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Medical Management of Ketogenic Diet Therapy

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Objectives

- Understand the medical management of ketogenic diet therapy during initiation and periods of prolonged NPO
- Identify acute and long term side effects of ketogenic diet therapy along with appropriate treatment guidelines
- Recognize micronutrient abnormalities associated with ketogenic diet therapy and commonly used supplements
- Discuss alternative uses for Ketogenic Diet therapy

Epilepsy

Epilepsy is a chronic neurologic disorder that causes seizures, or a disruption in the electrical communication of the brain.

- Defined as having two or more unprovoked seizures at least 24 hours apart

Stats:

65 million people worldwide

1/3 of which have uncontrolled seizures, refractory to medication

Treatment Options

Anti-epileptic drugs (AEDS)

- Unwanted side-effects
- Nutrient interactions with long-term use

Surgery

- Resection: removal of the area of the brain that causes the patient's seizures; the goal is to cure seizures
- Disconnection: interrupts nerve pathways that allow seizures to spread; the goal is to provide relief

Vagus Nerve Stimulation (VNS)

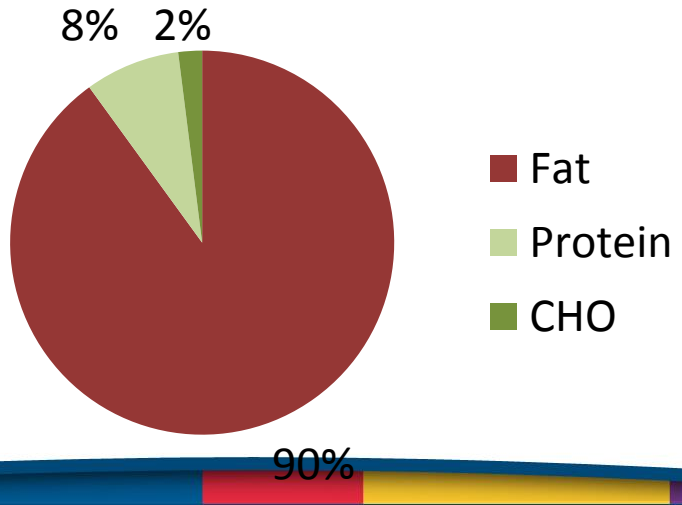
- Designed to prevent seizures by sending regular, mild pulses of electrical energy to the brain via the vagus nerve

Ketogenic Diet

- Typically used after 2 AEDs have failed. Is first line of defense for some dx (glut-1 deficiency)

Ketogenic Diet

- High-fat, adequate protein, low carbohydrate diet to help control seizures
  - High-fat = 85-90% of kcals from fat
- Developed in the 1920's at John Hopkin's Medical Center to mimic the biochemical changes associated with starvation
  - Ketosis = the presence of ketones in the body



Ketogenic Diet Ratio

Fat ⇒ Ketogenic

Carbohydrate & Protein ⇒ Anti-Ketogenic

Ketogenic diet ratios typically range from 3:1→4:1. Modified Atkins diet is usually a 1:1 ratio and Low Glycemic Index diet (LGIT) is <1:1.

Ex: If the patient is on a 3:1 diet…

3 grams of fat : ½ gram pro and ½ gram CHO

Ketogenic Diet (KD) Effectiveness

Diet may completely control epilepsy in 10-15% of children with intractable seizures

~30% have >90% seizure control

~20% have 50-90% seizure control

~20% have <50% seizure control

Efficacy is Seizure Reduction

- 2008 randomized clinical trail (Neal, EG. Lancet Neurol)
  - 4:1 classic KD
    - Seizure freedom in up to 55% patients after 3 months
    - Seizure reduction in 85%
  - Modified Atkins Diet (MAD)
    - Seizure freedom in 10% patients
    - Seizure reduction in 60%

Take away: Classic KD offer slightly higher efficacy, however, compliance is greater with modified KD (MAD/LGIT)

Efficacy in Seizure Reduction Infantile Spasms

IS after KD initiation	*>50%*	*50-90%*	*>90%*
1-3 mo after	15%	39%	46%
5-7 mo after	N/a	48%	52%
10-13 mo after	16%	21%	63%

The Relationship of Ketosis and Growth to the Efficacy of the Ketogenic Diet in Infantile Spasms. Numis et al 2011.

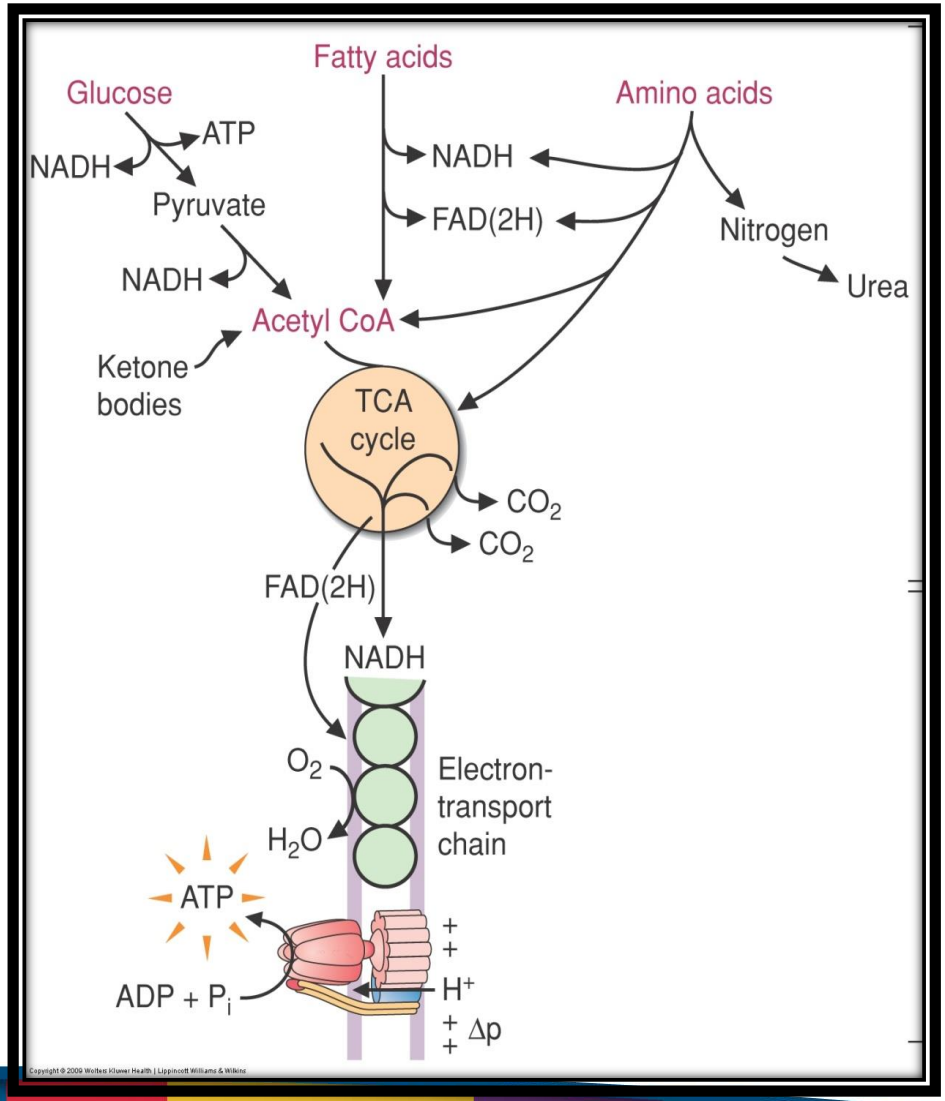
Comparison of diet therapies to regular diet

	Regular Diet	LGIT	MAD	Ketogenic diet
Ratio	0.2-0.3:1	</= 1:1	1:1-2:1	1:1-4:1
Carbohydrates	50-55% >/= 130 g/d	10% 40-60 g/d of carbohydrates with GI <50	5-10% 10-20 g/d	8 g/d: 4:1 16 g/d: 3:1 30 g/d: 2:1 40-60 g/d: 1:1
Protein	10-20%	20-30%	20-30%	6-10%
Fat	</= 30-35%	60%	60-65%	80-90%
Fluids	Unlimited	Unlimited	Unlimited	Maintenance

A Basic Review Of Metabolism

Glycolysis: glucose → pyruvate → acetyl CoA → TCA cycle → electron transport chain → ATP

Fed state: rise in blood glucose → insulin secreted → glycogen synthesis→ fatty acid synthesis → amino acid uptake and protein synthesis



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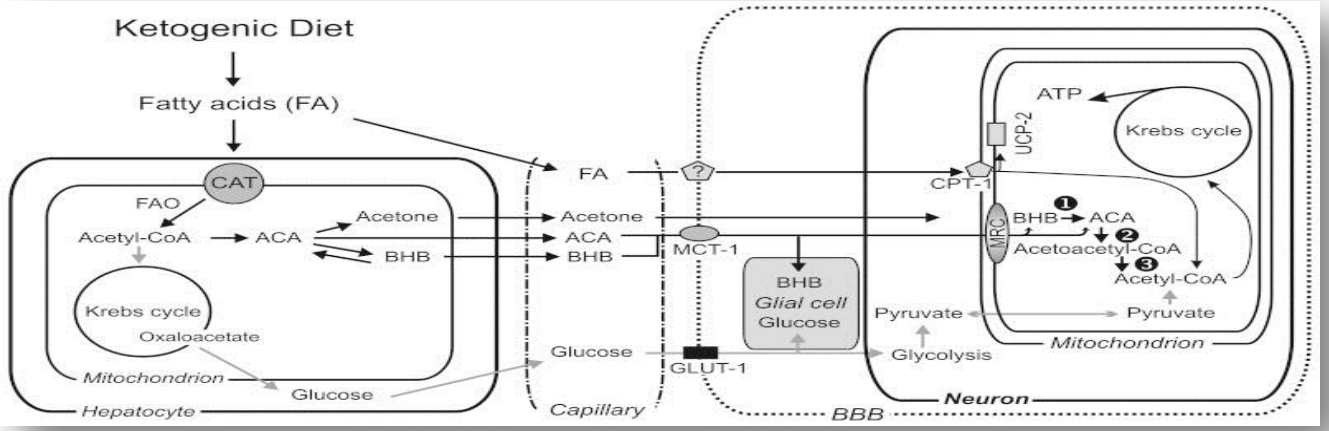
Fasted State

1. Low blood glucose stimulates release of glucagon
2. Glucagon→ glycogenolysis and gluconeogenesis
3. Gluconeogenesis:
   - glycerol from fatty acids (adipose tissue)
   - lactate from RBC and muscles
   - amino acids from muscle

*After 24 hours of fasting, gluconeogenesis is the only source of blood glucose and the liver begins to produce ketone bodies as alternative energy substrate.

Ketosis

- Depletion of exogenous CHO supply and liver glycogen stores → ↑ ketone body formation
- Increased fatty acid breakdown (liver) → excess acetyl-coA production → exceeds metabolic capacity of TCA cycle → acetyl-coA shunted to ketogenesis
- ***Ketogenesis:*** production of ketone bodies, mainly acetoacetate and ß-hydroxybutyrate, from excess acetyl-coA
- Ketone bodies excreted from liver into vascular lumen and travel to brain and other tissue for energy production.



Mechanism of Action?

Not completely understood

- Hypotheses
  - Alterations in neurotransmitter production, release and uptake
    - Keto bodies found to inhibit certain receptor-induced seizures
    - Membrane hyperpolarization
    - Reduce inflammation from seizure activity
  - Alterations in energy metabolism
    - Decreased BG
    - Increased fatty acid oxidation
    - Increased keto production

Indications

- Failure of ***2 or more*** medications for seizure control
- **Probable** benefit in the following conditions:
  - GLUT-1 deficiency
  - Pyruvate dehydrogenase deficiency
  - Myoclonic-astatic epilepsy (Doose syndrome)
  - Tuberous sclerosis complex
  - Rett syndrome
  - Severe myoclonic epilepsy of infancy (Dravet syndrome)
  - Infantile spasms
  - Children on complete formula diet

Contraindications

Absolute:

- Primary carnitine deficiency
- Carnitine palmitoyltransferase (CPT) I or II deficiency
- ß-oxidation defects: MCAD, LCAD, SCAD, long-chain 3-hydroxyacyl-CoA deficiency, medium-chain 3-hydroxyacyl-CoA deficiency
- Pyruvate carboxylase deficiency
- Porphyria

Relative:

- Inability to maintain adequate nutrition
- Surgical focus identified by neuroimaging and video EEG monitoring
- Parent or caregiver noncompliance

Nutrition Therapy Goals

- Promote normal growth and development while maintaining a consistent state of ketosis
- Maintain BG 55-75 mg/dL
- In collaboration with MD and pharmacist, prevent and/or treat potential complications common to ketogenic diet therapy such as:

Chronic	Acute
• Micronutrient deficiencies (e.g. selenium, zinc, vitamin D) • Metabolic acidosis • Cardiomyopathy • Osteopenia • Kidney stones • Elevated lipids • Excessive bruising	• Diarrhea • Constipation • Nausea • Metabolic acidosis • Hypoglycemia • Dehydration

Typical KD initiation: Nutrition

PO diet:

- Increase KD ratio slowly over 3 days by changing the macronutrient composition of recipes to ↑ fat and ↓ carbs until goal ratio is reached.
- Each ingredient in a recipe is weighed on a gram scale (must be weighed to the 0.1 gram) and cooked/assembled per instructions from RD

EN/formula diet:

- Increase KD ratio slowly over 3 days by combining ketogenic formula with the patient's regular home formula, until goal of only ketogenic formula is reached.

Example EN Ratio Increase	Example Neonate Formula Increase
Day 1—0.75:1 Ratio Day 2—1.75:1 Ratio Day 3—3:1 Ratio	Day 1—1/3 keto formula + 2/3 infant formula Day 2—2/3 keto formula + 1/3 infant formula Day 3—100% keto formula @ goal ratio

Check Meds, Supplements, and IVF

Check all existing and new medications and supplements and ensure they are the lowest carb form.

- Approved low carbohydrate meds include the following…
  - Tablet/capsules
  - IV form mixed with non-d5w solution
  - Home low carb supplements (see list on next page)
- Always consult pharmacist if you have questions

Monitoring during initiation

Baseline serum labs: Chem 14, CBC + platelets, Mg, Phos, selenium, zinc, CRP, fasting lipid panel, vitamin D 25(OH), AED levels

BG is checked until pt is on goal diet for 24 hours (typically not until day 3 or 4 of admission)

- If >1 y/o: Check BG q 4 hours
- If <1 y/o: Check BG q 2 hours
- If BG <50 mg/dl treat with 15 ml of fruit juice and re-check after 30 minutes.

Urine: Urine ketones and urine specific gravity per void

- Urine ketone goal is moderate to large ketones (40-160 mg/dL)
- Urine ketones will be checked BID once discharged

Ketogenic Diet

- 85-90% fat
  - Whipping cream, butter, mayo
- 3:1 to 4:1 ratio
  - g fat: grams of protein + carb
- 75-100% RDA for calories
- RDA protein
- 95% maintenance fluids
- Vitamins/minerals supplemented

1300 kcal, 22 g pro; 4 meals
4:1 ratio

- 15 grams raw egg, mixed well
- 8 g cooked bacon
- 14 g butter
- 46 g 36% heavy whipping cream
- 16 g strawberries

Add butter & 1/2 of the cream to the raw egg, cook. Serve with strawberries over whipped cream and bacon on the side.

How to calculate ratios?

FOUNDATION

solace NUTRITION

KETO DIET CALCULATOR

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Enteral Products

Ketocal 4:1 LQ (1.5 kcal/ml)

- vanilla and unflavored
- Oral and enteral
- Insoluble & soluble fiber

Ketovie 4:1 LQ (1.5 kcal/ml)

- Vanilla and chocolate
- Whey protein based
- 25% MCT oil

Other Ketogenic Products

Supplementation

Recommended Supplements:

- MVI
- Calcium and vit D

Optional (based on needs):

- carnitine (50 mg/kg/d)
- bicarbonate
- table salt/light salt
- selenium
- magnesium
- phosphorus
- fish oil
- MCT oil
- Miralax, senna
- probiotics
- iron

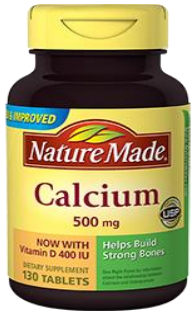
Common Keto Approved Supplements

MVI

- Centrum adults (350 mg carb)
- NanoVM (0 mg carb)
- Flinstone Complete(748 mg carb)

Calcium/vitamin D

- Naturemade Calcium and/or vitamin D
- Calcium carbonate 1250 mg tablet (Roxane)
- 100% calcium carbonate powder (nowfoods.com)
    - ½ tsp = 600 mg calcium



Vitamin D

Provide 2-3 times RDA 2/2 AED medications (2000 IU/day)

- Carlson For Kids, D drops

Other vitamins/minerals

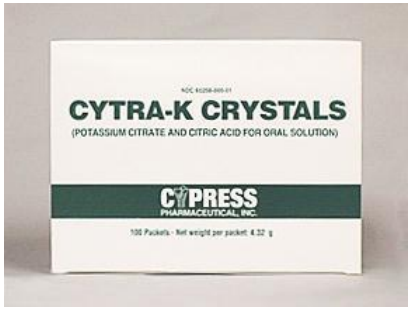
- Morton Lite Salt Mixture (provide Na, K, Cl)
- K Phos

Amino acids

- Levo-carnitine
  - 25-50 mg/kg/day

Buffering agents

- Cytra-K crystals (1-2 mEq/kg/day, up to 4 mEq/kg)
  - 1 packet contains 30 mEq bicarbonate
- Baking soda



Teaching

- Physiology of Ketogenic Diet
- Recipes & meal preparation
- Sick day and emergency guidelines
  - Who to call and when
- Label reading for carb content
- Guidelines for:
  - Dehydration
  - Nausea/vomiting
  - Break-through seizures
  - Hunger or lack of appetite

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Discharge Criteria & Needs

- Pt. can tolerate diet x 24 hours without nausea, vomiting or diarrhea
- Complete diet instruction by RD
- Caregiver can demonstrate ability to implement diet
- Child's seizure activity is at baseline or decreased.
- Family has all supplies, Ketocal, Ketostix, new medications (in tablet form), and recipes
- Formula or meal for the trip home as needed

PREVENTION, MONITORING AND TREATMENT OF POSSIBLE SIDE EFFECTS

Overview of required ketogenic diet testing

	Prior to or at hospital admit	At hospital admit	Check at 1-month f/u	Check every 3 months
Serum	Fasting lipid panel <u>Carnitine</u> Total, free and acyl <u>Vitamins & Minerals</u> Selenium Zinc Magnesium	CBC + platelets Chem 14 AED levels <u>Glucose</u> Check q2 hours if <1 y/o Check q4 hours if >1 y/o	Fasting lipid panel CBC + platelets Chem 14 AED levels Betahydroxybutryate <u>Carnitine</u> Total, free, and acyl <u>Vitamins & Minerals</u> 25(OH) vitamin D Magnesium Phosphorus	Fasting lipid panel CBC + platelets Chem 14 AED levels Betahydroxybutryate <u>Carnitine</u> Total, free, and acyl <u>Vitamins & Minerals</u> 25(OH) vitamin D Selenium Zinc Magnesium Phosphorus
Urine	Urine Calcium + creatinine	Urine ketones qvoid Urine specific gravity qvoid	Parents monitor urine ketones at home 2x/day	
Anthropometrics	Get baseline height and weight	All patients: daily weights <1 y/o: weekly HC and length measurements	Weight check Height check	
Vitals	n/a	Check q shift	PRN	
Testing	R/o metabolic disorders contraindicated with diet If pt or family h/o kidney stones need renal US and nephrology consult	Baseline ECHO	Recheck ECHO PRN or annually if abnormal; recheck bi-annually if normal; and recheck prior to any surgeries Check selenium and PFA100 prior to any surgeries. If PFA100 is abnormal, need hematology consult Get renal US or nephrology consult PRN DEXA	
Psychosocial	Ongoing assessment of ability of caregivers/patient to adhere to diet			

Acidosis/kidney stone prevention & treatment

Prevention:

- Maintain adequate hydration and promote strict adherence to a fluid schedule.
- Treat all high risk patients with a buffering agent (Cytra K-crystals). High risk patients include the following:
  - Patient has h/o or family h/o renal stones
  - Patient is on a carbonic anhydrase inhibitor (zonisamide, topiramate)
  - Patient is a poor feeder or has trouble maintaining hydration status
- Obtain a renal US and nephrology consult if patient or patient's family has h/o renal stones
- Wean carbonic anhydrase inhibitors if possible

Monitoring:

- Urine analysis and urine calcium/creatinine ratio prior to starting diet and q6 months
- Check C02 at every follow-up
- There is currently no evidence for routine renal US

Treatment:

- If the patient develops a kidney stone, this does not necessitate diet cessation or lithotripsy
- **If abnormal Urine to Creatinine ratio or C02 is <20 mEq/L, consider following treatment:**
  - Addition of buffering agent, preferably potassium citrate crystals
  - Consider increasing fluid provision
- If S/S of renal stones
  - A Renal US or CT of abdomen and nephrology consult should be obtained
  - Addition of buffering agent, preferably potassium citrate crystals

Types of buffering agents

Name	Ingredients	Dose	CHO content	Taste	Precaution
Carried in house					
Cypress pharm. Cytra-K Crystals **preferred buffering agent	K citrate monohydrate Citric acid monohydrate Sodium saccharine Fruit punch flavor FD & C Red Dye #3	0.5-2+ mEq/kg/d 1 packet = 30 mEq/bicarb Mix 1 packet with 6 oz of cool water	0.063 g CHO/packet 0.063-0.126 g CHO depending on dose	Fruit punch flavor	Concurrent admin of potassium-sparing diuretics, ACE inhibitors, potassium-containing meds can lead to toxicity
Pharmaceutical Associates, Inc (pai) Cytra-2, Bicitra®	Sodium citrate Citric Acid Flavoring Polyethylene glycol Propylene glycol Purified water Sodium benzoate Sorbitol solution	2-3 mEq/kg/d 5-15 mL BID diluted in 1-3 oz of water. Followed by additional water if desired 1 mL = 1 mEq bicarb	0.8g/5 mL 1.6-4.6 g CHO depending on dose	Grape flavor	
Other home regimen					
Baking Soda (any brand)	Sodium bicarbonate	0.5-2+ mEq bicarbonate/kg/d. 13.675 mEq per ¼ tsp Dose typically ¼ tsp in 3-8 oz H20 up to 4x/day	0g CHO	Salty taste, can be dissolved in sugar-free flavored water	High in sodium (each ½ t =616 mg Na) Can irritate stomach Can leach phosphorus from bones, may need phos supplement. Reported copper deficiencies with long-term use

Carnitine deficiency

Prevention

- Check baseline free, acyl, and total serum carnitine levels prior to start of diet
- Encourage carnitine rich food items for oral feeders (dairy, meat, eggs)
- For formula fed patients, ketocal provides 19.7 mg carnitine/tetrapack
- Provide more fat via medium chain triglycerides (MCT), which does not require carnitine for transport into mitochondria
- Provide empiric carnitine supplementation to patients starting ketogenic TPN on day 1. No data to support continued supplementation when patient transitioned to PO or EN.

Monitoring

- Physical S/S: fatigue, low energy, low ketosis, decreased muscle strength
- Check free, acyl, and total serum carnitine levels at every follow-up appointment
  - **Deficiency: <20-25 uM of free carnitine or acylated to free carnitine ratio of >/= 0.4**

Treatment

- Carnitine should be started at low dose and increased gradually (poor absorption, diarrhea, or increase in seizures seen with initial higher doses)

- Recommended to start at 10-20 mg/kg L-carnitine IV or orally and increase as needed (can give in 3-4 divided doses if higher supplementation need)

Elevated Lipids

Prevention

- Check baseline fasting lipid panel
- Prioritize soluble fiber
- Prioritize intake of poly unsaturated or mono unsaturated fatty acids over trans or saturated fats
  - Ketocal formula is trans fat free, has low amounts of saturated fat, has linoleic acid and a-linolenic acid and supplemented with DHA and ARA, contains soluble fiber

Monitoring

- Check fasting lipid panel at f/u.
- Continue to monitor as some children adjust and begin to better metabolize the higher fat and cholesterol of the ketogenic diet over time.

Treatment

- General changes
  - Decrease the ketogenic diet ratio
  - If patient is both formula and PO foods, increase formula provision and decrease food provision.
- For elevated cholesterol
  - Increase in poly and mono unsaturated fatty acids 1:1
  - Increase use of MCT in diet
  - Omega-3 fatty acid supplementation
  - Prioritizing soluble fiber
- For elevated TG
  - Carnitine supplementation
  - Omega-3 fatty acid supplementation
  - Reduce valproate levels if possible

Vitamin D/Ca & Bone Health

Prevention

- Calcium/vitamin D supplementation—may need 2-3x DRI for vitamin D to maintain adequate stores on AEDs
- If on PO diet, can encourage food sources of vitamin D (fatty fish like salmon/tuna/mackerel, egg, liver, beef)
- If formula fed, Ketocal has 220 IU per tetrapack (8 oz)

Monitoring

- Monitor vitamin D 25(OH) status at baseline and then at every follow-up. (The following vitamin D ranges for 25(OH) are not standardized levels for treatment, however these are the levels we chose to define as deficiency/insufficiency).
  - Insufficiency:
    - **20-29 ng/mL**
  - Deficiency:
    - **<20 ng/mL**

Treatment

- If patient has insufficient or deficient vitamin D status (<30 ng/mL), will need to increase vitamin D provision above baseline supplementation via low carbohydrate supplement.

Complications → Management

Constipation	• Increase fluids • Increase Fiber in diet (Avocado/ Lettuce) • Miralax daily • MCT oil
Metabolic Acidosis	• Adequate Kcal/protein • Adequate fluid • Phosphorus or Bicarbonate (.5-2 mEq/kg/d) • Consider weaning carbonic anhydrase inhibitor
Kidney Stones	• Fluids, fluids, fluids!!! • Treat Acidosis • Wean medications that can contribute towards acidosis
Hyperlipidemia	• Decrease saturated fats, Maximize Mono and Polys • Lower ratio • Add MCT oil

Fasting/NPO Guidelines

- Ketogenic diet patients fasting or with feeding intolerance > 12 hours may have increased risk for hypoglycemia and acidosis.
- BG and CO2 should be monitored.
- Note that goal BG range with ketogenic diet therapy is 55-75 mg/dl

Fasting/NPO Guidelines

Provide maintenance carbohydrate-free fluids

Blood sugars checks:

- –If patient is >/=1 y/o order: Check BG q4 hours. If BG <50 mg/dL give 15mL apple juice. If NPO give 50 mL d5w over 30 minutes. Re-check in 30 minutes.

- –If patient is < 1 y/o order: Check BG q2 hours. If BG <50 mg/dL give 15mL apple juice. If NPO give 50 mL d5w over 30 minutes. Re-check in 30 minutes

- –If BG does not improve to >50 mg/dL, may need to add 2.5% or 5% dextrose to maintain BG between 55-75 mg/Dl

•Check C02 level daily

Modified Ketogenic Diets

Modified Atkins Diet (MAD)

- Can we achieve and maintain ketosis with less structure and less dietary restriction?
  - Ketosis can be achieved especially when patients also utilize ketogenic diet supplements or oils (ketocal, MCT oil) in addition to following a low carbohydrate and high fat diet.
  - Studies show similar efficacy as ketogenic diet with less restrictions (pts can have more protein and carbohydrates each day)

MAD Protocol

- Patients can have 10-15 grams carb/day
  - May liberate up to 20 grams/day after 2 months
- Encourage fat & protein sources
  - Encourage 3 servings of cheese/day
- No fluid restrictions
- Check urine ketones 2x/week
- Weekly weights
- Daily MVI, calcium, vitamin D supplement
- F/u & labs q 3-4 months
- Note: research indicates that if pt does not respond to MAD therapy they are likely not going to respond to KD therapy either.

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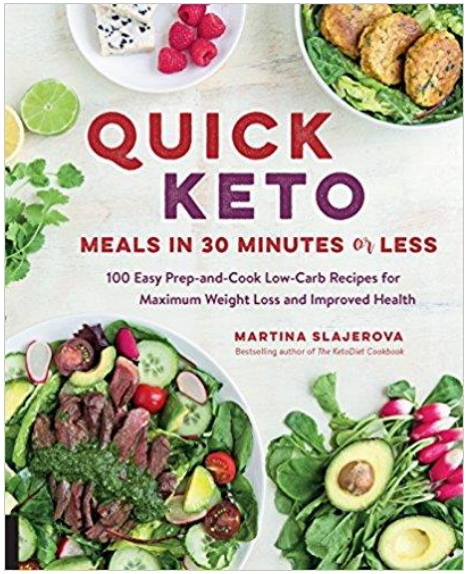
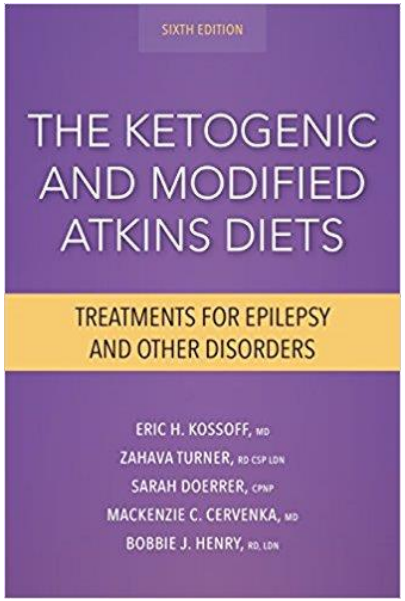
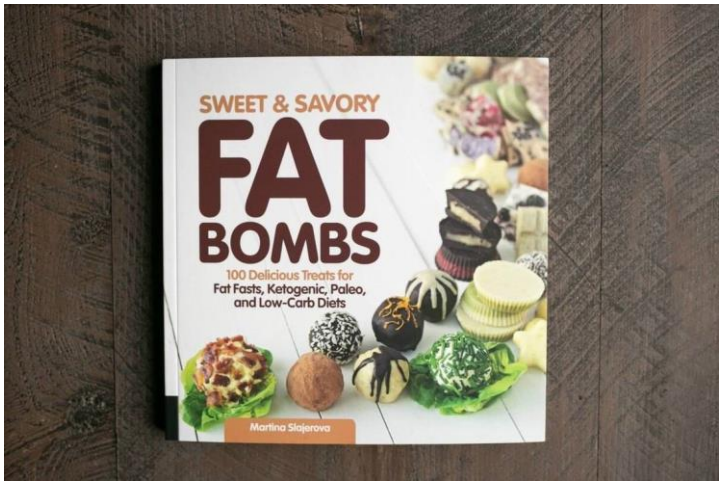
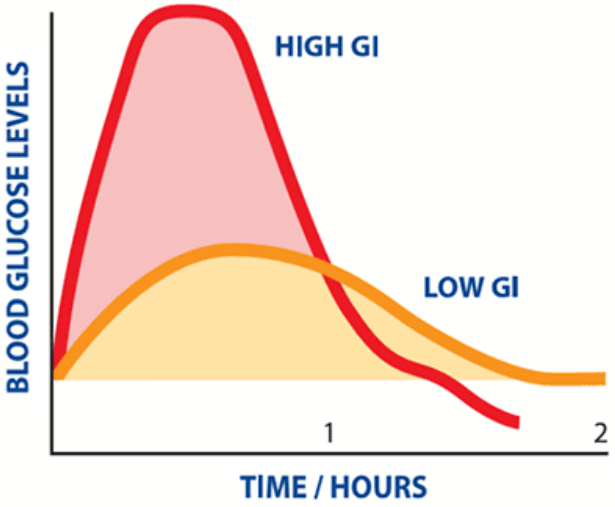






Low Glycemic Index Diet (LGIT)

Can seizures be improved by stabilizing or lowering blood glucose?
Studies show similar efficacy as ketogenic diet with less restrictions



Factors that affect GI:

Fat: adding fat to foods will slow down digestion and lower GI. Ex: spreading butter on whole grain bread

Acidity: foods with more acid are digested more slowly. Ex: adding vinegar, lemon juice, oranges to foods to lower GI

Fiber: high fiber foods will have slower digestion and have lower GI.

Size of the grain: courser grains such as whole grain, oatmeal, bran cereals, etc. will have lower GI.

LGIT Protocol

- 40-60 grams carb/day
  - Choose carbohydrates with glycemic index < 50
- Encourage fat sources (~60% kcal)
- Encourage protein intake
- Guided kcal intake to meet needs
- No fluid restriction
- Daily MVI, calcium & vitamin D
- f/u & labs q 3 months

No weighing or admission required

Using household measurement or exchanges

Other applications for KD diet therapy

Why other conditions might benefit from ketogenic diet

- Glucose metabolism is impaired
- Ketone bodies are the brain's main alternative metabolic substrate

Ketones

Other applications for KD diet therapy

Brain Tumors

- Cancer treatments ↑ food supply for glioma cells
  - Steroids → glucose
  - XRT/ cell lysis → glutamine
- Tumor growth correlates with glucose availability
- Glioma cells cannot use ketones
- Clinical trials ongoing

Alzheimer's

- 17-23% decrease in cerebral glucose metabolism (CMRglc) in dementia vs. control
- Degree of cognitive impairment correlated with rate of glucose utilization

Traumatic Brain Injury