

KETOGENIC THERAPY: EXPANDING BEYOND SEIZURE CONTROL

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Disclosure

Mary Susan Spears is employed by Cambrooke Therapeutics as a Senior Clinical Specialist.



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Objectives

- Introduce the history and principles of therapeutic ketogenic diet
- Review the use of ketogenic therapy with intractable epilepsy
- Explore the expanding research and use of ketogenic diet in other disorders

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Introduction to Epilepsy and Ketogenic Diets

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Statistics



- **65 MILLION:** Number of people around the world who have epilepsy
- **OVER 3.4 MILLION:** Number of people in the United States who have “active” epilepsy
- **1 in 26:** People in the US will develop epilepsy at some point in their lives
- **32:** Number of different classifications of Anti-Epileptic Medications (AED’s) each targeted at specific seizure types
- **25%** are refractory to current treatments and another **15%** are difficult to treat = Intractable or Refractory Epilepsy
- **6 OUT OF 10:** Number of people with epilepsy where the cause is unknown

Epilepsyfoundation.com

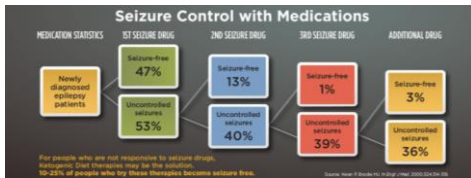
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Medication Efficacy in Epilepsy

Drugs

- If a first medication fails, the potential effectiveness of adding a second or third drug declines

Charliefoundation.org



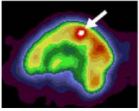
- The International League Against Epilepsy (ILAE) defines drug resistant epilepsy (refractory epilepsy) as the following:
 - When a person has failed to become and stay seizure free with adequate trials of 2 AED's
 - The AED's must have been appropriate for the individual's seizure type

Epilepsyfoundation.com

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Surgical Treatment Options

Surgery



Brain during a seizure.
www.childrens.com

- Epilepsy surgery is curative in 30-80% of eligible patients dependent on type of seizure and location of lesion
- Wedge Resection** - Remove part of the brain where the seizures are known to originate ("hot spot")
- Callosotomy** – separate the hemispheres to stop the spread of seizure activity from one side of the brain
- Hemispherectomy** – removal of the side of the brain that is triggering the seizures. Results in stroke like appearance



www.epilepsyresearch.org.uk

Vagus Nerve Stimulation (VNS)

- Pacemaker for the brain
 - A small device is placed under the skin of the chest
 - Device sends electrical pulses to the brain, through a large nerve in the neck called the vagus nerve
 - Prevents or interrupts seizures by sending small base line pulses of electrical energy to the vagus nerve
 - A magnet activates a larger pulse to stop break through seizure activity

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Dietary Treatment Option

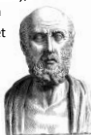
Therapeutic Ketogenic Diet Therapies (KD) Charliefoundation.org

- High fat, adequate protein, minimal carbohydrate diet
- Promotes use of fats as primary fuel for the brain
- Nutritionally incomplete without supplementation
- Efficacy: 50% of patients will have at least a 50% reduction in seizures and 10-15% will become seizure free
- Seizure type Treated: All types are responsive to diet therapy
- Adverse Effects:
 - GI: Constipation, slow gastric emptying, reflux
 - Endocrine: Low blood sugars
 - Acidosis: (CO2 levels <18 mEq/L) causes vomiting, lethargy, fast breathing, rapid heart rate
 - Renal: dehydration, kidney stones
 - Cardiac: Dyslipidemia, hyperlipidemia, cardiomyopathy
 - Bone: Osteomalacia, osteoporosis, slowing of linear growth

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History of the Ketogenic Diet: Timeline

- 500 BC Hippocrates** First mention of fasting to treat "fits" (Mathew 17:14-21)
- 1911 Guelpa and Marie (Paris)** 20 children & adults seizures less severe with fasting
- 1920 McFadden & Conklin (Michigan)** fasting for 3 days up to 3 weeks
- 1921 Geyelin (New York Presbyterian)** reported cognitive improvement with fasting, **Woodyatt** discovered ketones appear in the urine with fasting, and **Wilder (Mayo)** diet could be changed to high fat, low carb to "mimic" fasting
- 1925 Peterman (Mayo Clinic)** how to calculate the KD
- 1938 Dilantin** discovered- therapy shifts to **drug focus**
- 1971 Huttenlocher (U. of Chicago)**- **MCT diet**
- 1972 Livingston (Hopkins)**- *Comprehensive Management of Epilepsy in Infancy, Childhood and Adolescence* reported use of KD in over 1000 children
- 1978 Valproate**- branched chain fatty acid thought to take the place of diet
- 1994 Dateline** Charlie Abraham's story
- 1995** Charlie Foundation supports first multicenter study of KD
- 1997** "First Do No Harm" starring Meryl Streep
- 2008** First **International Ketogenic Symposium**-Phoenix
- 2008** Neal et al.- First RCT
- 2009** First **International Consensus Statement**



Whiteless JW. Epilepsia 2008; 49[suppl.8]:3-5.

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Keto and Epilepsy in the Literature



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Evidence & Efficacy of Ketogenic Diet Therapy

- Children with intractable epilepsy had a **24% higher death rate** if their seizures were not controlled over a five year period¹
- In 2009 Neal conducted the first randomized control trial using ketogenic diet in 145 children and adolescents with intractable epilepsy found²:
 - 38% of patients achieved >50% reduction of seizures** after 3 months of KD
 - Another 7% achieved >90% reduction in seizures**
- In 2018 the ILAE's published the updated Consensus Statement regarding ketogenic diets and the results indicate³:
 - Previously used as a "last resort" therapy once 2 or more AED's had failed
 - "Strongly advocates" that Keto Diet Therapy (KDT) be considered earlier in treatment for difficult to manage epilepsy syndromes that have demonstrated the greatest response
 - KDT can be safe in infants as young as 6 weeks and may be ideal in patients <2 years old
 - Adolescents and adults can also achieve seizure reduction with KDT, and adult centers need to be established for patients transitioning from pediatric care

1. Sillanpää M, Shinnar S. *N Engl J Med* 2010;363:2522-9

2. Neal EG, et al. *Epilepsia*. 2009 May;50(5):1109-17.

3. Kossoff EH, et al. *Epilepsia Open*. 2018:1-18.

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Indications and Contraindications

Strongly Beneficial <i>(Defined as more beneficial (>70%) than the average 50% KDT response defined as >50% seizure reduction)</i>	Modestly Beneficial <i>(Defined as not better than the average dietary therapy response, or in limited single center case reports)</i>	Contraindications
Angelman's syndrome Complex 1 mitochondrial disorders Dravet syndrome Epilepsy with myoclonic-atonic seizures (Doose syndrome) Glucose transporter protein 1 (Glut-1) deficiency syndrome Febrile infection-related epilepsy syndrome (FIREs) Formula-fed (solely) children or infants Infantile spasms Ohtahara syndrome Pyruvate dehydrogenase deficiency (PDHD) Super-refractory status epilepticus Tuberosclerosis complex	Adenylosuccinate lyase deficiency CDKL5 encephalopathy Childhood absence epilepsy Cortical malformations Epilepsy of infancy with migrating focal seizures Epileptic encephalopathy with continuous spike-and-wave during sleep Glycogenosis type V Juvenile myoclonic epilepsy Lafora body disease Landau-Kleffner syndrome Lennox-Gastaut syndrome Phosphofruktokinase deficiency Rett syndrome Subacute sclerosing panencephalitis (SSPE)	Absolute Carnitine deficiency (primary) Carnitine palmitoyltransferase (CPT) I or II deficiency Carnitine translocase deficiency β-oxidation defects (MCAD, LCAD, SCAD) Long-chain 3-hydroxyacyl-CoA def Medium-chain 3-hydroxyacyl-CoA def Pyruvate carboxylase deficiency Porphyria Relative Inability to maintain adequate nutrition Surgical focus identified Caregiver noncompliance Propofol concurrent use (risk of propofol infusion syndrome may be higher)

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Anticonvulsant Mechanisms of the KD

Metabolic pathways are shifted in the brain:

1. Reduction in glycolysis
2. Increase in beta-oxidation of fatty acids
3. Increase in ketone bodies
4. Activation of ATP Potassium channels
5. Increased GABA synthesis (neuro inhibitor)
6. Reduced 'reactive oxygen species' generation
7. Increased energy production in brain tissue

Bough JK & Rho JM. Epilepsia, 2007.48(1):43-58.

8. New research investigating the gut brain connection and shifts in the gut microbiome with epilepsy and KD therapy

Lindefeldt M. et al. NPJ Biofilms Microbiomes. 2019;5:5.

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Review of Fat Metabolism: LCT vs. MCT

www.nutritionreview.org

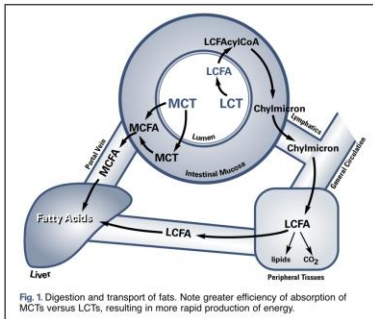


Fig. 1 Digestion and transport of fats. Note greater efficiency of absorption of MCTs versus LCTs, resulting in more rapid production of energy.

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Review of Fat Metabolism: Liver and Mitochondria

www.nutritionreview.org

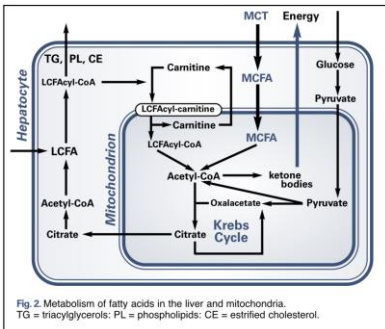


Fig. 2 Metabolism of fatty acids in the liver and mitochondria. TG = triacylglycerols; PL = phospholipids; CE = esterified cholesterol.

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Ketogenic Diet Lingo

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Net Carbs

- Total carbohydrates (CHO) minus the grams of fiber
- Unlike the original Atkins diet, sugar alcohols are counted with ketogenic therapies because they are metabolized into carbohydrates
- Some of the more liberal forms of the diet do not use the Net Carb concept



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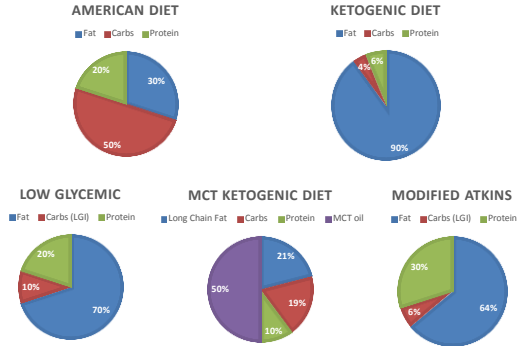
Ketogenic Ratio

- grams of fat: grams of protein + carbohydrate combined
- Some common ratios are 4:1, 3.5:1, 3:1, 2.5:1, 2:1
- The higher the ratio, the more restrictive and more vitamin and mineral deficiencies
- To increase a ratio
 - If seizures are not adequately controlled the ratio may be increased
 - Add more fat and reduce the carbohydrates
- To lower a ratio
 - Ratios are usually decreased due to excessive side effects like acidosis or low blood sugars
 - Increase the protein or carbs and reduce the fat
- Protein needs are always the limiting rate on the ratio



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Comparison of Ketogenic Diets vs American Diet

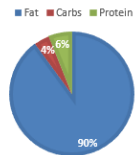


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Classic Ketogenic Diet (KGD)

- The strictest version of diet therapy
- Uses ratios like 4:1 or 3:1
- Each meal is calculated using a program like Keto Diet Calculator by the Charlie Foundation
- All foods are weighed on a gram scale
- Basic meals include
 - Heavy Whipping Cream
 - Protein
 - Fruit or Vegetable
 - Fat
- Ideal for patients receiving tube feedings and younger patients
- Usually initiated in the hospital

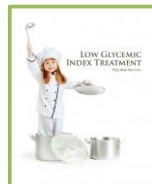
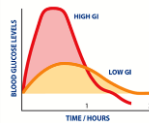
KETOGENIC DIET



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Low Glycemic Index Treatment (LGIT)

- LGIT encourages selection of carbohydrates that have a glycemic response <50
- Low glycemic carbohydrates are limited to 40-60 grams per day
- Count total carbohydrates (not net carbohydrates)
- Fats and proteins make up remaining calories
- The goal of LGIT is to limit blood glucose fluctuations
- Minimal to no ketone production
- Utilized for adolescents and adults
- Education occurs in the ambulatory setting with diet initiation at home

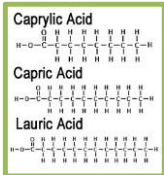


Resource: Low Glycemic Index Treatment Education Materials. Authors: Thiele EA, Pfeifer HH, Thibert, RL. Printed by The General Hospital Corporation, Edition 8/2016

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MCT Diet

- Total fat is 70-75% total calories with 30-60% of calories coming from MCT.
- MCT (C6-C12) are processed more efficiently into ketones (vs. LCT) allowing for more carbohydrates and protein in the diet.
 - Benefit to those patients who find other versions of a ketogenic diet too restrictive.
- MCT is typically introduced slowly to avoid GI upset.
 - Increase of 5-10% per day or 1-2 grams per meal is generally well tolerated.
- Any GI intolerance can be addressed by lowering MCT by 10% and continuing diet advancement again as tolerated.
- Adequate protein using the DRI for age is encouraged and remainder of energy is made up with carbohydrates.
- The diet can be calculated or prescribed in food exchanges.
- MCT can also be incorporated into the classic or alternative forms of a modified ketogenic diet to help boost ketosis or help with constipation.



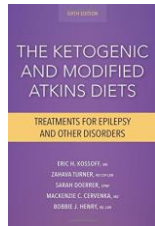
Lambrechts DA, *Epilepsy Behav.* 2015 Oct 15:261-6.

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Modified Atkins Diet (MAD)

- Net carbs limited to 10-25 grams per day
- Liberal fats are encouraged at each meal or snack
- Aim for adequate protein per Dietary Reference Intakes (DRI)
- Lower urine ketones or BHB levels seen with MAD
- MAD is appropriate for patients >3yrs and those for whom compliance may be a challenge
- Education occurs in the ambulatory setting with diet initiation at home

Net carbohydrate is the total carbohydrate minus fiber.



Resource: The Ketogenic And Modified Atkins Diets, 6th Edition. Authors: Kossoff, EH, Turner, Z, et al. pages 103-154.

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Comparison Meals (400 kcals)



Standard American Diet



Classic Ketogenic Diet 4:1 Ratio



Low Glycemic



MCT Oil Keto

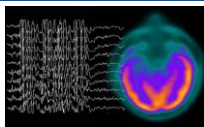


Modified Atkins 20g CHO

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Status Epilepticus (SE)

- Defined as: Epilepsyfoundation.com
 - Any single seizure that lasts > 5 minutes
 - A second seizure starts without initial recovery
 - Repeated seizures for 30 minutes or longer
- Prevalence in the US: ~150,000 cases annually
- More common in men and African-Americans www.webmd.com-treat-epilepsy-seizures
- Incidence twice as common in the elderly with a worse prognosis
- About 25-27% of patients with known epilepsy will experience at least 1 episode of SE
- 10-20% of patients will present with SE as their first seizure episode
- Between 10-30% of patients with SE will be dead within 30 days (~55,000 deaths annually)
- Most common causes include low AED levels in known epileptics, toxic metabolic encephalopathy, stroke, hypoxic ischemic injury, refractory epilepsy, brain tumor or meningitis/encephalitis



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Progression of Status

Features	Status Epilepticus (SE)	Refractory Status (RSE)	Super Refractory Status (SRSE)
Length of duration	1 seizure lasting >5 minutes, 2nd seizure without recovering from 1 st , or repeated lasting 30 minutes	1- 2 hours but < 24 hours	> 24 hours or recurrence when reducing anesthesia
Prevalence / Incidence	150,000 cases 2x higher in Elderly 25% of epilepsy pts	23-48% of patients with SE	15% of adults & 22% of patients with SE
Treatment	30% fail with 2 AED's & 15% will fail 3 AED's	Induce coma and intubate	
Mortality	10-30% ~55,000 annually	35 to 60% 3x higher than SE	
Common Etiology	Low AED levels, toxicity, stroke, hypoxia, brain tumor, or meningitis	Stroke & Drug withdrawal	
Prognosis for Recovery		75% "poor Outcome" 39% sever neurologic deficits	

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What does the Literature Show?

	Thakur (2014)	Cervenka (2017)	Arya (2018)	Francis (2018)
Study Design	Retrospective Multicenter (4)	Prospective Multicenter (5)	Retrospective Multicenter (6)	Retrospective Single Center
Age	Mean 33 y	Mean 47 y	Mean 4.7 y	Mean 48 y
Participants	10 (60% F)	15 (67% F)	14	11 (45% F)
Deaths	2 (20%)	5 (33%)	None reported	1 (9%)
Duration of SE before KD	29.2 days	10 days	13 days	1 day
# AED's before KD	8.5	8	5	3
Ketosis Achieved	90%	100%	93%	91%
Time to Ketosis	3.4 days	2 days	2 days	1.4 days
Ratio	3:1 (1), 4:1 (9)	4:1	3:1 (1), 3.5:1 (1) 4:1 (11), 5:1 (1)	3:1 to 4:1
Time to Resolution	7.2 days	5 days	<7 days in 10 (71%)	Not reported
N with Resolution of SE	9 (90%)	11 (73%)	11 (78.6%)	11 (100%)
Side effects	Acidosis (1) & Hyper Trig (2)	Acidosis (4), Hypo Gly (1), Hypo Na (1), Hyper Trig (2) & Constipation (2)	Gastroparesis (1), Hyper Trig (1) & Weight loss (1)	Acidosis (7), Hypo Gly (2) & Hypo Na (1)
LOS in ICU	40.4 days	32.9 days	Not reported	18.6 days

KD in Neurodegenerative Disease

- Specifically Alzheimer's and Parkinson's
 - Number of studies or case reports in the literature
 - Alzheimer's 32 Parkinson's 13
 - Reasons KD may slow progression of disorders
 - Oxidative stress and mitochondrial dysfunction in the brain are central features of Neurodegenerative disease
 - KD provides neuroprotective properties as a result of glycolysis inhibition and increased efficiency of mitochondrial respiration
 - Antioxidant action of KD due to increase in glutathione and glutathione peroxidase activity and reduced production of free radicals
 - Possible drawbacks/ concerns
 - Adherence to KD and known side effects of KD therapy
 - Appetite suppression in patients already at risk for reduced intake and malnutrition due to neurologic impairment
- Long term prospective clinical data is still lacking at this time

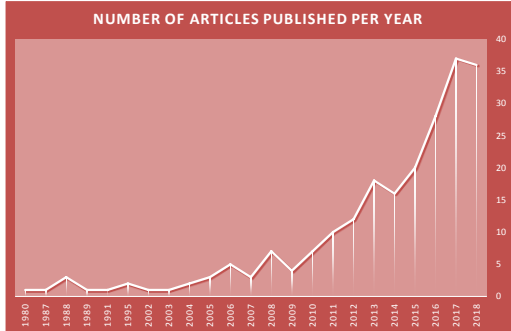
Wlodarek D. Nutrients. 2019, 11, 169.

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Ketogenic Diet and Metabolic Disorders

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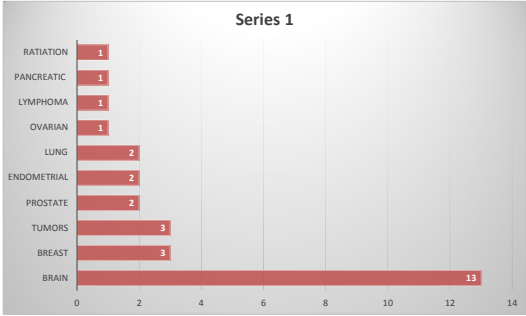
Keto and Cancer in the Literature



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Current Keto and Cancer Studies



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Review of Article—Literature Search Results

Wide variety in identified studies

- Study designs: case studies to RTCs (with a variety of statistical models)
 - 2 clinical trials, 1 RCT, 5 case reports, 1 retrospective study, 1 single-arm prospective study, 1 pilot clinical study, 1 prospective observational pilot study
- Cancer characteristics
 - Type
 - Staging
 - Passage of time since diagnosis/ time point of keto initiation
- Keto diet intervention
 - 13 days to 12 months in duration
 - 9 studies used keto as adjunct therapy, 5 as sole therapy
- Route of nutrition/composition:
 - Parenteral Nutrition
 - Enteral Nutrition
 - Oral—food, liquid/beverage, calorie-restricted, use of supplements



Oliveira, Camila L.P., et al. J. Acad. Nutr. Diet, March 2017.

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Review of Article—Outcomes

Oliveira, Camila L.P., et al. J. Acad. Nutr. Diet, March 2017.

Categories:

- Disease progression
 - Reported in 10 studies; variable responses including positive and negative
- Alterations in cancer cell metabolism
 - Reported in 1 study; positive response
- Metabolic Outcomes
 - Reported in 11 studies; variable responses including positive and negative
- Anthropometrics and body composition
 - Reported in 9 studies; unchanged in 2, decreased in 7
- Quality of life
 - Reported in 3 studies; positive response
- Adverse Events and Diet Tolerance
 - Adverse Events: Reported in 3 studies; mild in nature (e.g., fatigue, constipation, cramps)
 - Diet Tolerance: Reported in 8 studies; variable to well-tolerated

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Conclusions for Keto and Cancer



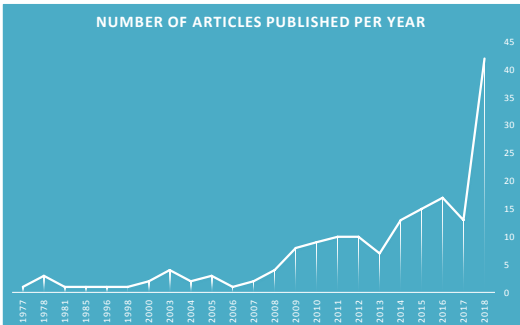
- There is increasing evidence cancer cells exhibit a defect in cellular respiration
- This creates an opportunity to utilize the ketogenic diet to exploit this defect and disrupt cancer cell energy creation
- Great opportunity for collaboration between oncology and ketogenic dietitians
- Provision of KD in oncology is very similar to epilepsy with a greater focus on blood sugar control
- Use of ketogenic diet in oncology is experimental but evidence is growing that the diet is an effective adjunctive therapy for managing cancer

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Ketogenic Diet and Diabetes

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Keto and Diabetes in the Literature



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RCT Comparing KD and Plate Method

Parallel randomized longitudinal interventional trial

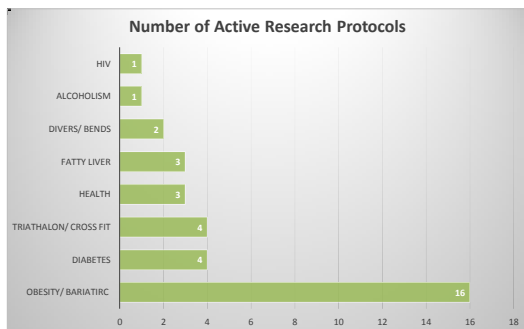
- Inclusion criteria: *Saslow LR, et al. J. Med. Internet. Res. 2017, v.19(2)*
 - 18 + years, BMI ≥25, with an elevated HgA_{1c} and regular internet access
 - Metformin was the only allowed antidiabetic medication
 - Readiness to change was evaluated to reduce drop out rates

	KD (n=12)			Plate Method (n=13)		
	53.0 Y (50% F)			58.2 Y (69% F)		
Mean Age	BL	16 w	32 w	BL	16 w	32 w
Non-Fiber CHO Intake	163.6 g	40.4g	43.5 g	152.0 g	127.1 g	144.8 g
N with HgA _{1c} <6.5%		75%	55%		13%	0%
N with 5% Weight Loss		83%	90%		38%	29%

- Conclusions:
 - KD improved glycemic control and promoted more weight loss
 - When compared to additional clinical trials using KD for at least 3 months all found HbA_{1c} dropped by 1% with an 8% reduction in weight

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Other Research Using Keto



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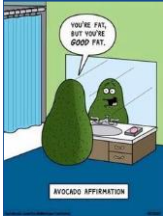
Final Conclusions

- Therapeutic Ketogenic diet is standard of care for Intractable Epilepsy and Status Epilepticus
- Growing evidence of using of KD as an adjunctive therapy for solid tumor cancers especially brain tumors
- Growing evidence for use of KD to improve glycemic control in Type 2 DM
- Additional evidence needed for additional uses of KD in neurodegenerative disorders
- Researchers actively investigating additional therapeutic uses for KD therapy

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Questions?



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Appendix

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What causes Cancer?

- Genetic or metabolic disease?
 - Somatic mutation theory
 - Genetic alteration acquired by a cell that is passed on to progeny during cell division
 - Mitochondrial/respiration defect theory
 - Defects in mitochondria and cellular respiration give rise to cancer
 - Chicken vs egg
 - Somatic theorists say respiratory insufficiency occurs after genetic alteration
 - Respiration defect theorists say respiratory insufficiency occurs first
- Warburg Effect

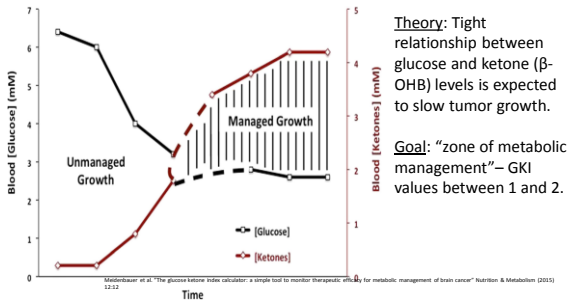
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Application of Keto In Oncology Setting

- Can use classic or modified ketogenic diet
 - Many different approaches can be used
 - Example: following classic diet when receiving chemotherapy/radiation and modified diet when between cycles
 - Choose based on goals and what will work for your patient to be successful
- Goal is to maximize ketosis and minimize glucose/insulin
 - Adjusting net carb amount
 - Intermittent fasting
 - Avoiding excess protein intake
 - Exogenous ketones
 - Use of supplements
 - Need ketone/glucose meter
 - Incorporate use of Glucose Ketone Index (GKI) (currently studied in brain tumors)

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Glucose Ketone Index (GKI)



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