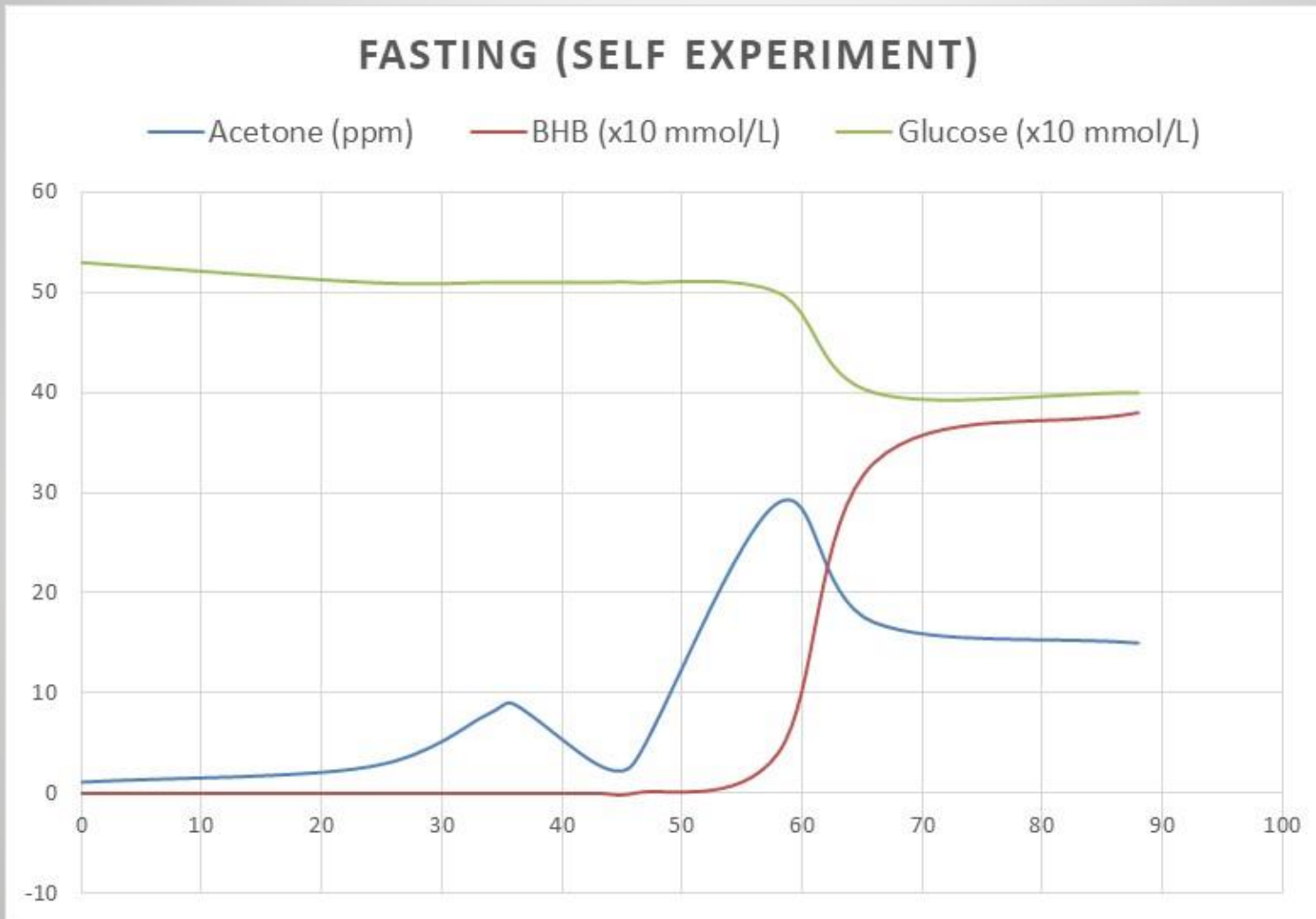
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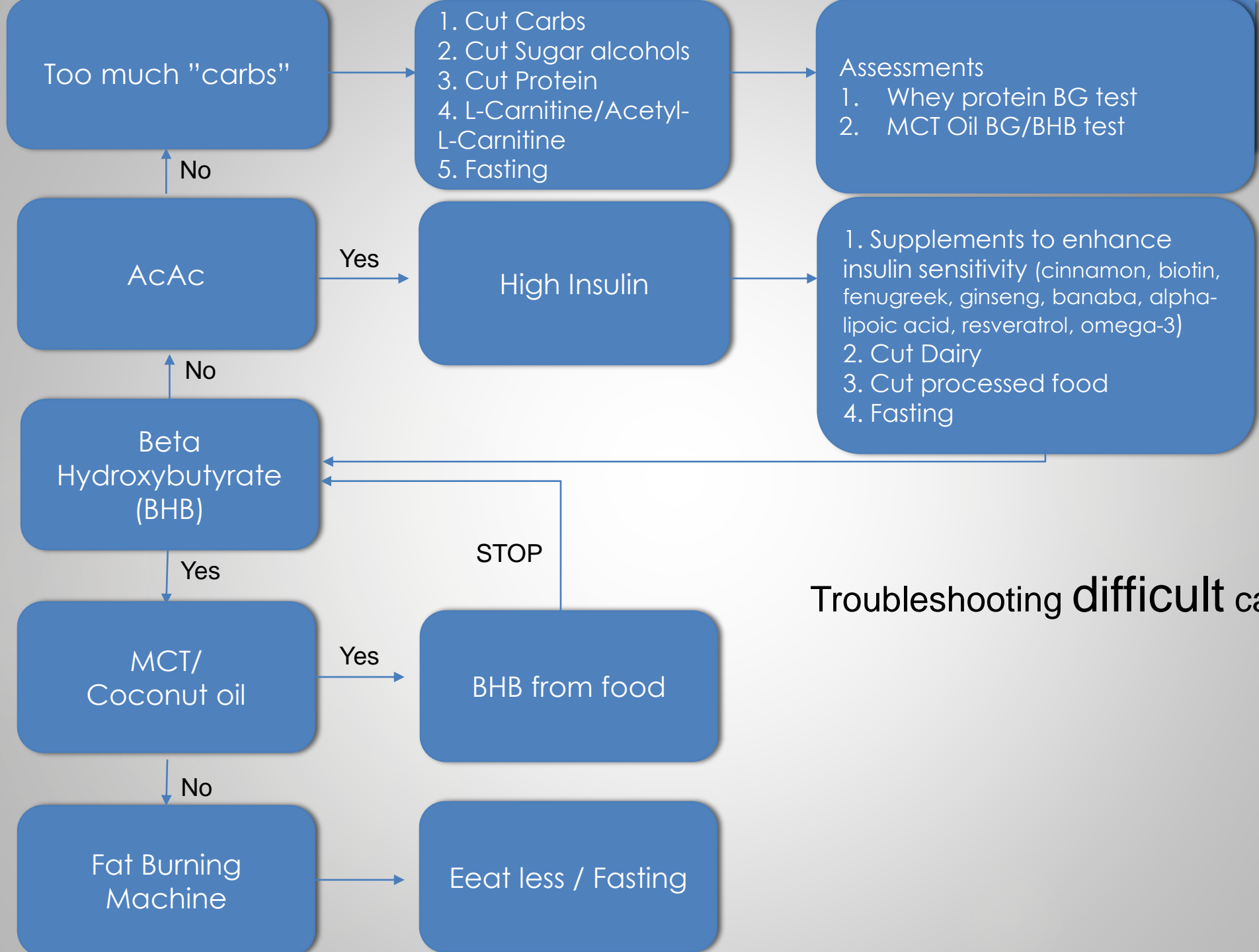
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<https://www.ncbi.nlm.nih.gov/pubmed/26524104>

The Hunt for Ketones

Fasting Experiment





Troubleshooting **difficult** cases

Advanced Troubleshooting

What to do when the Diet Doesn't Work

Carnitine

L-carnitine prevents progression of non-alcoholic steatohepatitis in a mouse model with upregulation of mitochondrial pathway. PLoS One. 2014 Jul.

<http://www.ncbi.nlm.nih.gov/pubmed/24983359>

Modulation of tissue fatty acids by L-carnitine attenuates metabolic syndrome in diet-induced obese rats. Food Funct. 2015 Aug

<http://www.ncbi.nlm.nih.gov/pubmed/26190559>

L-carnitine prevents metabolic steatohepatitis in obese diabetic KK-Ay mice. Hepatol Res. 2016 Apr.

<http://www.ncbi.nlm.nih.gov/pubmed/27062266>

Insulin sensitivity

Attenuation of oxidative stress, inflammation and insulin resistance by allium sativum in fructose-fed male rats. J Clin Diagn Res. 2013 Sep.

<http://www.ncbi.nlm.nih.gov/pubmed/24179882>

Resveratrol improves hepatic steatosis by inducing autophagy through the cAMP signaling pathway. Mol Nutr Food Res. 2015 Aug.

<http://www.ncbi.nlm.nih.gov/pubmed/25943029>

Natural supplements for improving insulin sensitivity and glucose uptake in skeletal muscle. Front Biosci (Elite Ed). 2015 Jan

<http://www.ncbi.nlm.nih.gov/pubmed/25553366>

Comparison of a carbohydrate-free diet vs. fasting on plasma glucose, insulin and glucagon in type 2 diabetes. Metabolism. 2015 Feb

<http://www.ncbi.nlm.nih.gov/pubmed/25458830>

Effects of n-3 pufas on fasting plasma glucose and insulin resistance in patients with impaired fasting glucose or impaired glucose tolerance. Biofactors. 2016 Apr

<http://www.ncbi.nlm.nih.gov/pubmed/27040503>

Metabolic effects of ketosis

Advanced Nutrition References

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<http://www.ncbi.nlm.nih.gov/pubmed/27040503>

Atherosclerosis

Impact of a High Fat Diet

RTC 6 weeks	Insulin	Postprandial triacylglycerol	Flow-mediated dilation
Low Fat High Carb	-6%	-15%	-34%
Low Carb High Fat	-51%	-47%	+26%

Effects of dietary carbohydrate restriction versus low-fat diet on flow-mediated dilation. Metabolism. 2009.
<http://www.ncbi.nlm.nih.gov/pubmed/19632695>

Atherosclerosis

Impact of a High Fat Diet

RTC 2 years	Mean carotid vessel wall volume
Mediterranean	-38 mm ³
Low Fat High Carb	-61 mm ³
Low Carb High Fat	-84 mm ³

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www.BlackBeltNutrition.org