



Ketogenic Diet in Neuroscience

Nina Curvis, MS, RD, LD, CNSC
Abbott Northwestern Hospital

December 11, 2023




1



Objectives

- Understand how ketogenic diet therapy can improve outcomes for patients with epilepsy and status epilepticus
- Learn what ketosis is...and what it is not
- Discover implementation strategies for diet therapy
- Appreciate the importance of dietitian monitoring for this therapy


2



Useful vocabulary

- Carbs – ingested carbohydrate (incl starch, sugar), non-fat foods
 - Carb excipients – compounds that can block ketosis (ex: sugar alcohols, sugar substitutes, glycerol, maltodextrin, etc)
- Proteins – ingested protein, non-fat foods
- Fats – ingested fat (incl saturated, unsaturated, trans)
- Ratio – diet ratio of fat to non-fat foods used in ketogenic diet therapy
 - 3:1 = 3 gm fat for every 1 gm non-fat
- RSE = refractory status epilepticus, SRSE = super refractory status epilepticus


3



Ketogenic Diet

The myth, the legend


4



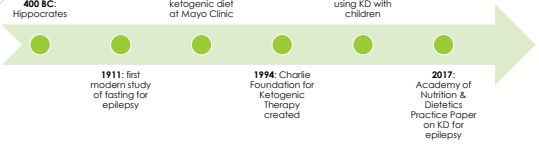
What is the ketogenic diet?

- High fat, moderate protein, low carb
- Promotes formation of ketone bodies to fuel brain, muscle, organs
- "Glucose-starving"
- Liver cannot use ketones for fuel
 - Still need small amount of carb in diet

5



Brief history of ketogenic diet



400 BC: Hippocrates

1911: first modern study of fasting for epilepsy

1921: Dr. Russel Wilder proposed ketogenic diet at Mayo Clinic

1934: Charlie Foundation for Ketogenic Therapy created

2008: first RCT using KD with children

2017: Academy of Nutrition & Dietetics Practice Paper on KD for epilepsy

6

"Oh, I've heard of Keto..."

- Ketogenic diet therapy is NOT the popular "Keto" fad diet

Ketogenic diet	"Keto" (fad diet)
High fat, very low carb, moderate protein	High fat, avoid carb
Diet ratio controlled to achieve ketosis	Usually don't achieve ketosis (too much protein)
Monitored by RD and medical team	Not monitored by healthcare professionals
Goal varies with medical diagnosis (seizure control, weight loss, blood sugar control, other)	Goal is usually weight loss or body toning

Types of ketogenic diets

- Classic ketogenic diet
 - 4:1 or 3:1 ratio
- Modified ketogenic diet
 - 2:1 or 1:1 ratio
- MCT Oil Diet
 - MCT as main fat source, up to 50-60% of calories

Adults cannot stay on 4:1 ratio (not enough protein)
4:1 is used primarily in pediatrics

Types of ketogenic diets

- Low Glycemic Index Diet (LGIT)
 - Originally a "pre-ketogenic" diet, found to reduce or eliminate seizures
 - Does not always achieve ketosis
- Modified Atkins Diet (MAD)
 - Emphasis on low carb intake, no strict ratios
 - Typically limited to 20-30 gm/day carb

Adults often have compliance concerns
MAD is best

Ketosis

Back to biochemistry!

Ketones (or ketone bodies)

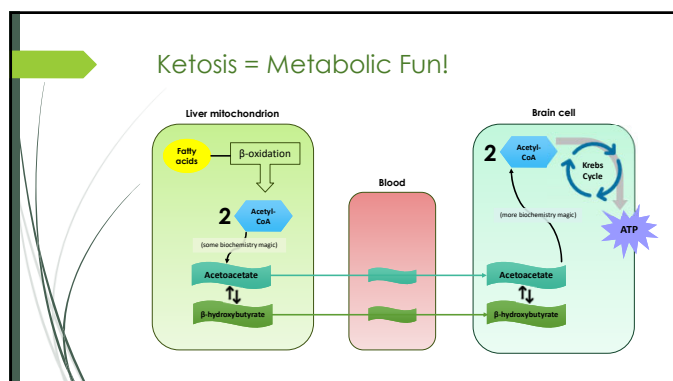
β-hydroxybutyrate (BHB)	<ul style="list-style-type: none"> Measured in blood – current ketosis, expensive Target range: 2-3 mmol/L in adults, not to exceed 5 mmol/L Affected by acute stress
Acetoacetate (AA or AcAc)	<ul style="list-style-type: none"> Measured in urine – past ketosis, cheap Target range: medium (40 mg/dL) to large (80-160 mg/dL) Affected by hydration status
Acetone (Ac)	<ul style="list-style-type: none"> Measured in the breath Not used much in US, expensive equipment, insurance doesn't cover Not affected by stress or hydration status

What is ketosis?

- Ketosis is the metabolic state in which the body uses ketone bodies for fuel instead of glucose
 - Can also be defined by BHB > 0.6 mmol/L

WHAT?

- Remember the Krebs / TCA / Citric Acid cycle...
 - Usually use glucose to run this for energy
 - In ketosis, ketone bodies are used instead



13

High BHB is ketoACIDosis, isn't it?

- Not necessarily, we need to look at other markers as well
- Ketosis:
 - BHB controlled, (adults ~2-3 mmol/L and <5 mmol/L)
 - Glucose controlled, lower than normal (adults ~50-80 mg/dL and >50 mg/dL)
- Ketoacidosis:
 - BHB uncontrolled (adults >0.6 mmol/L, sometimes gets over 5 mmol/L)
 - Glucose uncontrolled, higher than normal (into 500-600 mg/dL)

14

Ketogenic Diet Therapy

Bringing it all together

15

Goals of therapy – for epilepsy

- Status epilepticus: cessation of uncontrolled seizures
 - Ketogenic diet especially useful for RSE and SRSE
- Epilepsy (non-status): reduction of seizure burden & better quality of life
 - Some adults can even reduce # medications
- Note: I did not include a measurement of ketone levels!
 - We use target ranges for BHB (blood) or AA (urine)
 - If goals are met before reaching the target range, no need to push the diet further

16

Nutrition Considerations

- Nutritionals
 - Adequate energy – no long-term calorie restriction
 - Moderate protein (start at 1 gm/kg)
- Diet type determined by nutrition evaluation and goals of therapy
 - Most non-tube-fed adults do best with MAD
 - Tube-fed adults are often on 2:1 or 3:1 ratio
- Supplementation
 - Ca, Vit D, multivitamin
 - Evaluate need for: Se, Mg, Zn, Fe, Phos, K, various B-vitamins
 - Carnitine (often started later)

17

Monitoring

Labs	Ongoing	Meds
<ul style="list-style-type: none"> Lipid panel CMP CBC Amylase, lipase Vit D level Mg, Phos BHB Triglycerides Hgb A1c Blood glucose Pregnancy test* 	<ul style="list-style-type: none"> Hydration Acid/base balance Blood or urine ketones Blood glucose levels Weight Diet adherence Seizure control Cognitive function Quality of life 	<ul style="list-style-type: none"> IV – no dextrose Tabs instead of liquid Carb content of meds Anti-epileptics

18

Multidisciplinary Intervention

- Dietitian
 - Initial screening before diet initiation
 - Assign diet ratios (fat, carbs, protein) and fluid needs
 - Initial lab draws + follow up lab monitoring
 - Regular follow up to monitor progress toward goal and side effects of treatment
 - Extensive education with patient and/or family/caregivers
- MD
 - Refer for diet intervention / initiate protocol in hospital
 - Monitor medical status while on diet and assess for medical safety
 - Determine medication regimen and whether medication adjustments/reductions are appropriate while on diet therapy
 - Specialist evaluations as needed for comorbidities

19

Multidisciplinary Intervention

- Pharmacist
 - Assess medication for carb and carb excipients
 - Assist with adjusting formulation of medication to meet diet ratios (carb amount)
 - Change IV meds with dextrose to non-dextrose solutions
- Nurse
 - Measure ketosis (blood or urine)
 - Monitor blood sugar levels
 - Implement replacement protocol if blood sugar drops too low
 - Change out hygiene products for daily cares

20

Other neurologic disorders may benefit from ketogenic diet therapy

Migraines	Autism
Dementia	Depression
Alzheimer's disease	Bipolar disorder
ALS*	Mitochondrial disorders
Parkinson disease*	
Multiple sclerosis	
Brain tumors	
Brain trauma*	
Ischemic stroke*	

21

How does it work? (well, we have some theories...)

- Ketone bodies are neuroprotective
 - Raise ATP levels & reduce reactive oxygen species
 - Increase mitochondrial biogenesis – regulates synaptic function
 - BHB & Ac reduce spontaneous discharges of GABAergic neurons in rat models
- Ketogenic diet alters metabolism
 - Reduces metabolism of glucose
 - Reduces insulin levels
 - Reduces CNS aspartate levels / increases glutamate levels
 - Alters mitochondrial function/efficiency
- Ketogenic diet is associated with anticonvulsant effects
 - Neurons may resist depolarization

22

Okay, but is it safe?

- Yes*
 - High fat, low carb diets have not been shown to increase general risk of chronic disease
 - Cardiovascular disease risk has not been shown to increase on ketogenic diet regimens
 - Improves insulin-resistance
 - Medical work-up prior to diet initiation is very important!
 - All interventions come with risk – individual evaluation is key
 - *there are some contraindications and side effects

23

Contraindications & Symptoms

There's always a catch...

24

Contraindications

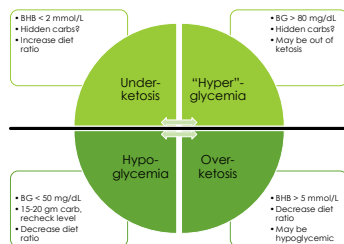
Absolute Contraindications	Relative Contraindications
Disorders of fatty acid transport & oxidation	Cardiac / Cardiovascular disease
Organic acidurias	Hyperlipidemia
Porphyria	Familial hyperlipidemia
Inborn errors of metabolism	Osteopenia/osteoporosis
Acute pancreatitis	Renal failure
Liver failure	Nephrolithiasis
	Cachexia
	Pancreatitis
	Carnitine deficiency
	Concomitant tx with propofol
	Pregnancy
	Diabetes on SGLT2 inhibitor

Symptoms & Side Effects

- Acidosis*
 - pH < 7.2, HCO₃ < 17 mmol/L
- Dehydration*
- Constipation*
- Kidney stones*
 - Uncommon if monitoring hydration status
- Carnitine deficiency/depletion
- "Keto flu"
 - Electrolyte imbalance – replete!
 - Also: adequate hydration

***Adequate hydration can improve or prevent these symptoms**

Troubleshooting



Pop Quiz!

Who was taking notes?

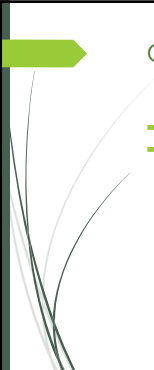
Just kidding...

Key Take-aways

- Ketogenic diet therapy effective for adults with epilepsy, RSE, SRSE
 - Goal is seizure cessation (SE) or reduced seizure burden
- Further study on efficacy of ketogenic diet therapy for other neurodegenerative diseases
- Ketogenic diet ≠ "Keto" fad diet
- Dietitian and physician monitoring essential for safe treatment
- HYDRATION!!!!

References


- Bergqvist, A. C. (2018, October). Dietary Treatments for Patients with Epilepsy. *Practical Neurology*, 36-40.
- Cervenka, M. C., Wood, S., Bogary, M., Bolanos, A., Bercovich, E., Brown, M. G., ... Zupanc-Kozaric, B. (2021). International Recommendations for the Management of Adults Treated with Ketogenic Diet Therapies. *Neurology: Clinical Practice*, 11(5), 385-397.
- Ebbeling, C. B., Knapik, A., Johnson, A., Wang, J. M., Grieco, F. F., Ma, C., ... Ludwig, D. S. (2021). Effect of a low-carbohydrate diet on insulin-resistant cardiometabolic risk: a randomized controlled feeding trial. *Annals of Internal Medicine*, 175, 1-9.
- Kirpatrick, C. F., Bolick, J. P., Klu-Elliott, P. M., Skand, D., Agyi, E. E., Soffer, D. E., ... Maki, E. C. (2019). Review of current evidence and clinical recommendations on the effects of low-carbohydrate and very-low-carbohydrate (including ketogenic) diets for the management of body weight and other cardiometabolic risk factors. *Journal of Clinical Lipidology*, 13, 689-711.
- McDermott, J. J., Das-Arora, L., Vothurn, D., Henry-Batson, B. J., Schwaiblmair, H., Kossuth, E. W., & Cervenka, M. C. (2022). Six-month effects of 1367/22 Adult diet implementation on indices of cardiovascular disease risk in adults with epilepsy. *Neurology: Neuroscience*, 2(2), 1367-22.
- Pilo, R. (2017). Ketosis as a treatment for multiple metabolic and neurodegenerative pathologies. *Journal of Translational Science*, 3(6), 1-6.
- Stallman, C. E., & Rho, J. M. (2012). The ketogenic diet as a treatment paradigm for diverse neurologic disorders. *Frontiers in Pharmacology*, 3, 1-8.
- Woratanabe, M., Tuccinardi, D., Bressi, L., Basciani, S., Moriaki, S., Genco, A., ... Onesti, L. (2020). Scientific evidence underlying contraindications to the ketogenic diet: An update. *Obesity Reviews*, 21, e13303.
- Whetless, J. W. (2008). History of the ketogenic diet. *Epilepsia*, 49 (Suppl 8), 3-5.
- Williams, T. J., & Cervenka, M. C. (2017). The role for ketogenic diets in epilepsy and status epilepticus in adults. *Clinical Neurophysiology Practice*, 154-160.



Contact Info

- Nina Curvis, MS, RD, LD, CNSC
- nina.current@allina.com

(Note: soon to be nina.curvis@allina.com but the old email will still work!)



31