Ketogenic Program

Nutrition Masters Course

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Learning Objectives

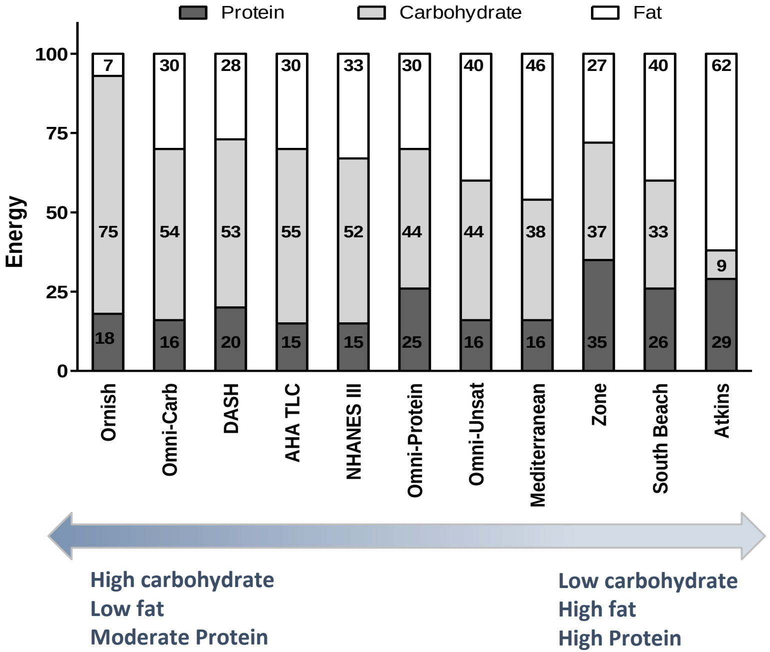
- Review the impact of dietary macronutrient composition in human health, with a focus on low-carbohydrate approaches
- Understand the physiology and mechanisms of action of ketogenic approaches
- Discuss the clinical implications of ketogenic diets, from peripheral metabolism to brain health
- Examine nutritional ketosis: safety and monitoring
- Explore supporting factors for ketogenic lifestyle
  - Nutritional supplement support (e.g. medium-chain triglycerides [MCT], beta-hydroxybutyrate [βHB])
  - Collagen supplementation as adjunct wellness support
  - Fasting protocols

One diet doesn't fit all:
Diets with different compositions of fat, protein, and carbohydrates

- Different diets varying in their fat, protein, and carbohydrate composition have been shown to successfully support weight loss and benefit cardiovascular disease and diabetes[1]
- **Diets that are tailored** to the patient's metabolic and health status, as well as personal and cultural preferences, may have the best chance for long-term success

The best diet is one that you can stick with for the long-term. Any lifestyle modification should be closely monitored and modified as needed

The macronutrient contents of diet plans



1. Sacks et al. *N Engl J Med*. 2009;360(9):859–873.

Adapted from: de Souza et al. *Am J Clin Nutr*. 2008;88(1):1–11.

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High carbohydrate intake and its impact on human health

- Diets with high-starch, low-fiber ratio are associated with **a higher risk of type 2 diabetes**[1]
- High carbohydrate intakes (≥74 En%) may increase the risk for **metabolic syndrome**, while moderate fat intakes (≥20 En%) may reduce the risk for metabolic syndrome in women[2]
- Dietary carbohydrate intake, glycemic index and glycemic load are positively associated with risk of **gastric cancer in male and Asian subgroups**[3]
- Sedentary lifestyle and high-carbohydrate intake are associated with **low-grade chronic inflammation and increased cardiovascular disease risk in post-menopausal women**[4]
- Higher blood glucose levels are associated with an **increased risk of dementia**[5]

1. Alessa HB et al. *Am J Clin Nutr.* 2015;102(6):1543-1553.
2. Park S et al. *Int J Food Sci Nutr.* 2017;68(4):479-487.
3. Ye Y et al. *Eur J Nutr.* 2017;56(3):1169-1177.
4. Alves BC et al. *Rev Bras Ginecol Obstet.* 2016; 38(7):317-324.
5. Crane PK et al. *N Engl J Med*. 2013;369:540-548.

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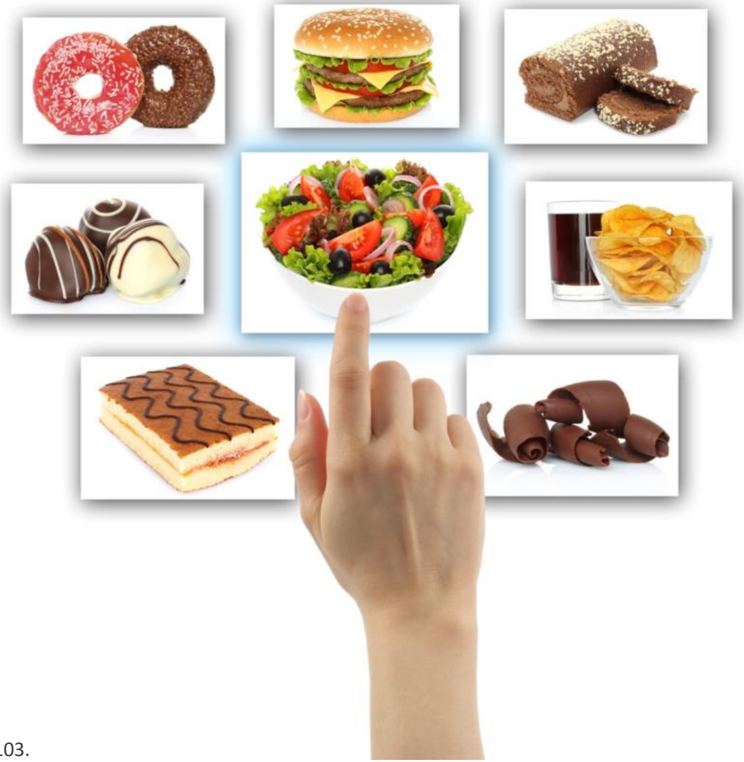
Benefits of low carbohydrate intake on human health

- In a study with type 2 diabetics, a low-carbohydrate ketogenic diet led to **greater improvements in glycemic control**, and more frequent **medication reduction/elimination** than the low glycemic index diet[1]
- In a study of highly trained ultra-endurance athletes, a long-term, low carbohydrate ketogenic diet resulted in **high rates of fat oxidation**[2]
- The low-carbohydrate ketogenic diet has also been shown to induce **significant weight loss and improve fatty liver disease**[3]
- Low-carbohydrate diet is associated with **better vigilance attention and reduced self-reported confusion**[4]
- In a preclinical study, a low carbohydrate diet **slowed cancer development and progression** [5]



1. Westman EC et al. *Nutr Metab.* 2008;19(5):36.
2. Volek JS et al. *Metab.* 2016;65(3):100-110.
3. Tendler D et al. *Dig Dis Sci.* 2007;52(2):589-593.
4. D'Anci KE et al. *Appetite.* 2009;52(1):96-103.
5. Ho WV et al. *Cancer Res.* 2011;71(13):4484–4493.

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Evolution of ketogenic diets (KD)

1920s – 1940s
KD for treatment of epilepsy [1]

1960s
Ketones as alternative fuel for brain [2]

1960/70s
Metabolism during starvation and ketones studies [3]

1971
MCT oil as treatment for epilepsy [4]

1980s
Impaired brain glucose uptake discussed in Alzheimer's Disease [5]

1980 and 1983
KD and exercise with no loss of performance after adaptation period [6]

1990-2000s
Continued interest and animal work on ketone in brain and role in cognition and aging – lack of human interventions [7]

2000s
Renewed interest in low carbohydrate approaches grow in popularity for weight reduction [8]

~2000s onwards
Renewed interest in KD for epilepsy, larger trials in children and adults and clinical guidelines [9]

2000s/2010s
Growing literature and interest on KD in weight management and metabolic health including cardiometabolic risk markers, insulin resistance and type 2 diabetes [10]

2010s
Meta-analysis on KD in animal models of cancer indicates potential [11]

2012
Beta-hydroxybutyrate esters show safety in human subjects [12]

2017
Systematic review of KD in cancer indicates potential. Clinical evidence is necessary [13]

Emerging Science
Potential benefits of KD on lifespan and health span. Human studies on exogenous ketone products [14]

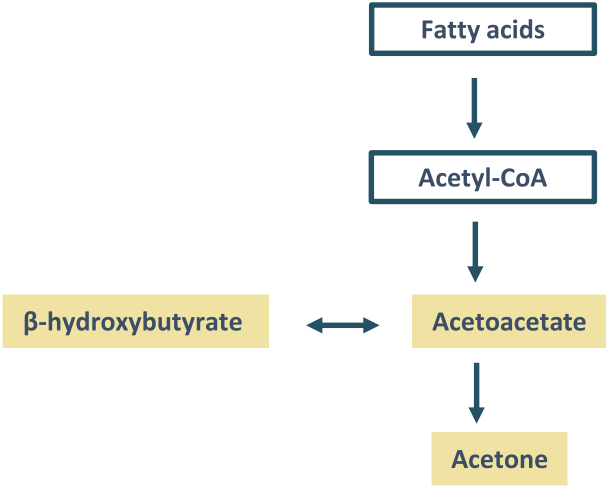
1. Wheless JW *Epilepsia* 2008;Suppl8:3-5.
2. Owen OE et al. *J Clin Investig.* 1967;46(10):1589-1595.
3. Cahill GF. *Ann Rev Nutr.* 2006;26:1-22.
4. Huttenlocher PR et al. *Neurology* 1971;21(11):1097-1103.
5. Hoyer et al. *J Neurol*. 1988;235:143–148.
6. Phinney SD et al. *Metab.* 1983;32(8):757-768.
7. Kashiwaya et al. *PNAS.* 2000;97(10):5440-5444.
8. Volek & Westman. *Cleve Clin J Med.* 2002;69(11):849-853.
9. Lefevre et al. *Pediatrics.* 2000;105(4):e46.
10. Paoli et al. *Eur J Clin Nutr.* 2013;67:789–796.
11. Seyfried T et al. *Biochim Biophys Acta.* 2011;1807(6):577-594.
12. Clarke K et al. *Regul Toxicol Pharmacol.* 2012;63(2).
13. Erickson N et al. *Med Oncol.* 2017;34(5):72.
14. Newman JC et al. *Cell Metab.* 2017;26:547-557.

What are ketone bodies and how are they produced?

- Production of ketone bodies in the liver is **a normal physiological process**

- When glucose availability is low (for example during fasting, prolonged exercise, or when following a low carbohydrate diet plan), and the body utilizes fat to produce ketone bodies which are used as an alternative fuel source

- The main endogenous ketone bodies are **acetone, acetoacetate and beta-hydroxybutyrate (βHB)**[1-2]



1. Prins ML. *J Cereb Blood Flow Metab.* 2008;28(1):1-16.
2. Paoli A et al. *Eur J Clin Nutr.* 2013;67(8):789–796.

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What is ketosis?

- When ketone bodies accumulate in the bloodstream (>0.5 mmol/L), causing a metabolic state called ketosis
- The most efficient approach that results in nutritional ketosis is following **a ketogenic diet**[1]

1. Paoli A et al. *Eur J Clin Nutr.* 2013;67(8):789–796.

What is a ketogenic diet?

- Low carbohydrate (<50g/day)
- High fat (generally ~70% daily energy)*
- Adequate protein (~20% daily energy)*

- Some clinical indications require more strict adherence (e.g. epilepsy)

* Depending on overall kcal intake and physical activity

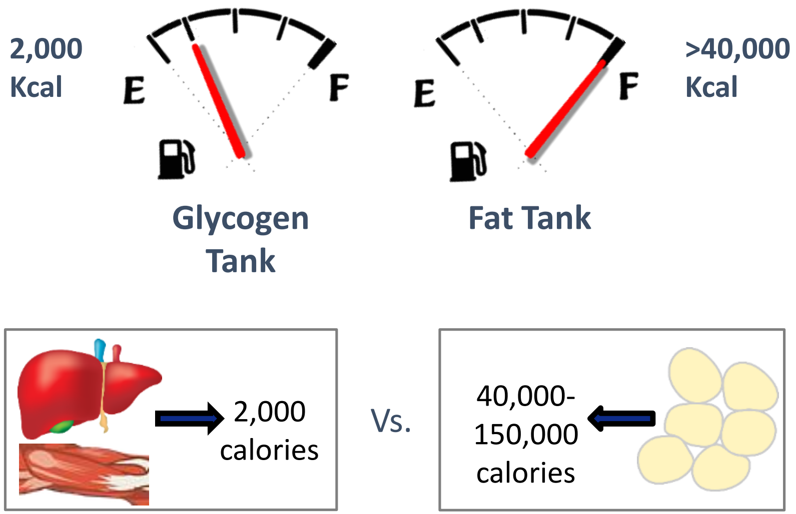
Adapted from: Paoli A et al. *Eur J Clin Nutr.* 2013;67(8):789–796.

β-hydroxybutyrate (βHB): much more than an energy source

- In addition to acting as an energy molecule, βHB has a variety of **cell signaling functions**, highlighting its broad regulatory role
- For instance, βHB can modulate **epigenetic mechanisms** and interact with cell surface receptors
- These mechanisms likely play a large role in mediating βHB's effects on **cellular protection and reduced oxidative stress**
- These regulatory functions serve to link the outside environment to **cellular function and gene expression**, highlighting its **implications for the pathogenesis and treatment of metabolic diseases**

Newman JC et al. *Diab Res Clin Pract.* 2014;106(2):173-181.

Which fuel tank do you want to access?



Adapted from: Volek & Phinney. *The Art and Science of Low-Carbohydrate Performance*. 2012.

- **Limited energy stored as glycogen** (liver and muscle)
- Fat deposits provide large energy stores
- High carbohydrate diets can reduce the metabolic flexibility needed to utilize fat deposits following glycogen depletion
- **Keto-adaptation promotes access to fat deposits as fuel source**

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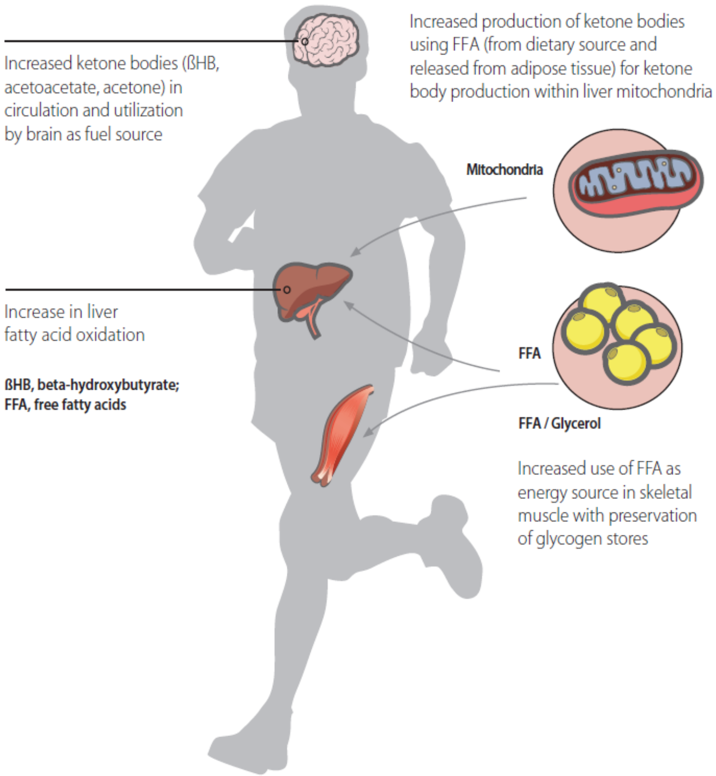
The metabolic adaptation (keto-adaptation) that occurs with a ketogenic diet

Ketogenic diet
- Low carbohydrate
- High fat
- Adequate protein

→

Reduced circulating glucose and insulin due to reduced dietary carbohydrate intake

→



Ketogenic diet’s impact on:

Weight management

Cardiometabolic risk markers

Insulin resistance

Type 2 diabetes

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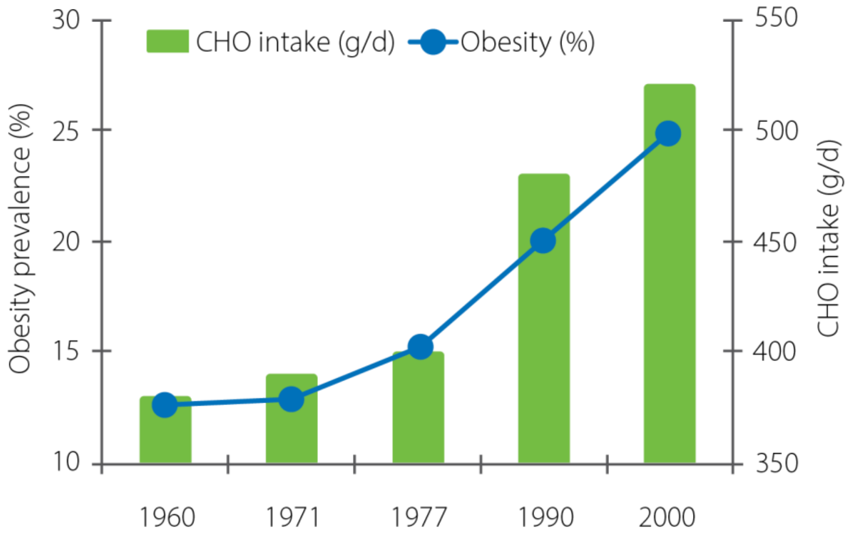
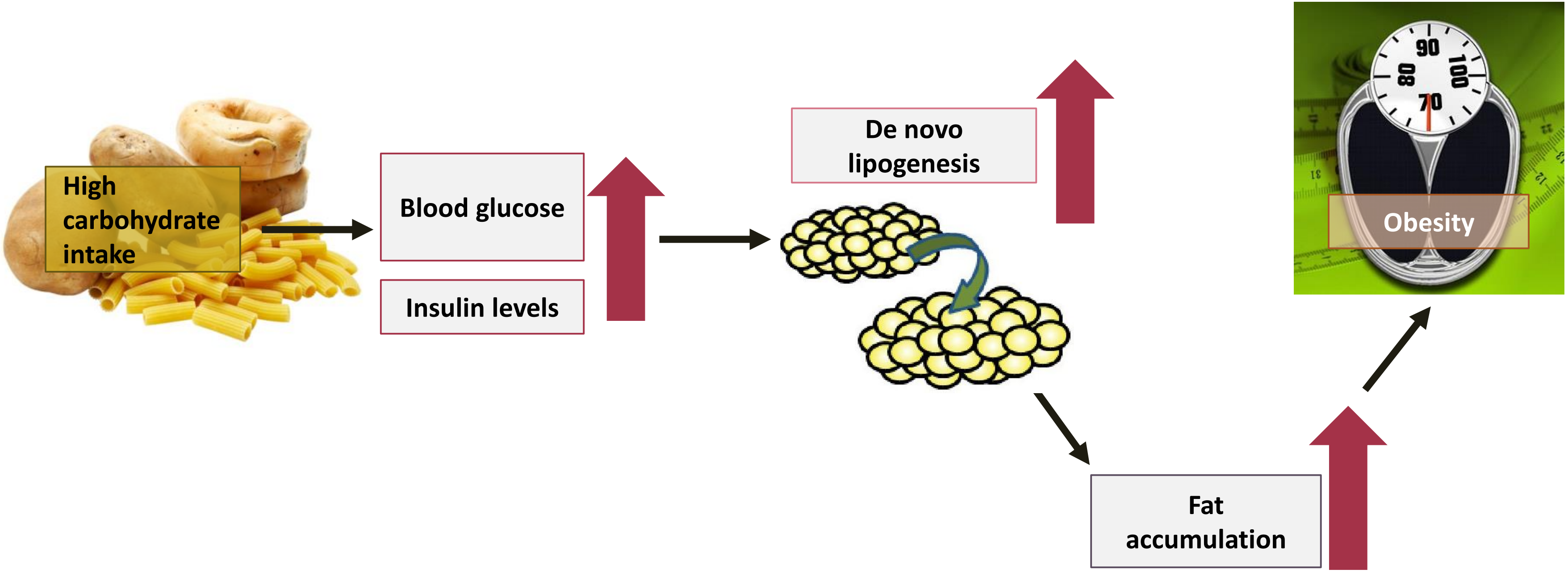
Carbohydrate intake and obesity prevalence over time in the US between 1960 and 1997

Prevalence of obesity and diabetes increased proportionately to the increase in consumption of refined carbohydrates in the US



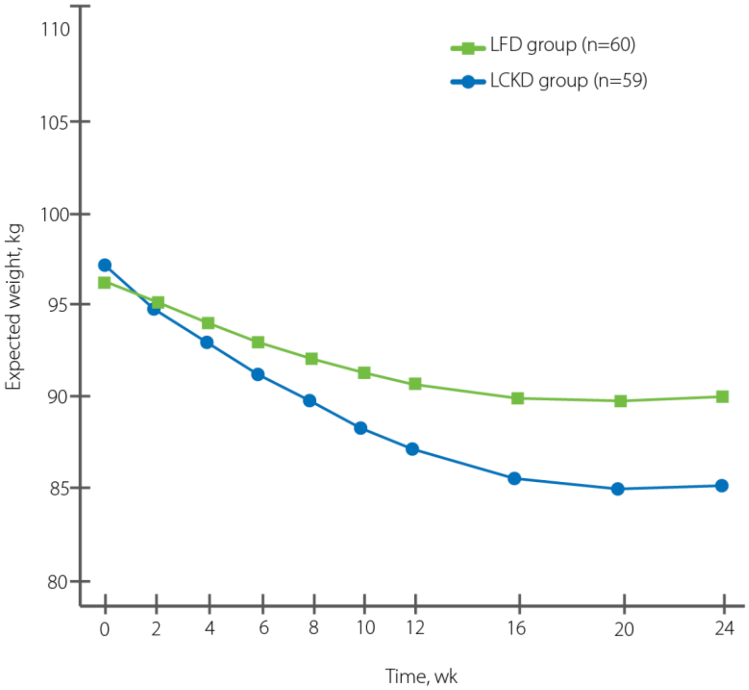
Adapted from: Gross LS et al. *Am J Clin Nutr.* 2004;79(5):774-779.

Link between high carbohydrate intake and onset of obesity



Can ketogenic diets be used for weight management?

- In subjects with BMI >30kg/m^2, intervention with:
  - LCKD: Energy-reduced, low-carbohydrate ketogenic diet or
  - LFD: Low-fat diet
- Over 24 weeks, the change in body weight was −12.0 kg (95% CI, −13.8 to −10.2 kg) in the LCKD group compared with −6.5 kg (95% CI, −8.4 to −4.6) in the LFD group
- **61% of recipients on LCKD lost >10% of their initial body weight at 24-weeks**



Adapted from: Yancy WS et al. *Ann Intern Med.* 2004;140(10):769-777.

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Change in appetite in response to ketogenic low carbohydrate diet

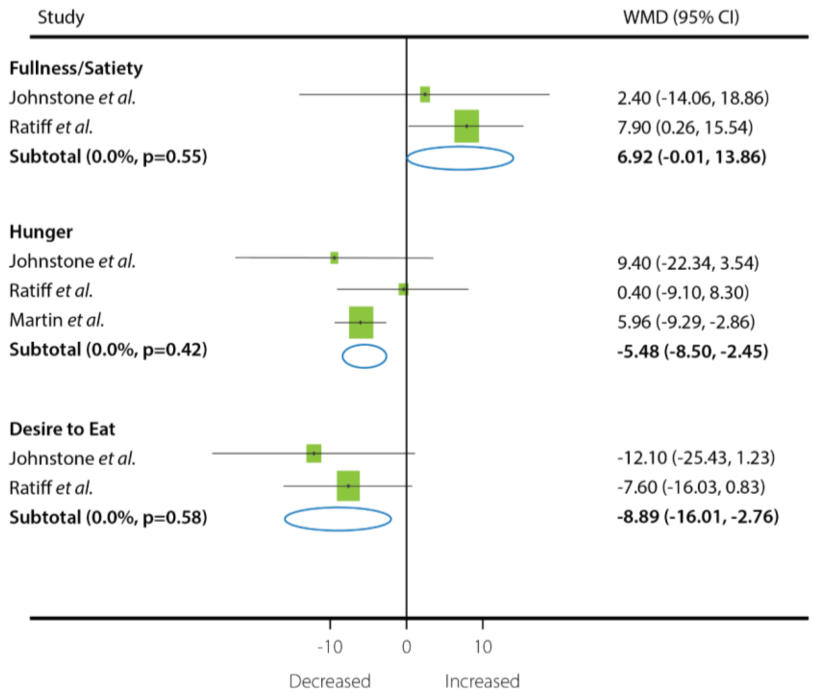
Method

- Systematic review and meta-analysis of ketogenic diets*
- Primary outcome assessed was subjective measures of appetite using visual analogue scale (VAS) data

Conclusions

- ***Individuals following ketogenic diet were significantly less hungry and had reduced desire to eat when compared with baseline values. Furthermore, there was no significant increase in hunger following ketogenic diet.***
- **This may help facilitate adherence to lower kcal intakes**

*defined as those resulting in raised fasting β-hydroxybutyrate to ≥0.3mM, positive urinary ketone dipstick or dietary prescription consistent with inducing ketosis



Adapted from: Gibson AA et al. *Obes Rev.* 2015;16(1):64–76.

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The effectiveness of ketogenic diet to combat the adverse metabolic pathologies of obesity

30 adults diagnosed with MetS—randomly assigned to one of 3 groups—10 wk

Sustained ketogenic diet no exercise	Standard American diet (SAD)—no exercise	SAD 3-5 days per week of exercise (30 min)

Results

The change over time from week 0 to week 10 was significant in the ketogenic group for **weight, body fat percentage, BMI, HbA1c and ketones**

Gibas MK et al. *Diab Metab Syndr.* 2017;11(1):385-390.

How ketogenic diets regulate obesity and its associated pathologies?

Weight loss →

- Reduction in appetite and hunger
- Reduction in lipogenesis
- Increased lipolysis
- Increased thermic effect of proteins

Diabetes →

- Reduction of HbA1c, blood glucose and insulin levels
- Reversal of hepatic insulin resistance

Cardiovascular risk parameters →

- Reduction of endogenous cholesterol synthesis
- Reduction of blood cholesterol and TGs
- Increased LDL particle size
- Reduction of blood insulin levels

Adapted from: Paoli A et al. *Eur J Clin Nutr.* 2013;67(8):789–796.

Ketogenic diet's impact on:

Athletic performance

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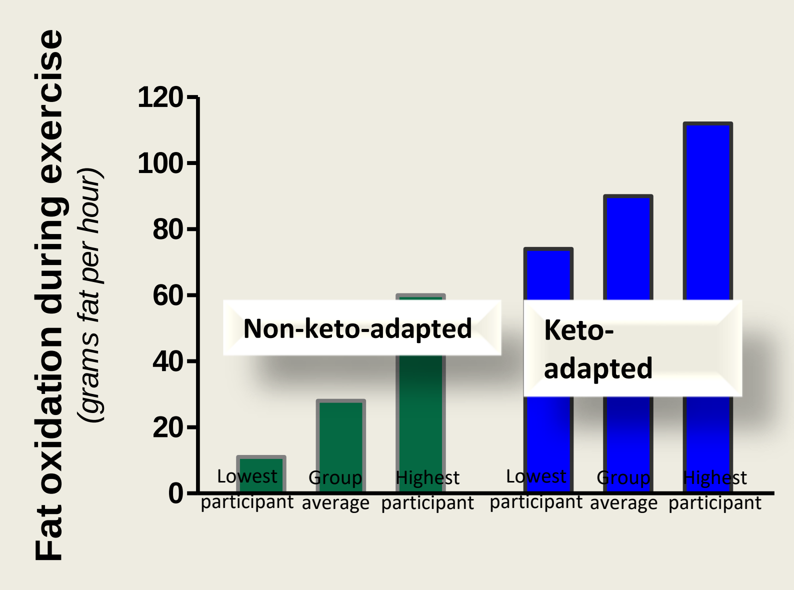
Keto-adaptation enhances endurance performance and body composition in athletes

- Keto-adaptation **improves endurance capacity** and **improves fat mobilization and oxidation** during exercise performance[1,2]
- Liver and muscle **glycogen deposits are maintained**, attenuating glycogen depletion observed in athletes consuming high-carbohydrate diets[1]
- Keto-adaptation **improved aerobic and anaerobic exercise capacity, as well as body composition** in endurance athletes



Adapted from: Volek JS et al. *Eur J Sport Sci.* 2015;15(1):13-20.

1. Volek JS et al. *Eur J Sport Sci.* 2015;15(1):13-20.
2. McSwiney FT et al. *Metab.* 2018;81:25-34.

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Ketogenic diet’s impact on:

Fuel for the brain

Alzheimer’s disease

Cognition and aging

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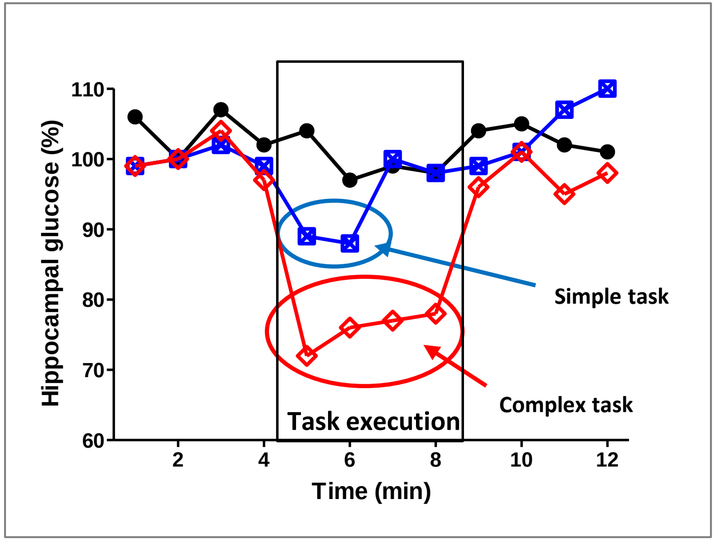
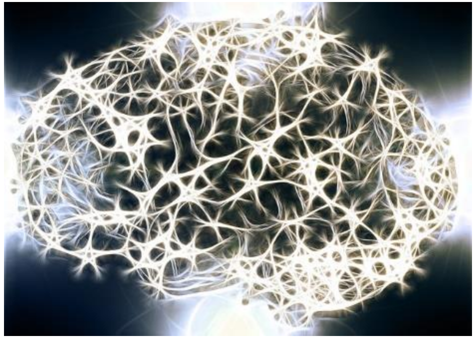
The human brain is extraordinarily expensive

- The human brain comprises 2% of body mass, while requiring approximately 25% daily energy demands (500 kcal)[1]
- **Despite its significant energy requirements, the brain has limited capacity to store glucose**
- The hippocampus is a brain area associated with the execution and retention of learning and memory processes



Adapted from: McNay EC et al. *PNAS.* 2000;97(6):2881-2885.

- During the execution of cognitively demanding tasks, a decrease in hippocampal glucose levels is observed[2]
- More complex tasks deplete hippocampal glucose levels further
- ***Cognitive performance is limited by fuel availability in the hippocampus***



1. Mink JW et al. *Am J Physiol.* 1981;241(3):R203-212.

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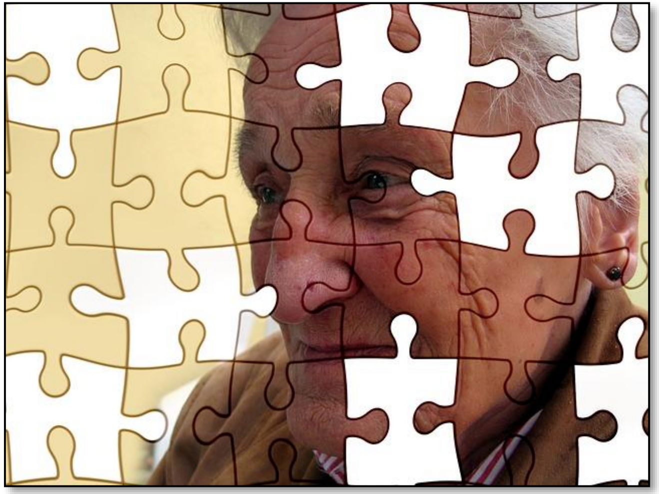
Impaired brain glucose utilization and cognitive decline

The healthy young brain relies solely on glucose to obtain energy for its functional and structural needs[1]



During healthy aging, brain **glucose uptake is 10-15% lower and can be up to 35% lower in certain brain areas in neurological disorders** such as Alzheimer's Disease (AD)[1-5]

This hypometabolism has led researchers to coin the term 'Type 3 Diabetes' when referring to AD

Brain uptake of ketones appears to remain normal in the brains of patients with Alzheimer's Disease[5]

1. Hoyer S. *Ann NY Acad Sci.* 1991;640:53-58.
2. Nugent S et al. *Neurobiol Aging.* 2014;35:1386-1395.
3. Mosconi L et al. *Neurobiol Aging.* 2008;29:676-692.
4. Castellano C et al. *J Alzheimer's* Dis. 2015;43(4):1343-1353.
5. Cunnane S et al. *Front Mol Neurosci.* 2016;9:53.

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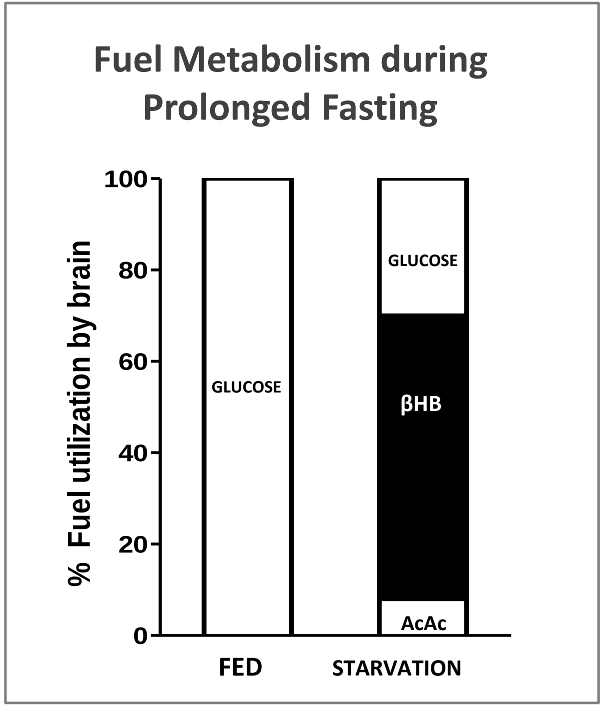
Can the brain use ketone bodies?

- Common misconception: brain can only use glucose
- Ketone bodies are the main alternative source of energy for the brain
- Both rodent and human studies have shown **increased uptake of ketone bodies by the brain**[1,2] following:
  - ✓ Peripheral infusion of ketones
  - ✓ Prolonged fasting
  - ✓ Ketogenic diet

1. Pifferi F et al. *Epilepsia.* 2008;14(2):51-58.
2. Cunnane S et al. *Front Mol Neurosci.* 2016;9:53.

Can the brain use ketone bodies?

- When obese subjects underwent prolonged fasting (water access only for 4 to 6 weeks), researchers were able to investigate cerebral energy metabolism during nutrient (glucose) deprivation
- They observed that **up to 70% of brain's energy demands were provided by ketone bodies** available in circulation (blood) and taken up by the brain



Adapted from: Owen OE et al. *J Clin Invest* 1967;46(10):1589-1595.

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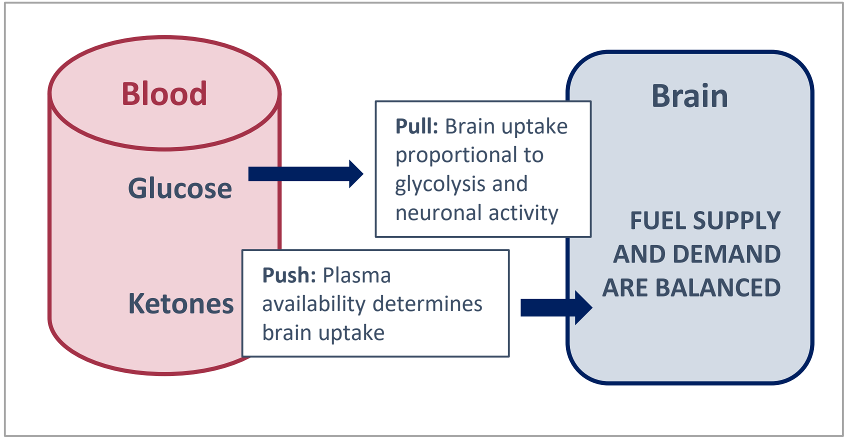
Can the brain use ketone bodies?

- Higher circulating levels of ketone bodies result in **higher brain uptake and utilization of ketones** for its energy demands[1]
- **Preserved uptake and utilization of ketone bodies** in the brains of mild cognitively impaired (MCI) patients, whereas glucose uptake and utilization decreases 20-30%[1-5]

***'Push and Pull'* mechanism comparing brain uptake of ketones vs glucose**



Adapted from: Cunnane S et al. *Front in Mol Neurosci.* 2016;9:53.

1. Hoyer S. *Ann NY Acad Sci.* 1991;640:53-58.
2. Nugent S et al. *Neurobiol Aging.* 2014;35:1386-1395.
3. Mosconi L et al. *Neurobiol Aging.* 2008;29:676-692.
4. Castellano C et al. *J Alzheimer's Dis.* 2015;43(4):1343-1353.
5. Cunnane S et al. *Front Mol Neurosci.* 2016;9:53.

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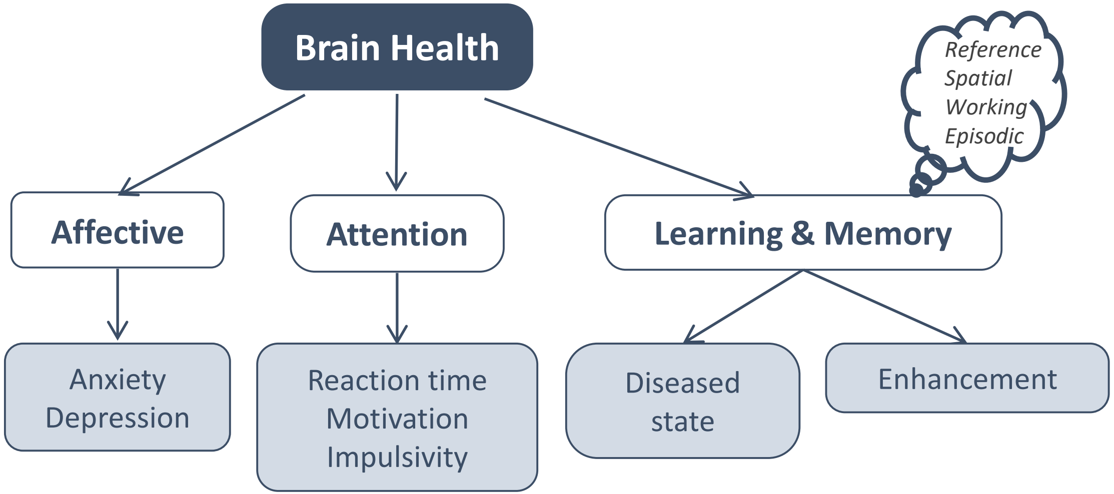
Brain health comprises more than memory

- Emerging science suggests that *optimizing cerebral energy metabolism with ketone bodies* may benefit a wide array of neurological conditions[1]
- Research groups have recently started investigating the *potential therapeutic benefits* of ketogenic diets on neurodevelopmental and affective disorders[1,2]
- ***Subjective reports and anecdotal evidence*** **suggest a beneficial effect of ketogenic diets on mood[3], anxiety and attention and further research is needed to validate these claims**



1. Stafstrom CE et al. *Front Pharmacol.* 2012;3:59.
2. Murphy P et al. *Biol Psych.* 2004;56:981-983.
3. El-Mallakh RS et al. *Med Hyp.* 2001;57(6):724-726.

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Testing and Monitoring

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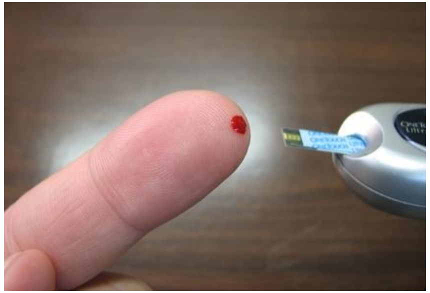
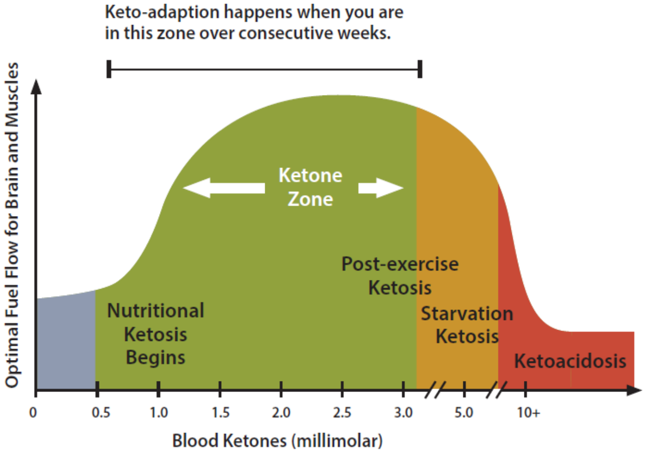
How to test ketone levels and monitor ketosis?

- **Urine:** measures urinary excretion of acetoacetate—although this is the easiest and most common test, it may provide false negative results following keto-adaptation
- **Blood:** finger stick measuring circulating βHB levels—most accurate
- **Breath:** measures breath acetone





Adapted from: Volek JS & Phinney SD et al. *The Art and Science of Low Carbohydrate Performance.* 2012.

- **Optimal levels of ketosis**
  - Overnight fasting: 0.2-0.5mM
  - Nutritional Ketosis (KD): 0.5-3.0mM
  - KD with exogenous ketones: 0.5-8.0mM
  - Ketoacidosis: >10mM
- **Glucose Ketone Index (GKI):**[1]

$$\frac{[\text{glucose (mg/dl)} / 18]}{\text{ketones (mM)}}$$

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1. Meidenbauer JJ et al. *Nutr Metabol.* 2015;12:12.

Supporting factors for ketogenic lifestyle

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Supporting factors for ketogenic lifestyle

- With growing popularity of low-carbohydrate and ketogenic diets, interest has increased in exploring additional nutritional strategies and solutions to facilitate:
  - Achieving or sustaining ketosis
  - Keto-adaptation process
  - Convenience to ensure long-term adherence to ketogenic program
- Examples considered:
  - Exogenous ketones (βHB)
  - Medium chain triglycerides (MCT)

Exogenous ketone (βHB) salt

- Exogenous ketone supplementation **induces acute ketosis**
- Anecdotally, keto salts have been **associated with a reduction of the adverse events observed in patients**, and therefore, can facilitate adherence to ketogenic diet
- In animal models, acute and chronic oral βHB salts:
  - Increase plasma ketone levels
  - *Average ketone levels correlated positively with HDL-C and negatively with blood glucose levels, adipocyte volume and serum lipolysis products*[1-2]
- Combination of βHB salt + MCT:
  - In rodents, combining βHB salt and MCT sustained ketosis for longer periods than βHB administration alone[1]

1. Kesl et al. *Nutr Metab (Lond).* 2016;13:9.
2. Caminhotto RO et al. *Nutr Metab (Lond)*. 2017;14:31.

Limited human intake data for βHB salt[1-3]

Rationale and objectives of Functional Medicine Research Center (FMRC) study

- ***Primary objective***
  - To characterize the change in circulating ketone bodies over a 4-hour period after consumption of varying doses of βHB, compared with placebo control.
- ***Secondary objective***
  - To assess tolerance and adverse events in response to acute intake of each formulation.

1. Stubbs BJ et al. *Front Physiol.* 2017;8:848.
2. O'Connor A et al. *J Nutr Health Food Eng.* 2018;8(4):324-328.
3. Fischer T et al. *J Nutr Metab.* 2018;23:9812806.

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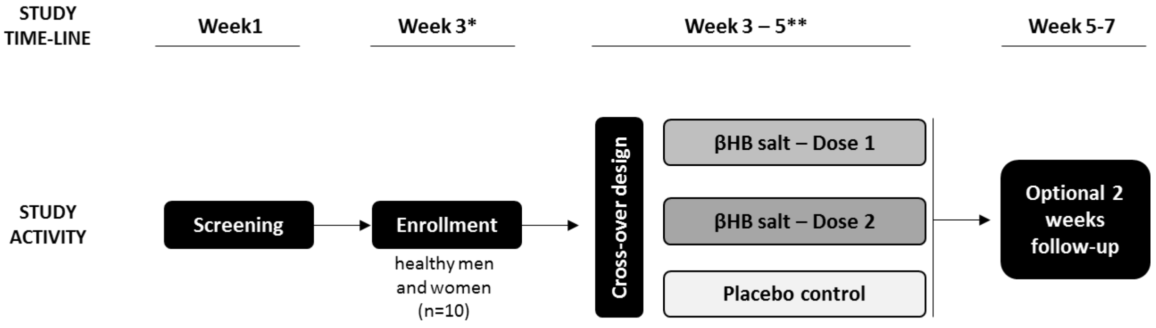
Study Design[1]



Each treatment arm completed in random order. Each treatment delivered on a separate study day, each separated by a wash-out period of 2-7 days

*Enrollment must take place within 2 weeks of screening date
**Each study visit can be separated by up to a 1 week wash out period (minimum 2 days)

PR#	Treatment	βHB dose
PR-761	βHB salt – Dose 1	11.7g βHB
PR-763	βHB salt – Dose 2	5.85g βHB
PR-762	Placebo control	No βHB

Subject characteristics	Mean	SD
Age (years)	31.4	11.96
Fasting βHB (mmol/L)	0.17	0.08
Body mass index (BMI) (kg/m^2)	23.7	1.28

- 10 generally healthy men and women completed all 3 study arms
- All participants were Caucasian
- 2 men and 8 women were enrolled and included in the final analysis

On basis of reported medical history and results of screening bloods (liver and renal function tests, comprehensive metabolic panel)

1. O'Connor A et al. *J Nutr Health Food Eng.* 2018;8(4):324-328.

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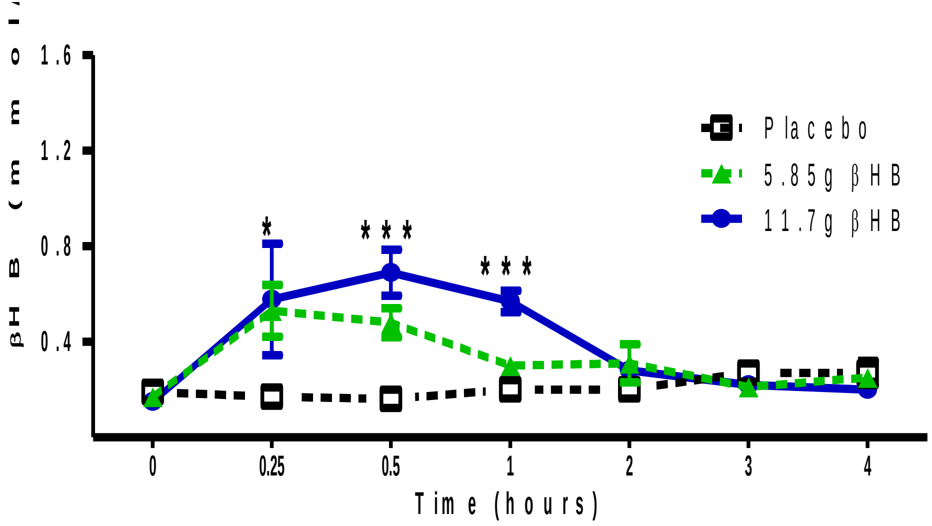
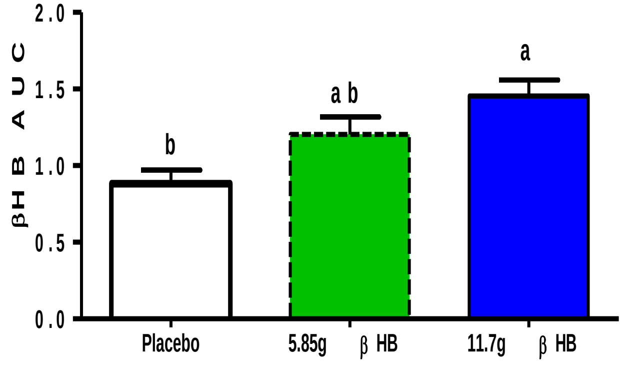
Acute intake of βHB salt increases circulating βHB concentrations within 15 minutes[1]



Differences between groups assessed with Friedman test. *'s denote significant (p<0.05) main effect indicated



Data displayed as mean ± SEM. Differences between groups assessed with Friedman test, with Dunnett's test. Between-treatment differences denoted as [a, b] with treatments not sharing a letter considered significantly different (p<0.05).

Additional considerations

- **No changes in blood glucose** levels were observed following acute intake of βHB salt
- Adverse events: only one subject reported mild AE (loose stool) following intake of dose 1

1. O'Connor A et al. *J Nutr Health Food Eng.* 2018;8(4):324-328.

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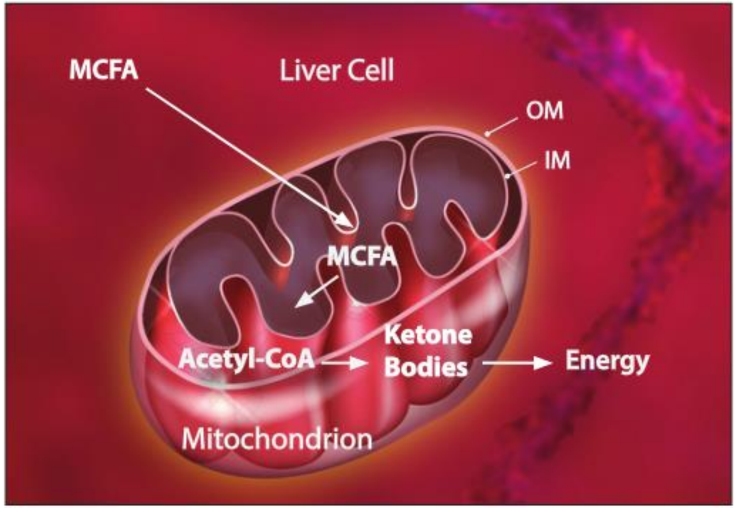
Choosing the right fat for ketogenic programs

How do medium chain triglycerides (MCT) increase ketone bodies?

- MCTs contain 6 to 12 carbon atoms, including caproic acid (C6:0), caprylic acid (C8:0), capric acid (C10:0), and lauric acid (C12:0)
- In the liver, MCFA **can freely cross the inner mitochondrial membrane**, while other types of fatty acids must enter in a more regulated manner
- This more rapid absorption of MCFA into **the inner mitochondrial space <u>transiently</u> increases ketone body formation**[1]



MCFA= medium chain fatty acids, OM = outer membrane, IM = inner membrane

Adapted from: 1. Bach AC et al. *Am J Clin Nutr*. 1982;36(5):950-962.

Effects of MCTs on weight loss, body composition, satiety and cognition:

- A meta-analysis of randomized controlled trials has shown that replacement of long-chain triglycerides (LCT) with MCT (combination of C8:0 and C10:0) in the diet resulted in **greater reduction in body weight and more favorable changes in body composition in both healthy and overweight individuals**[1]
- MCTs supplementation (C8:0 and C10:0) **increased energy expenditure and lipid oxidation compared with LCTs**[2-3]
- In healthy and overweight men, supplementation with MCT **increased satiation at the next meal and reduced food intake compared to LCT** [3-4]
- Ketones derived from MCTs **improved cognition in diabetic and AD patients and attenuate neurodegeneration in mouse models of ALS, MS and AD**[5-7]

1. Mumme K et al. *J Acad Nutr Diet.* 2015;115:249-263.
2. St-Onge M et al. *Obes Res.* 2003;11(3):395-402.
3. Van Wymelbeke V et al. *Am J Clin Nutr.* 2001;74:620-630.
4. St-Onge M et al. *Eur J Clin Nutr.* 2014;68(10):1134-1140.
5. Zhao W et al. *PLoS One.* 2012;7(11):e49191.
6. Kim DY et al. *PLoS One.* 2012;7(5):e35476.
7. Henderson S et al. *Nutr Metab.* 2009;6:3.

Majority of human clinical studies have been performed with the mixture of C8+C10

Outcomes	C8	C10	C8+C10
Increased circulating ketones	Henderson S et al. *Nutr Metab.* 2009;6:31. Vandenberghe C et al. *Curr Dev Nutr* 2017;1:1-5.	Vandenberghe C et al . *Curr Dev Nutr.* 2017;1:1-5.	Courchesne-Loyer A et al. *Nutr.* 2013;29:635-640. Ota M et al. *Psychopharmacol.* 2016;233(21-22):3797-3802. Tsuji H et al. *J Nutr.* 2001;131(11):2853-2859. Vandenberghe C et al. *Curr Dev Nutr.* 2017;1:1-5.
Improved weight loss and body composition, increased satiety	St-Onge M et al. *Eur J Clin Nutr* 2014;68(10):1134-1140.		Mumme K et al. *J Acad Nutr Diet.* 2015;115:249-263. St-Onge M et al. *Obes Res.* 2003;11(3):395-402. Tsuji H et al. *J Nutr.* 2001;131(11):2853-2859. Van Wymelbeke V et al. *Am J Clin Nutr* 2001;74:620-630. Krotkiewski M et al. *Int J Obes.* 2001;25:1393-1400.
Enhanced cognitive performance	Henderson S et al. *Nutr Metab.* 2009;6:31. Henderson S et al. *BMC Med Genet.* 2011;12:137.		Page KA et al. *Diabetes.* 2009;58:1237-1244. Ota M et al. *Psychopharmacol.* 2016;233(21-22):3797-3802.

Additional actions including activation of PPARγ and improvements in mitochondrial efficiency have been demonstrated with both C8 and C10

Liberato MV et al. *PLoS One.* 2012;7(5):e36297.
Malapaka RRV et al. *J Biol Chem.* 2012;287(1):183-195.

Emerging science—separating fact from fiction

Headlines	Study findings	References
KD increases longevity	Preclinical studies on male mice show that KD *reduced midlife mortality*	Newman JC et al. *Cell Metab*. 2017;26:547-557. Roberts MN et al. *Cell Metab.* 2017;26:539-546.
KD induces mental clarity	Preclinical studies on male rodents show that *KD improves learning and memory outcomes in models of neurodegenerative diseases*	Kashiwaya Y et al. *Neurobiol Aging.* 2012;1-10. Reger M et al. *Neurobiol Aging.* 2004;25:311-314. Kim DY et al. *PloS ONE.* 2012;7(5):e35476. Zhao W et al. *PLoS ONE.* 2012;7(11):49191.
KD improves cognition	KD research has historically focused on *neurological disorders* whereas cognitive outcomes in healthy subjects have been *anecdotally* reported	Kashiwaya Y et al. *Neurobiol Aging.* 2012;1-10. Reger M et al. *Neurobiol Aging.* 2004;25:311-14. Kim DY et al. *PloS ONE*. 2012;7(5):e35476. Zhao W et al. *PLoS ONE.* 2012;7(11):49191.
KD and mood	Preclinical studies have shown *anxiolytic effects* associated with KD whereas few case reports have been published showing benefits in humans	Ari C et al. *Front Mol Neurosci.* 2016;9:137. El-Mallakh RS et al. *Med Hyp.* 2001;57(6):724-726. Bostock ECS et al. *Front Psychol.* 2017;8:43.
Collagen is necessary for ketogenic lifestyle and helps build muscle	Collagen contains only low levels of the essential amino acids necessary for muscle protein synthesis. It can, however, be used as *adjunct wellness support* due to a number of benefits associated with collagen supplementation	Fu Y et al. *Crit Rev Food Sci Nutr.* 2018;2:1-17. Rodriguez MIA et al. *J Cosmet Dermatol.* 2018;17:20-26. Juher TF et al. *Nutr Hosp.* 2015;18:32Suppl1:62-66.

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Collagen supplementation as adjunct wellness support to ketogenic lifestyle

- Preclinical and clinical studies show that **supplementation with collagen**:
  - Supports **healthy joints in athletes** (both healthy and with knee problems)[1,2]
    - Improvements in activity-related pain intensity
    - Reduction of risk of joint deterioration
  - Supports **bone health**[3,4]
    - Stimulates the proliferation and differentiation of osteoblasts
    - Increased bone mineral density in postmenopausal women
  - Supports **extracellular matrix and cartilage**[5,6]
    - Stimulation of chondrocytes to synthesize extracellular cartilage matrix
    - Increased collagen synthesis and decreased extracellular matrix disruption
  - Improves **age-related effects on skin**[7,8]
    - Increased skin hydration and elasticity
    - Reduced appearance of eye wrinkle

1. Zdzieblik D et al. *Appl Physiol Nutr Metab.* 2017;42(6):588-595.
2. Clark KL et al. *Curr Med Res Opin.* 2008;24(5):1485-1496.
3. Daneault A et al. *Crit Rev Food Sci Nutr.* 2017;57:1922-1937.
4. König D et al. *Nutrients.* 2018;10(1)pii:E97.
5. Oesser S and Seifert J. *Cell Tissue Res.* 2003;311:393-399.
6. Flechsenhar K et al. *J Arthritis.* 2016;5(5):1000219.
7. Proksch E et al. *Skin Pharmacol Physiol.* 2014;27:47–55.
8. Proksch E et al. *Skin Pharmacol Physiol.* 2014;27:113–119.

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Types of Fasting Protocols

Fasting Protocol	How to implement	Benefits
Time Restricted / Intermittent Fasting (IF)	6-8h daily eating window (> 16h fast)	• Improved glycemic regulation and reduced CRP[1] • Aligned with circadian rhythms[2]
Alternate Day Fasting *(also considered a form of IF)*	No caloric intake (food or drinks) on fasting days, which alternate with *ad libitum* eating days	• Improved markers of oxidative damage and inflammation in asthma patients[3] • Body fat, blood pressure, and glucose metabolism improved in obese subjects[4, 5]
5:2 Fasting *(also considered a form of IF)*	*Ad libitum* eating 5 days and restricted calories (500-600 kcal) for 2 days (can be consecutive, but not necessarily)	• Reduced oxidative stress and inflammation in overweight women at risk for breast cancer[6] • Reductions in body weight and fat and improved mood in elderly men[7]
Prolonged Fasting	No caloric food or drinks for ≥ 72h	• Reduction in circulating glucose, insulin, and IGF-1 levels[8] • Reduced side effects when chemotherapy combined with fasting[9] • Decreased blood pressure in hypertensive subjects[10] • Decreased pain and inflammation in RA patients[11]
Short-term Fasting	No caloric food or drinks for < 72h	• 5-fold increase in GH[12] and improved BDNF[13]
Fasting Mimicking Diet (FMD)	Diet consisting of plant-based, low protein, reduced caloric intake for 3 cycles of 5 days/month	• Improved metabolic parameters associated with age-related conditions[14, 15] • Improved overall quality of life scores in multiple sclerosis patients and reduced inflammatory profile in preclinical model[16] • Increased tumor sensitization to chemotherapy[17]

1. Marinac CR et al. *Cancer Epidemiol Biomarkers.* 2015;24(5):783-789.
2. Longo VD et al. *Cell Metab.* 2016;23(6):1048-1059.
3. Johnson JB et al. *Free Radic Biol Med.* 2007;42(5):665-674.
4. Klempel MC et al. *Metab.* 2013;62(1):137-143.
5. Varady KA et al. *Am J Clin Nutr.* 2009;90(5):1138-1143.
6. Harvie MN et al. *Int J Obes.* 2011;35(5):714-727.
7. Teng NI et al. *Physiol* Behav. 2011;104(5):1059-1064.
8. Thissen JP et al. *Endocr* Rev. 1994;15(1):80-101.
9. Safdie FM et al. *Aging.* 2009;1(12);988-1007.
10. Goldhamer AC et al. *J Altern Complement Med.* 2002;8(5):643-650.
11. Muller H et al. *Scand J Rheumatol.* 2001;30(1):1-10.
12. Hartman M et al. *J Clin Endocrinol Metab.* 1992;74(4):757-65.
13. Mattson MP *Ageing Res Rev.* 2012;11(3):347-352.
14. Brandhorst S et al. *Cell Metab.* 2015;22(1):86-99.
15. Wei M et al. *Sci Transl Med.* 2017;9(377):eaai8700.
16. Choi IY et al. *Cell Rep.* 2016;15(10):2136-2146.
17. Di Biase S et al. *Cancer Cell.* 2016;30(1):136-146.

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Fasting and Keto

- ***Positive metabolic and cellular effects*** that affect oxidative damage and inflammation, optimize energy metabolism, and enhance cellular protection[1]
- ***Increased metabolic flexibility*** and facilitates switch to fat-burning[2]
- ***Hormesis concept:*** adaptive response to moderate stress resulting in increased cytoprotective and restorative mechanisms[3]

Benefits to a ketogenic lifestyle

- ***Increased lipolysis***[2] possibly reduces time needed for keto-adaptation process
- ***Reduced glucose and higher ketone levels****:* 12-24h fasting depletes hepatic glycogen, leading to metabolic switch into fat-burning mode and utilization of ketones and fatty acids[2]
- By facilitating ketogenesis and reducing keto-adaptation time, it may shorten period of time with 'keto-flu' symptoms

Caution

- Fasting regimens have not been investigated in children, elderly, nor underweight individuals
- Fasting periods longer than 24h should be overseen by healthcare provider
- Proper intake of non-caloric fluids to ensure hydration
- Possible effects on circadian rhythms of endocrine and gastrointestinal systems

1. Brandhorst S et al. *Cell Metab.* 2015;22(1):86-99.
2. Reviewed in Longo VD et al. *Cell Metab.* 2014;19(2):181-192.
3. Mattson MP. *Crit Rev Toxicol.* 2008;38(7):633-639.

Emerging science—novel research areas

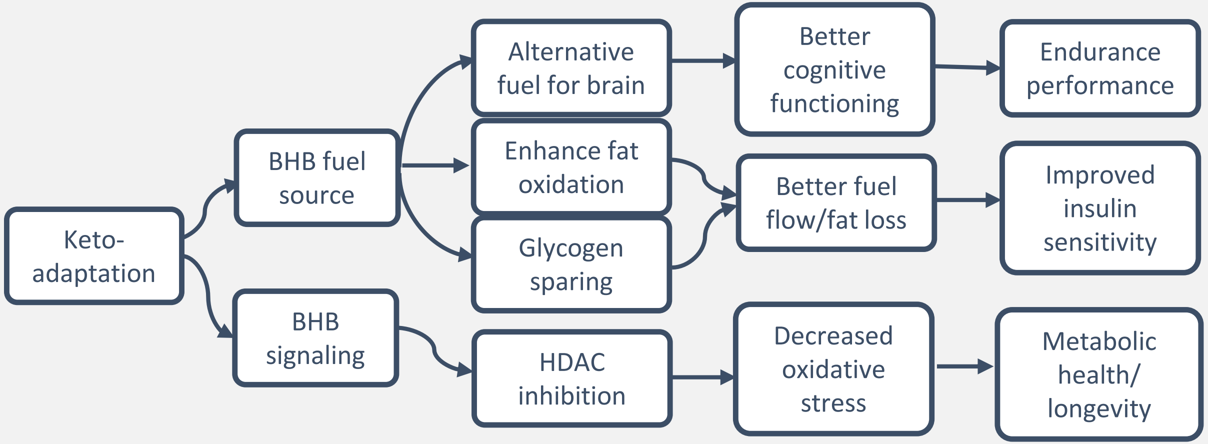
Healthy aging	Cognition	Stress	Microbiome
• Longevity • Reduce age-associated morbidity	• Augmentation • Prevention of decline • Biohacking	• Resilience • Prevention	• Gut-brain axis • Increased diversity

Clinical Applications of Therapeutic Ketosis – Where Are We?

Strong Evidence	Emerging Evidence
Weight Loss and Management	Type 1 Diabetes, NAFLD
Type 2 Diabetes, Cardiometabolic	PCOS
Inborn Errors in Metabolism (GLUT1DS, MADD, GSDII, PDHD, etc.)	Wound Healing, Inflammation
	Motor Function
	Brain Tumors, Cancer
Neurological Applications	
Epilepsy	Alzheimer's, Parkinson's
Dravet Syndrome	Autism, Angelman's
Lennox-Gastaut Syndrome	Kabuki Syndrome, Anxiety
Rett Syndrome	Neurotrauma
Doose Syndrome	Anesthesia Resistance
	CNS-OT

Adapted from: D'Agostino D. 2018.

In Summary



Adapted from: Volek JS et al. *Eur J Sport Sci.* 2015;15(1):13-20.

- ❑ **Ketogenic diets:**
  - ✓ Increase liver fat oxidation
  - ✓ Support weight management
  - ✓ Improve insulin sensitivity
  - ✓ Reduce hunger and increase both satiety and satiation
  - ✓ Likely beneficial for cognition
- ❑ **Ketone bodies:**
  - ✓ Efficient fuel source
  - ✓ Improve mitochondrial bioenergetics
  - ✓ Cellular signaling molecule
  - ✓ Preserved uptake by the brain

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