

Ketogenic Diets – The Next Anti-Cancer Therapy?

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Disclosures

- **Speaker:** Angela Martens, RD
- **Relationships with commercial interests:**
 - Grants/Research Support:** none
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 - Consulting Fees:** none
 - Other:** none

Mitigating Potential Bias

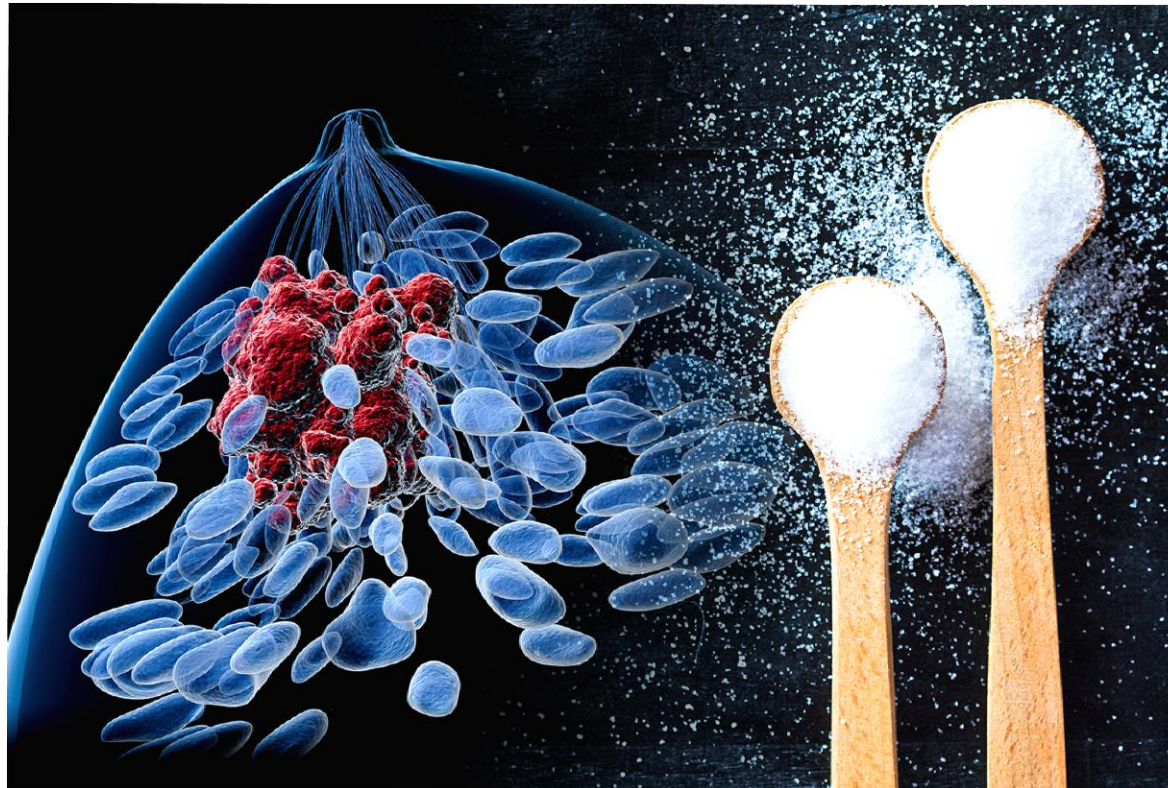
- Not applicable

Learning Objectives

At the end of the presentation the learner will be able to:

- 1) Describe the ketogenic diet as an emerging metabolic treatment for cancer.
- 2) Appraise the scientific evidence pertaining to ketogenic diets and cancer.
- 3) State the potential benefits and challenges associated with the ketogenic diet.
- 4) Discuss how to assist patients in making informed decisions regarding ketogenic diets.

Does Sugar Feed Cancer?



Otto H. Warburg

Warburg Theory of Cancer

- Cancer arises from damage to cellular respiration.
- Energy through fermentation gradually compensates for insufficient respiration.
- Respiratory damage eventually becomes irreversible.
- Cancer cells continue to ferment glucose in the presence of oxygen (aerobic glycolysis or Warburg effect).

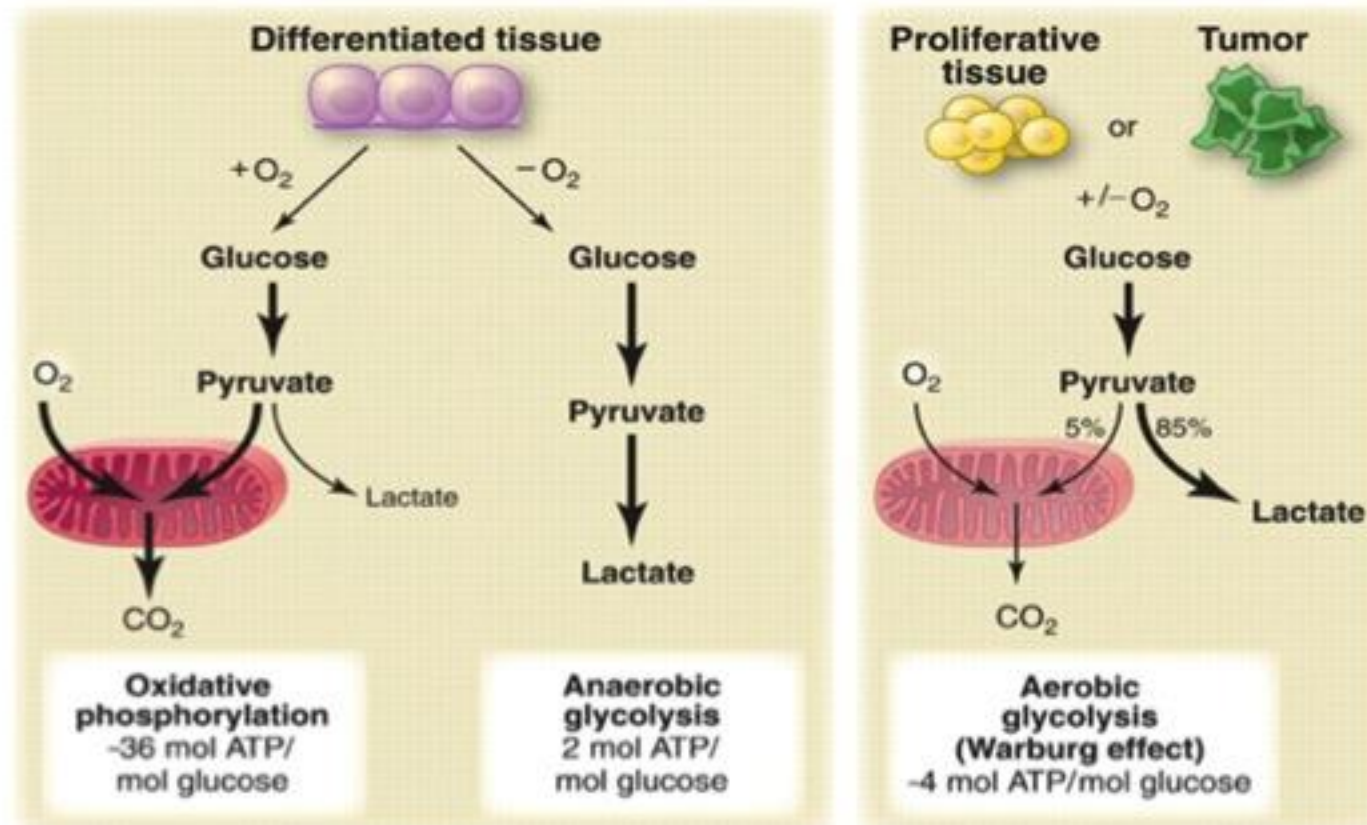
Cancer metabolism:

.....exploiting the metabolic difference

1920's Otto Warburg:

'Cancer cells defined by aerobic glycolysis'

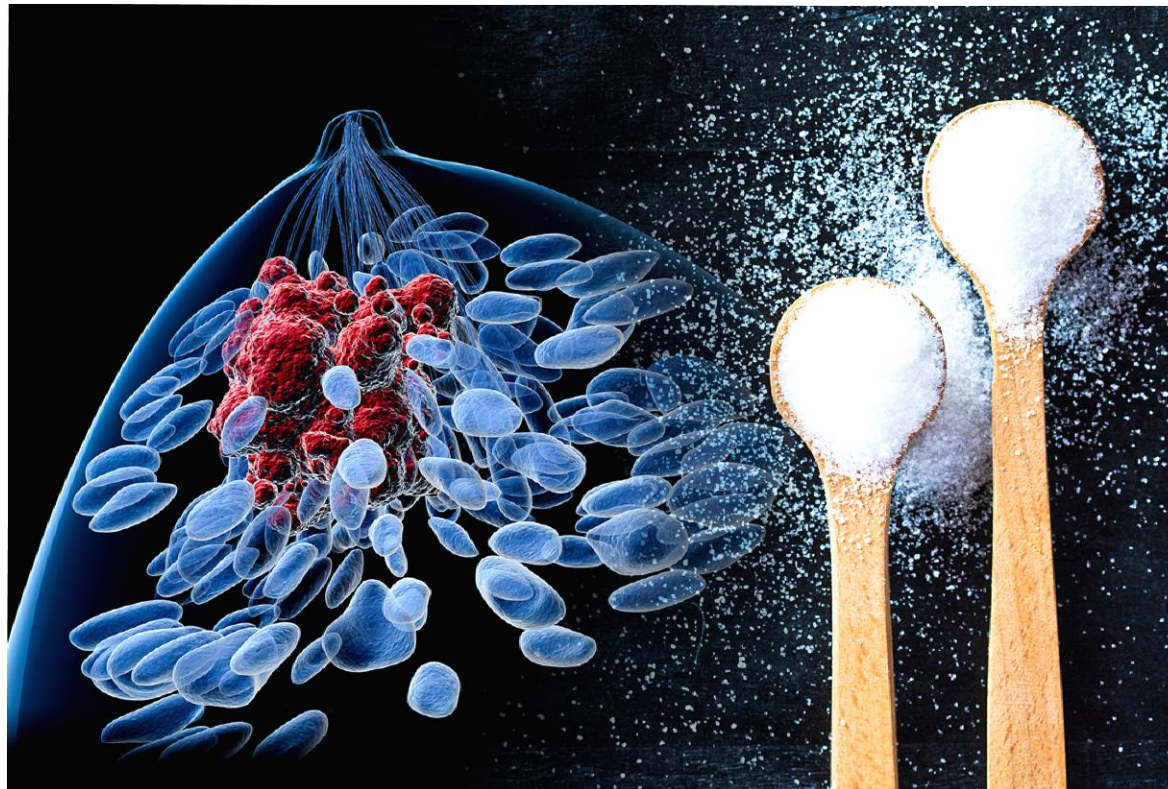
Less efficient and reliant on glucose



Can we selectively “starve” cancer by

~~Does Sugar Feed Cancer?~~

decreasing glucose availability?



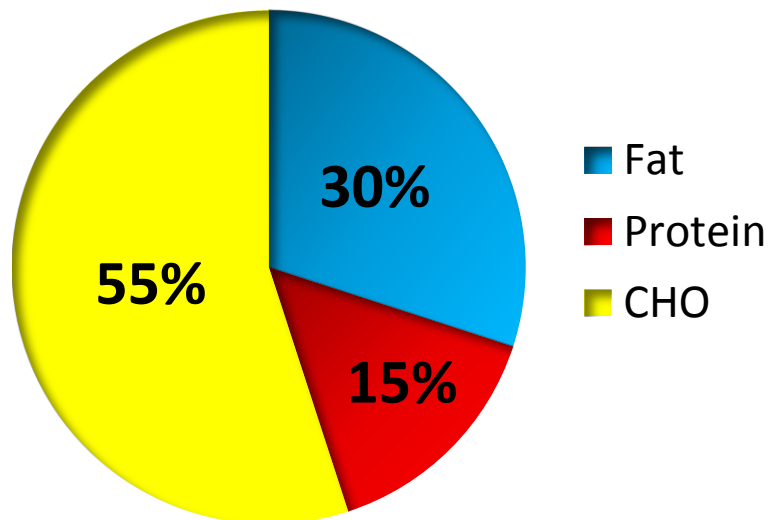
What is a Ketogenic Diet?



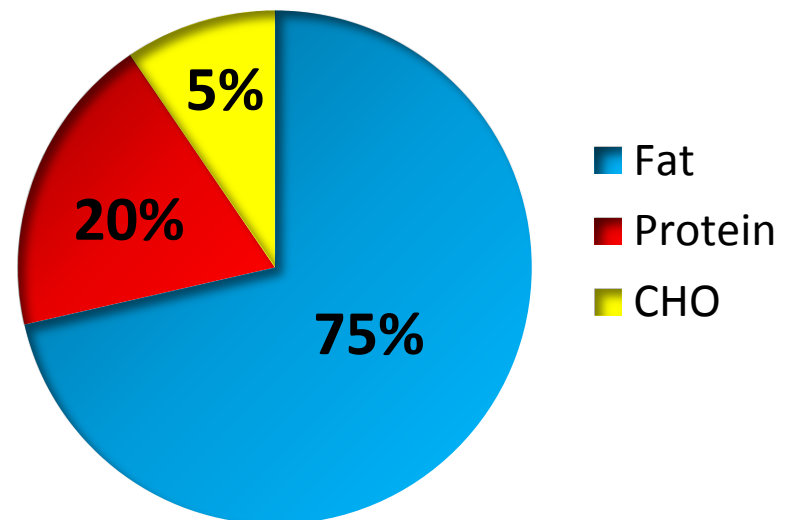
Ketogenic Diet (KD)

- Very low carbohydrate, high fat diet which alters metabolism in the body.

Standard Diet



Ketogenic Diet



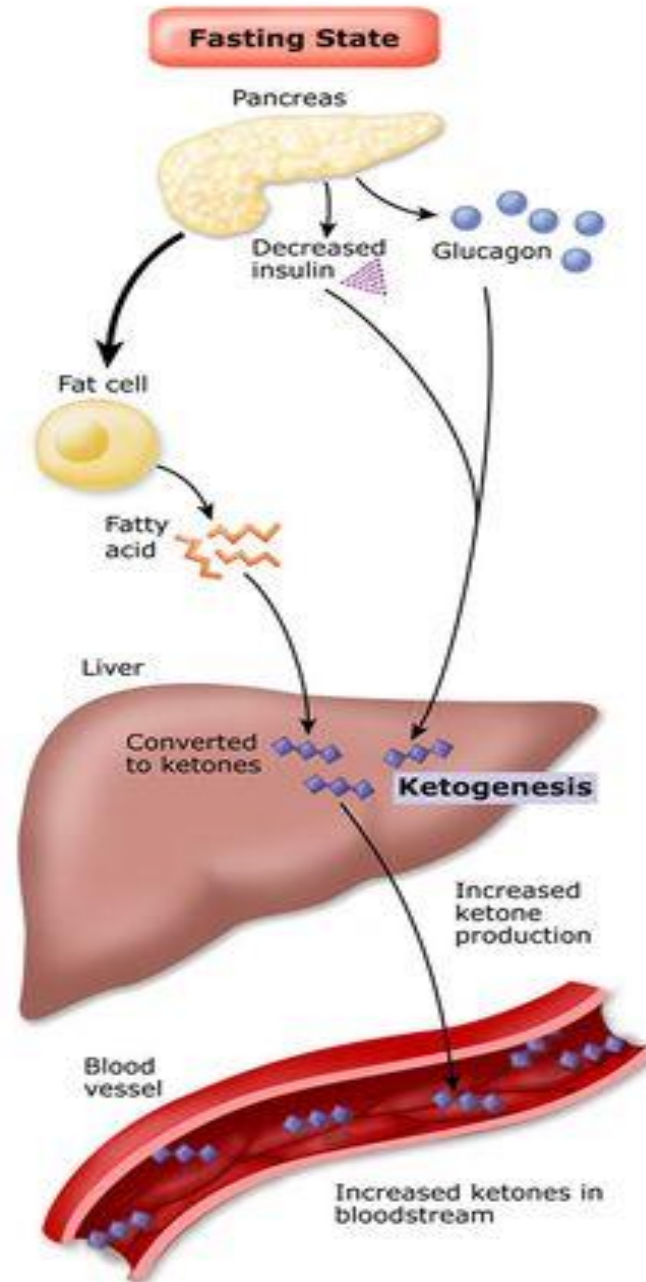
Ketogenic Diet → Ketosis

- Body switches from burning glucose to burning fat for energy.
- Carbohydrate restriction and fasting promote ketosis or the formation of ketone bodies;
 - beta-hydroxybutyrate (found in blood; most prevalent)
 - acetoacetate (found in urine)
 - acetone (found in the breath)
- “Nutritional ketosis” – not the same as ketoacidosis.
- Ketone bodies can be used as an energy source for normal cells but not cancer cells.

Ketone Production by Liver During Fasting Conditions (Ketosis)

Ketosis

- Stimulated by fasting or carbohydrate restriction.



Testing for Ketosis

Urine Ketones

- ketone urine strips (Ketostix[®])
- not very reliable
- influenced by hydration status
- cheap (<\$10 for 50 strips)

Breath Ketones

- Ketonix[®] Breath Analyzer
- doesn't always correlate to blood ketones
- can be influenced by alcohol and water intake
- low long term cost

Blood Ketones

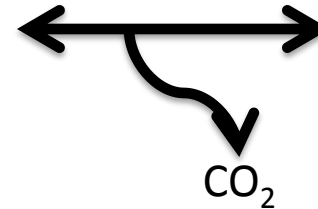
- blood glucose/ketone meter (Precision Freestyle Neo[™])
- very accurate
- requires finger prick for blood
- best indicator of your true state of ketosis
- can be costly (\$2-\$4 per strip)

Ketone Clearance

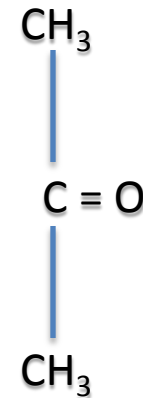
beta-
hydroxybutyrate
(blood)



acetoacetate
(urine)



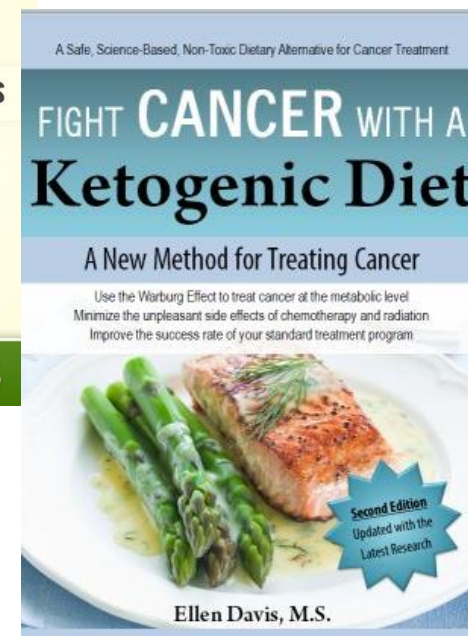
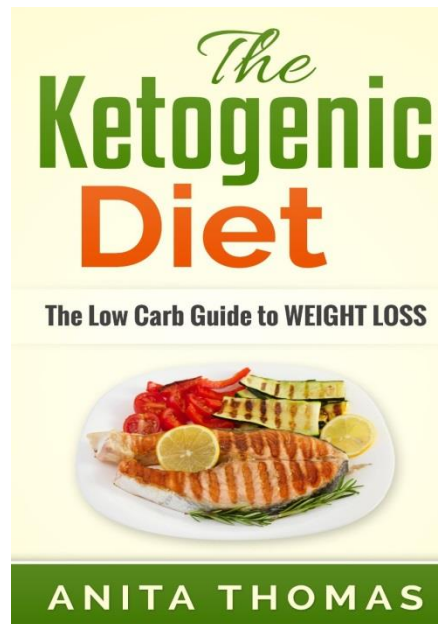
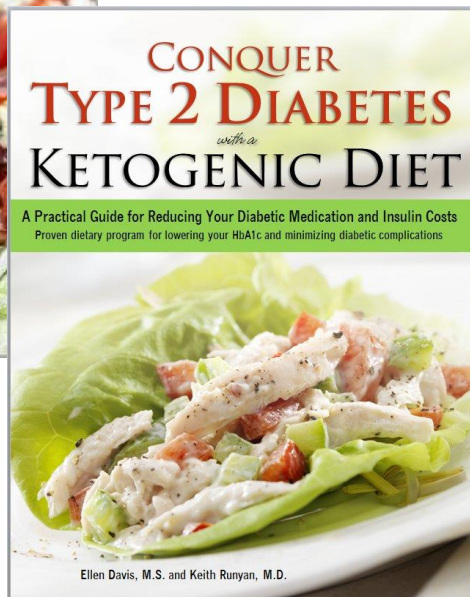
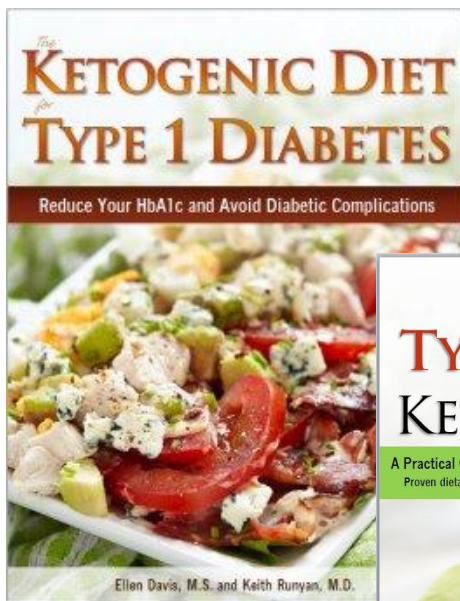
acetone
(breath)



Ketogenic Diets

- Recognized treatment for seizure disorders since 1920s.
- 15 to 45% of all cases are inoperable or medication-resistant epilepsy.
- KD is administered under the care of a neurologist and dietitian.
- KD is widely accepted in varying cultures and cuisines around the world.
- Other potential uses are being investigated or promoted.

Other Promoted Uses



Types of Ketogenic Diets

- Classic Ketogenic Diet (4:1)
- Modified Atkins Diet (1:1)
- MCT Diet
- Low Glycemic Index Diet

more restrictive



less restrictive

Comparison of various ketogenic diets can be found at;

www.charliefoundation.org

Classic Ketogenic Diet (4:1)

- KD are calculated by using a ratio of fat to combined carbohydrate (CHO) and protein
- 4:1 ratio → fat (grams): CHO (grams) + protein (grams)
- For a 2000 calorie, 4:1 ketogenic diet;

Fat	200 grams (90% of calories)
Carbohydrate	10 grams (2% of calories)
Protein	40 grams (8% of calories)

Classic Ketogenic Diet (4:1)

- Uses heavy cream, olive oil, MCT, coconut oil, butter and mayonnaise for the majority of fat.
- Protein-rich foods with high biological value are recommended.
- Carbohydrates are limited to small amounts of fruits and vegetables (no grain products allowed).
- Special meal plans and recipes are required.
- All foods need to be weighed.

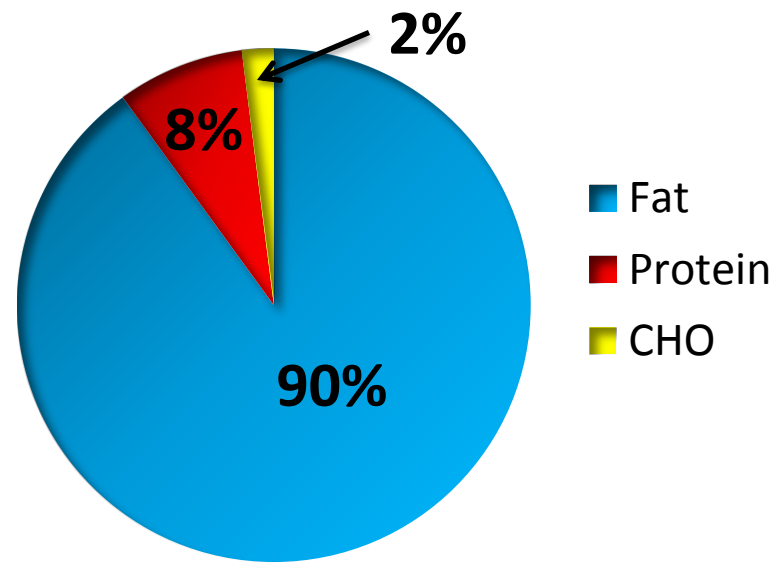
Modified Atkins Diet (1:1)

- 1:1 ratio → fat (grams): CHO (grams) + protein (grams)
- Carbohydrates are not to exceed 20 grams per day.
- Protein is *generally* not limited.
- For a 2000 calorie, 1:1 ketogenic diet;

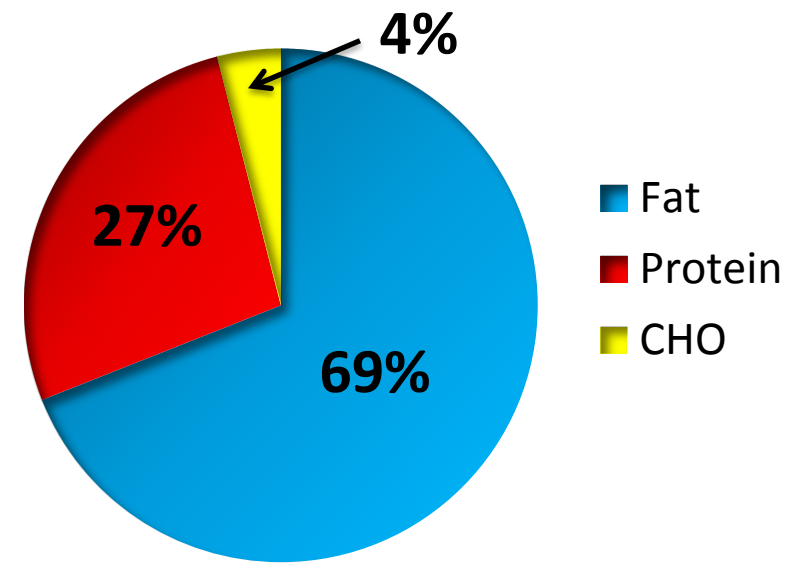
Fat	150 grams (69% of calories)
Carbohydrate	20 grams (4% of calories)
Protein	130 grams (27% of calories)

Energy Distribution

Classic 4:1 Diet



Modified Atkins 1:1



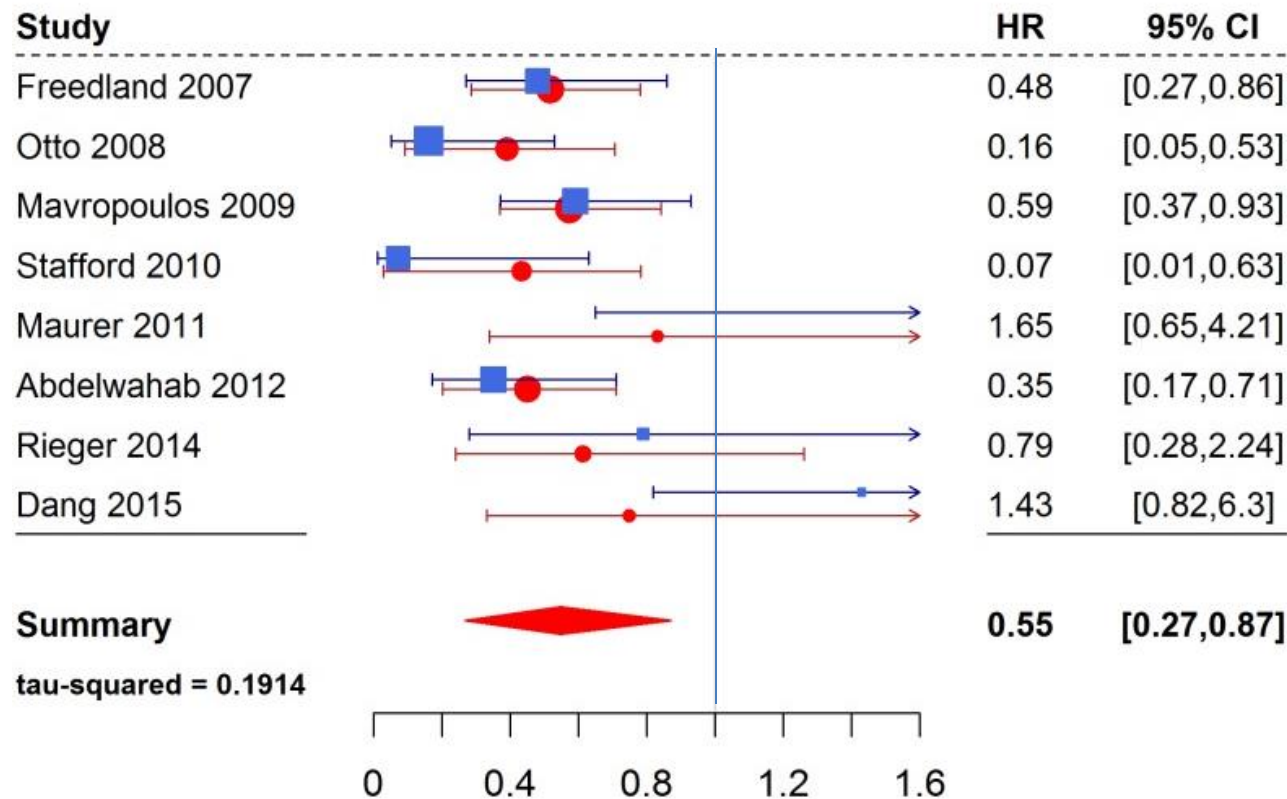
Ketogenic Diet – Cancer Evidence

- Ketogenic diets inhibit growth of brain tumors in;
 - pre-clinical studies in animals
 - published human case studies^{1,2}
- Anecdotal evidence.
- A number of case reports in the literature show ketogenic diets are safe and tolerable.
- Increasing number of clinical trials (especially using ketogenic diets with standard cancer therapy).

¹Nebeling L et al. 1995. Effects of a ketogenic diet on tumor metabolism and nutritional status in pediatric oncology patients: two case reports. *J Am Coll Nutr* 14(2): 202-208.

²Zuccoli G et al. 2010. Metabolic management of glioblastoma multiforme using standard therapy together with a restricted diet: case report. *Nutri Metab.* 7:33-53.

Pre-Clinical Anti-Cancer Effects





"It's an award for a cancer cure, but it only works on mice."

Ketogenic Diet – Cancer Evidence

- Limitations → heterogeneity of study designs, timing of KD initiation, inconsistency in outcome measures, etc.
- Some studies show better anti-tumor effects with KD plus calorie-restriction (pre-clinical evidence).
- Some studies report no significant ↓ in serum glucose levels, especially if calories are unrestricted (↑ in serum ketones is likely more important).

ERGO Study

- Patients with recurrent glioblastoma.
- N = 20
- Unrestricted ketogenic diet (<60 grams CHO).
- 3 subjects dropped out due to diet intolerance.
- Tested urine ketones 2-3 times per week.

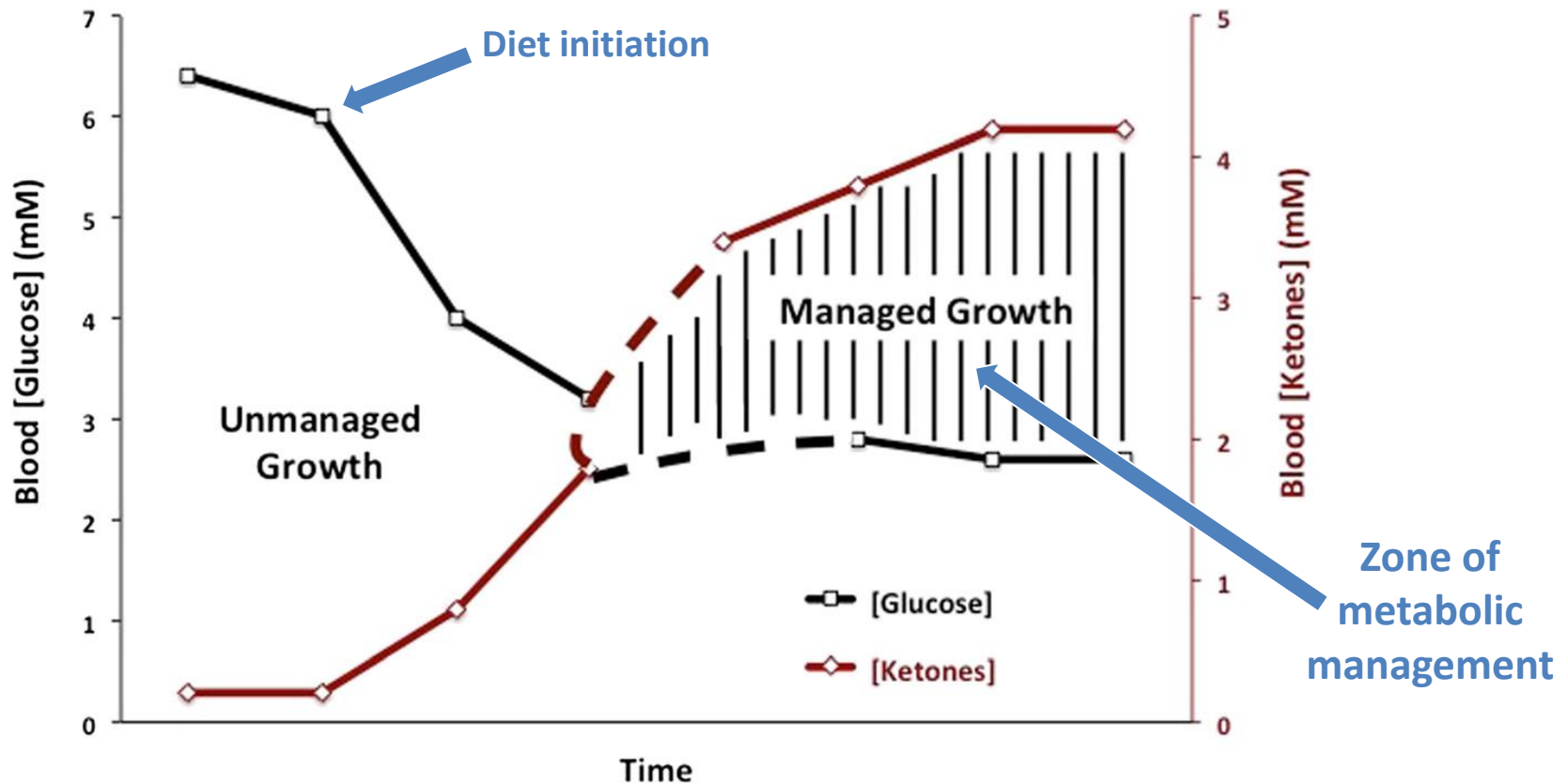
Rieger, Johannes et al. "ERGO: A Pilot Study of Ketogenic Diet in Recurrent Glioblastoma." *International Journal of Oncology* 44.6 (2014): 1843–1852. *PMC*. Web. 2 Oct. 2016.

ERGO Study

- Not all subjects achieved ketosis.
- Average weight loss was 2.2%.
- All progressed on diet alone (median time to progression was 5 weeks).
- Overall, diet was shown to be safe.
- Subjects on KD and bevacizumab had best results.

Rieger, Johannes et al. "ERGO: A Pilot Study of Ketogenic Diet in Recurrent Glioblastoma." *International Journal of Oncology* 44.6 (2014): 1843–1852. *PMC*. Web. 2 Oct. 2016.

Figure 1: Relationship of plasma glucose and ketone body levels to brain cancer management.



Glucose/Ketone Index (GKI)

- A clinical biomarker to predict therapeutic success of metabolic therapy in brain cancer.

$$\text{GKI} = \frac{\text{Glucose (mmol/L)}}{\text{Ketones (mmol/L)}}$$

- Therapeutic efficacy in humans is likely considered best with GKI between 1.0 and 2.0.
- Serum glucose and ketone values should be measured 2-3 hours post-prandial, twice a day if possible.

Ketogenic Diet – Cancer Evidence

- Currently, 19 clinical trials listed at www.clinicaltrials.gov when searching “ketogenic diet and cancer” (3 terminated due to poor accrual).
- Most studies are focusing on brain tumors.
- Many are Phase I or II studies (assessing diet safety, tolerability).

Clinical Trial for Malignant Brain Tumors

NCT02046187 (Clinicaltrials.gov)

St. Joseph's Hospital and Medical Center, Phoenix, AZ

- Newly diagnosed high grade glioma.
 - Target → 20 gross total resection + 20 subtotal resection
- Ketogenic diet plus standard care (surgery & radiation/temozolomide & maintenance temozolomide).
- 2 year survival rates, adverse events, QoL.
- Compare to historic controls in treatment arm of EORTC temozolomide study (NEJM, Mar 2005).
- Study dates → Oct 2013 to Mar 2018

Clinical Trial for Malignant Brain Tumors

NCT02046187 (Clinicaltrials.gov)

St. Joseph's Hospital and Medical Center, Phoenix, AZ

- Quality of life – patient & caregivers.
- Karnofsky & health-related QoL tests;
 - changes in seizure activity & medications
 - changes in steroid medications
- Neurocognitive tests.
- Daily monitoring of blood glucose & ketones;
 - Ketone levels >3 mmol/L (ideally ~4)
 - Glucose levels ~4 mmol/L

Clinical Trial for Malignant Brain Tumors

NCT02046187 (Clinicaltrials.gov)

St. Joseph's Hospital and Medical Center, Phoenix, AZ

- Patient/caregiver meet with RD to receive education on KD after surgery.
- 4:1 KD is implemented one week prior to start of RT and maintained for 2-4 weeks after RT completion.
- Calorie requirement is ↓ to “resting” calorie needs (REE).
- Protein requirement is based on 0.8 g/kg/day.
- When ketosis is achieved (3-5 days after diet initiation), diet is liberalized to meet total calorie needs (TEE).

Clinical Trial for Malignant Brain Tumors

NCT02046187 (Clinicaltrials.gov)

St. Joseph's Hospital and Medical Center, Phoenix, AZ

- Ensure adequate water intake (2 litres/day).
- May need OTC medications for constipation.
- Daily multivitamin/mineral supplement.
- Meal pattern of 3 meals/day plus snacks as needed.
- Regular food and KetoCal[®] supplement (if desired).
- Transfer to Modified Atkins diet (1:1) for maintenance (long term).
- Using Ketocalculator[®] online database.

Case Report

- 62 yo female; “Anne”
- Stage IV glioblastoma multiforme (IDH1 neg)
- Jul 2016 → seizures; left parietal lesion
- Aug 2016 → craniotomy and debulking
- completed 60 Gy RT/temozolomide in Oct 2016
- Nov 2016 → maintenance temozolomide
- ketogenic diet was recommended by Anne’s relative (pediatric neurologist)

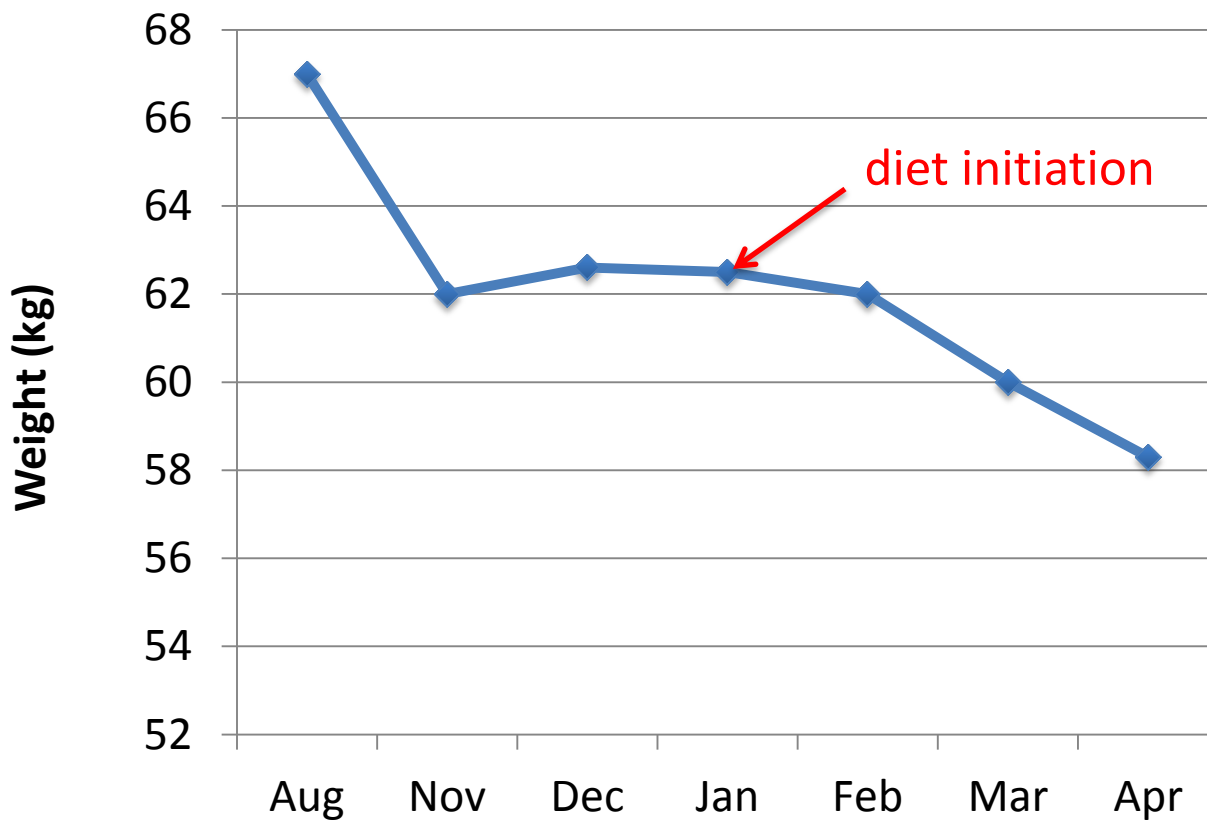
Case Report

- Jan 2017 → implemented 2:1 ketogenic diet;
 - 1600 calories based on her TEE (26 calories/kg)
 - 53 grams protein (0.8 grams/kg)
 - 20 grams net carbohydrate (net = total carbohydrate minus fibre)
 - 145 grams fat
- Recommended by RD;
 - Food scale
 - Glucose/ketone meter with strips → prescription from oncologist
 - Urine ketone strips
 - Subscription to MyFitnessPal™ (patient's preference instead of KetoCalculator®)

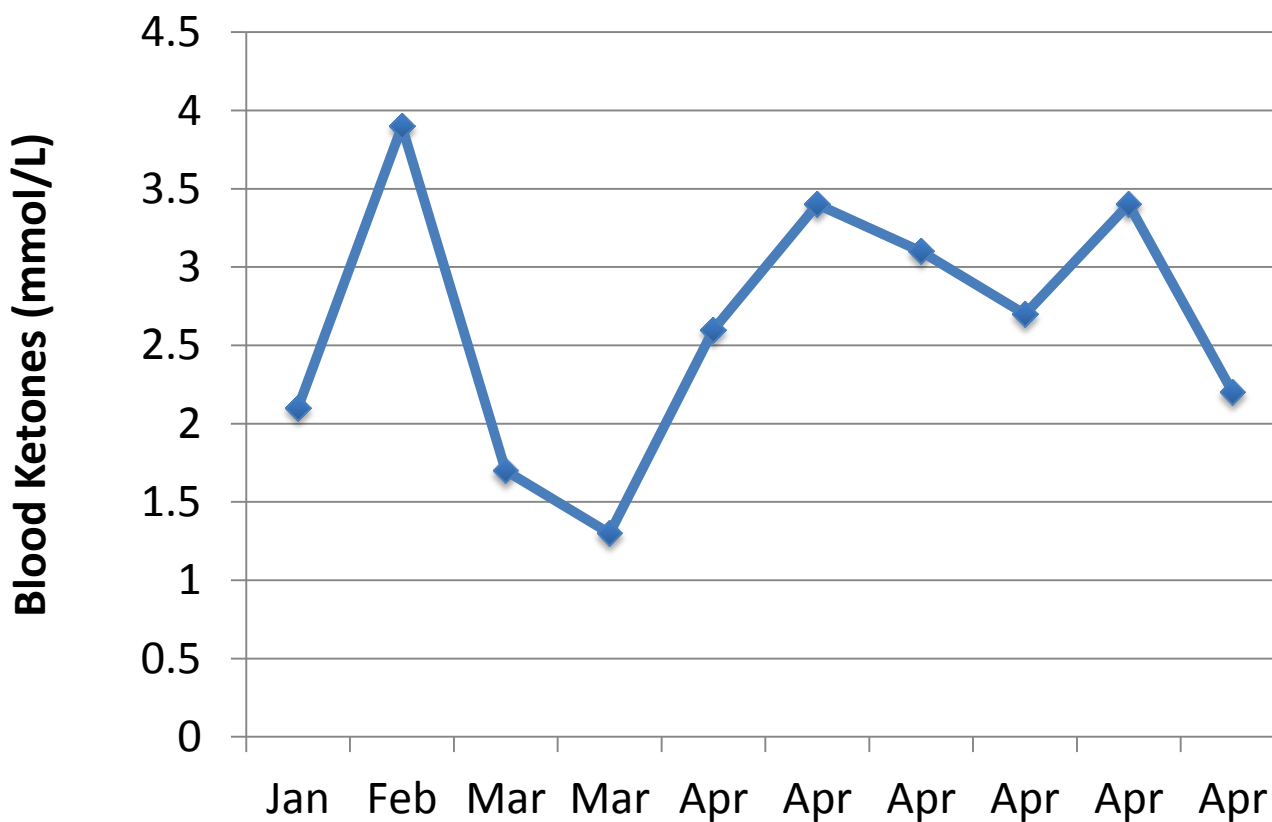
Case Report

- Supplements → multivitamin/mineral, vitamin D₃
- OTC laxative
- Dexamethasone dose → 4 mg bid
- QoL → good energy levels, travelling
- Fatigue on week of chemotherapy
- Anthropometrics (Nov-16)
 - Height = 154 cm; Weight = 62 kg; BMI = 26
 - Prior weight loss of 5 kg or 7.5% since surgery

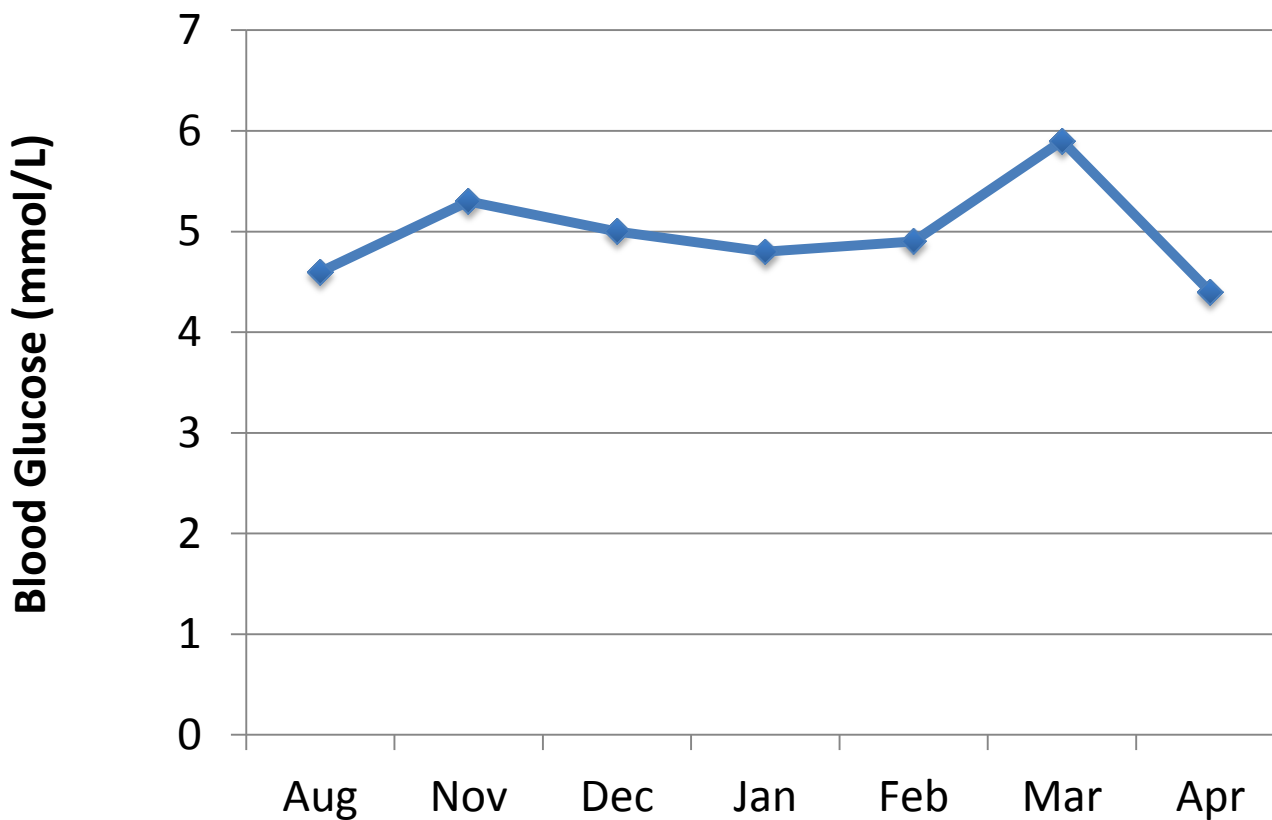
Case Report



Case Report



Case Report



*dexamethasone
4 mg bid

Nutrition Goals: 1600 kcal – 20 g net Carb – 145 g Fat – 55 to 60 g Protein

<u>BREAKFAST</u>	<u>LUNCH</u>
1 egg	50 g sockeye salmon
15 g cheddar cheese	1 Tbsp mayo
100 g Portobello mushroom	1 cup green leaf lettuce
1 cup raw spinach	70 g English cucumber
50 g zucchini	3 cherry tomatoes
5 cherry tomatoes	¼ cup red bell pepper
5 g coconut oil	1/5 medium avocado
1.5 Tbsp olive oil	1 Tbsp whipping cream (35% MF)
<u>DINNER</u>	<u>EVENING SNACK</u>
1 sausage stuffed with feta/spinach	0.5 servings of pumpkin cheesecake
60 g Portaoello mushroom	2 Tbsp blueberries
11.6 g Boursin cheese	5 Tbsp whipping cream (35% MF)
50 g cauliflower	
1 cup raw spinach	
2 Tbsp olive oil	

Benefits/Challenges of Ketogenic Diets

- Long safety record in pediatric epilepsy.
- Shown to be well-tolerated in case studies.
- Low toxicity profile other than risk for kidney stones and constipation.
- Cost effective → inexpensive compared to current cancer therapies.
- Patients feel “a sense of control”.

Benefits/Challenges of Ketogenic Diets

- Comprehensive nutrition education & monitoring required (especially in early implementation).
- Some expense involved for patient (food scale, glucose/ketone meter and testing strips).
- Important to monitor for weight loss.

Communicating with Patients



"You're eating too much sugar."

Communicating with Patients

- Key responsibility of healthcare providers → assist our patients in making “informed” decisions.
- Due to lack of “robust” clinical evidence at the current time, ketogenic diets are not currently being routinely prescribed or recommended in oncology.
- For those patients motivated to implement a KD;
 - Discuss the current state of scientific evidence.
 - Consider the pros and cons on an individual basis.
 - Refer to “keto-friendly” registered dietitian.

Summary

- 1) Pre-clinical and early clinical evidence that ketogenic diets can influence cancer progression is promising.
- 2) Ketogenic diets are safe and tolerable but require effort to implement and maintain (medical & nutritional monitoring is highly recommended).
- 3) Clinicians need to stay up-to-date in this area in order to help guide informed decision-making.
- 4) More clinical research is needed (and is underway).

Key Issues for Future Research

- 1) Lack of a prescribed “dose” of dietary restriction → what is the optimal diet?
- 2) Concerns regarding associated weight loss.
- 3) Need to define optimal endpoints or clinical biomarkers for response and efficacy.
- 4) Examine safety and efficacy of combination strategies (ketogenic diets & treatment approaches).

QUESTIONS?

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