

Sugar, Cancer, & the Ketogenic Diet: *Can I Eat a Piece of Cake?*

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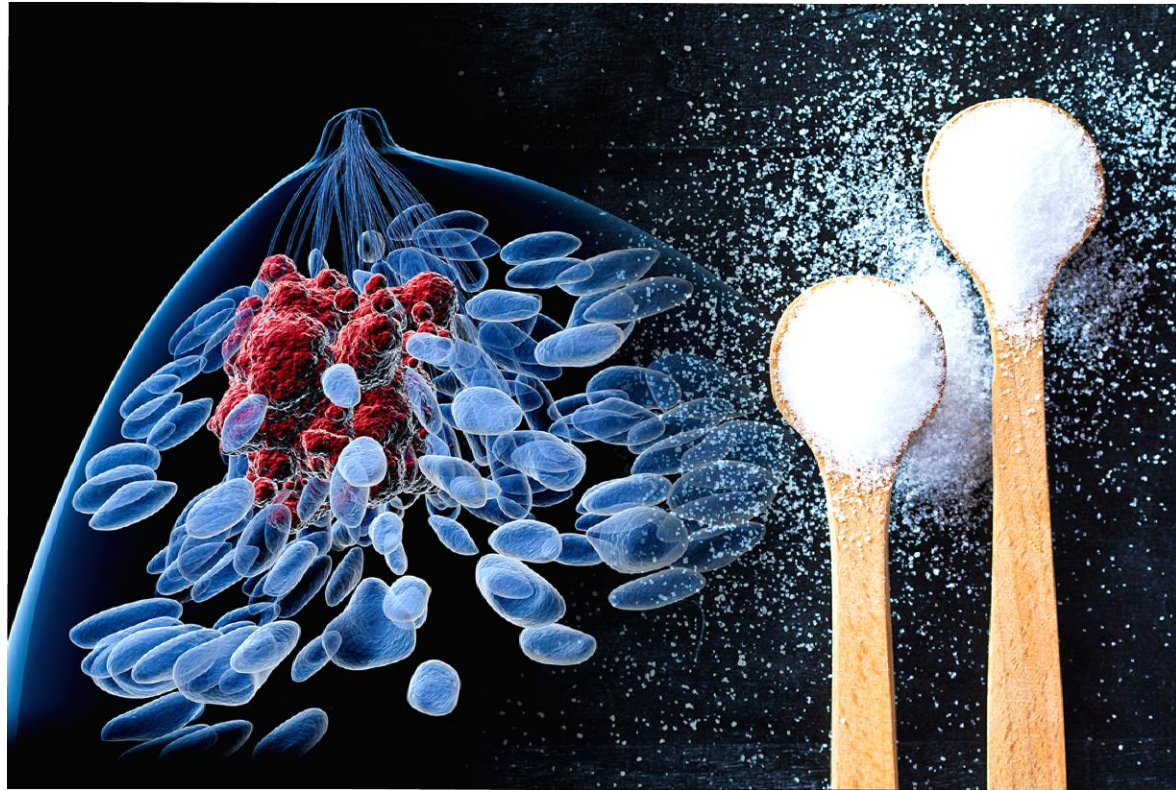
Presenter Disclosure

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 - Other:** none

Mitigating Potential Bias

- Not applicable.

Does Sugar Feed Cancer?



Learning Objectives

At the end of this session, participants will be able to:

- 1) Describe the potential links between sugar and cancer.
- 1) Appraise the scientific evidence pertaining to low carbohydrate or ketogenic diets and cancer.
- 1) Discuss how to assist cancer patients in making informed decisions regarding sugar intake and ketogenic diets.

Sugar & Cancer Link

Hyperglycemia & Cancer

- Epidemiologic evidence suggests that individuals with diabetes are at significantly higher risk for many types of cancer (liver*, pancreatic*, colorectal, breast, endometrial and bladder)¹.
- Hyperglycemia occurs more frequently in cancer patients than in the general population.
- Prevalence in cancer patients ranges from 39% to 99%².
- Meta-analysis of 23 articles → 41% increase in cancer mortality in cancer patients (endometrial, breast, colorectal) with pre-existing diabetes compared with normoglycemic patients³.

Sugar & Cancer Link

Hyperglycemia & Cancer

- Although the exact mechanisms are still not clear, research shows that hyperglycemia may contribute to *enhanced*;
 - cancer cell proliferation
 - apoptosis inhibition
 - metastasis
 - perineural invasion
 - chemotherapy resistance
 - reduced treatment tolerance
- Inconsistencies in measuring and assessing hyperglycemia in cancer patients².
- Lack of standardized guidelines in treating hyperglycemia².

Sugar & Cancer Link - Mechanisms

Metabolism



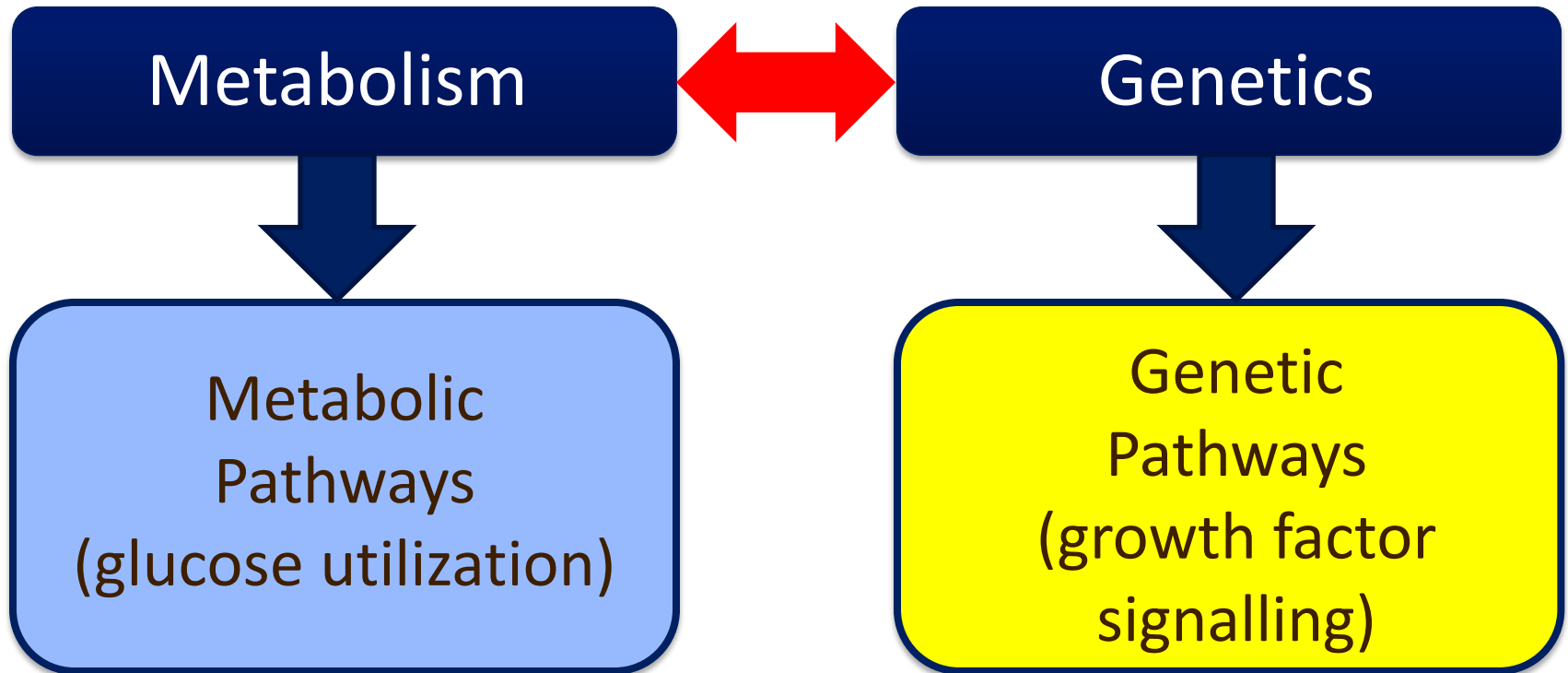
Metabolic
Pathways
(glucose utilization)

Genetics



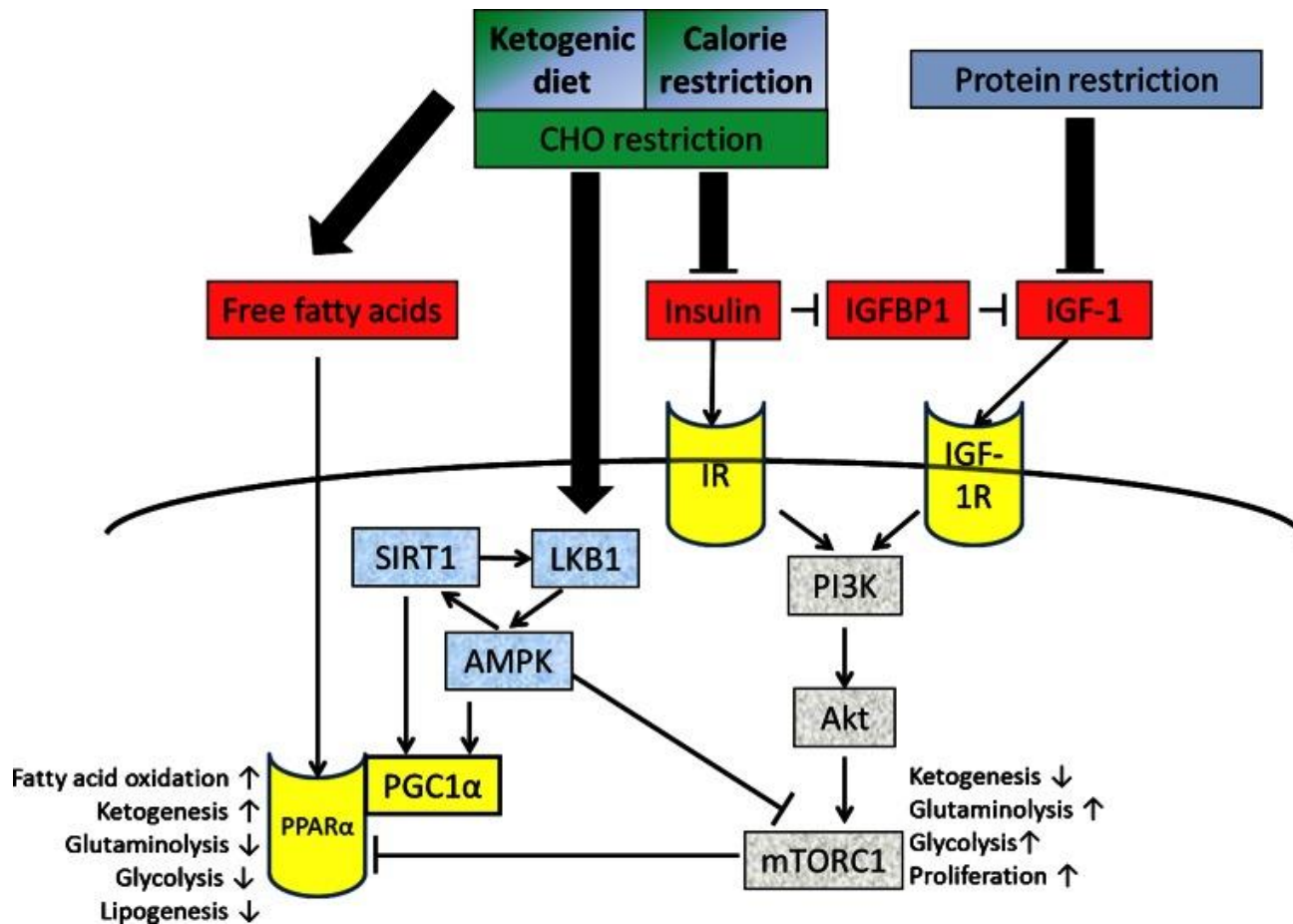
Genetic
Pathways
(growth factor
signalling)

Sugar & Cancer Link - Mechanisms



Metabolism & genetics regulate each other!

Sugar & Cancer Link⁴



Cancer Metabolism – Otto 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).

Origin of Cancer Cells, Science, Feb 1956

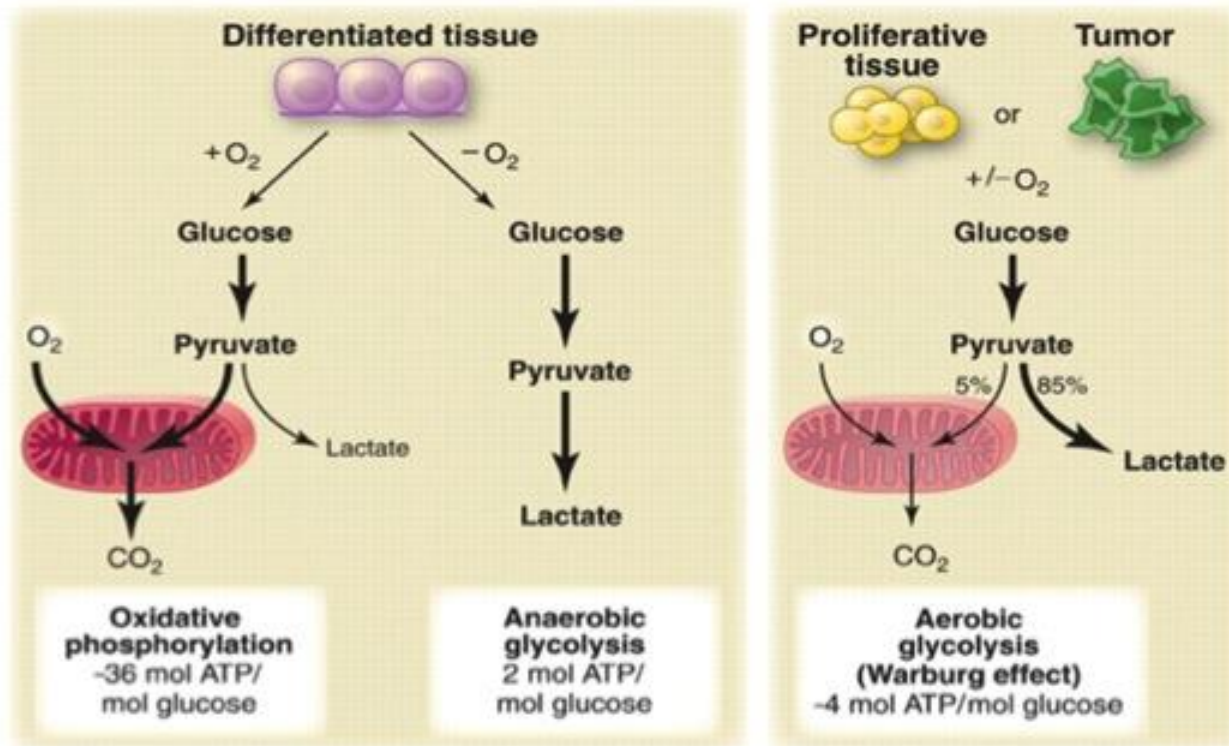
Cancer metabolism:

.....exploiting the metabolic difference

1920's Otto Warburg:

'Cancer cells defined by aerobic glycolysis'

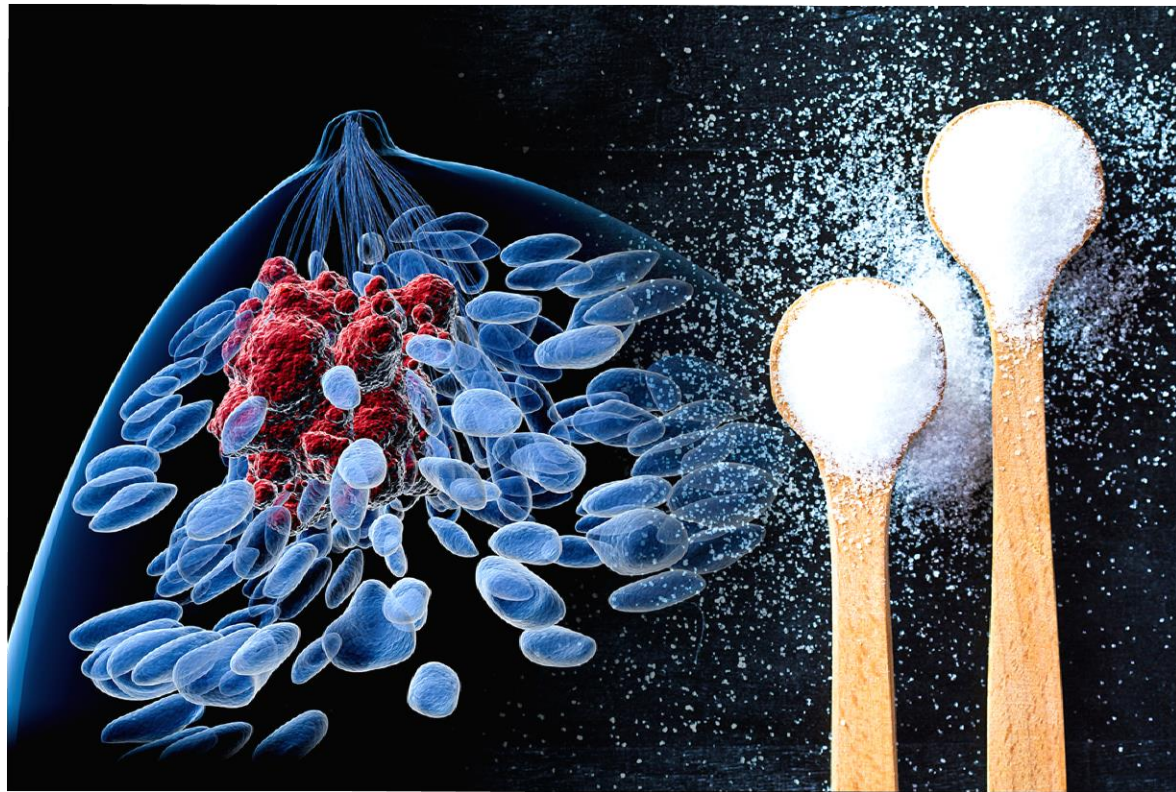
Less efficient and reliant on glucose



Klement R, Kammerer U. Is there a role for carbohydrate restriction in the treatment of and prevention of cancer. Nutrition & Metabolism. 2011; 8:75

~~Does Sugar Feed Cancer?~~ **YES!**

Can we selectively “starve” cancer cells...



... by limiting glucose availability?

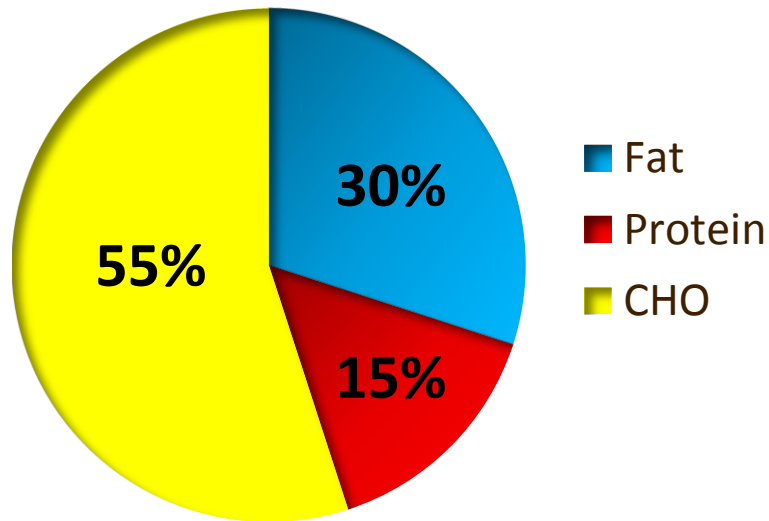
What is a Ketogenic Diet?



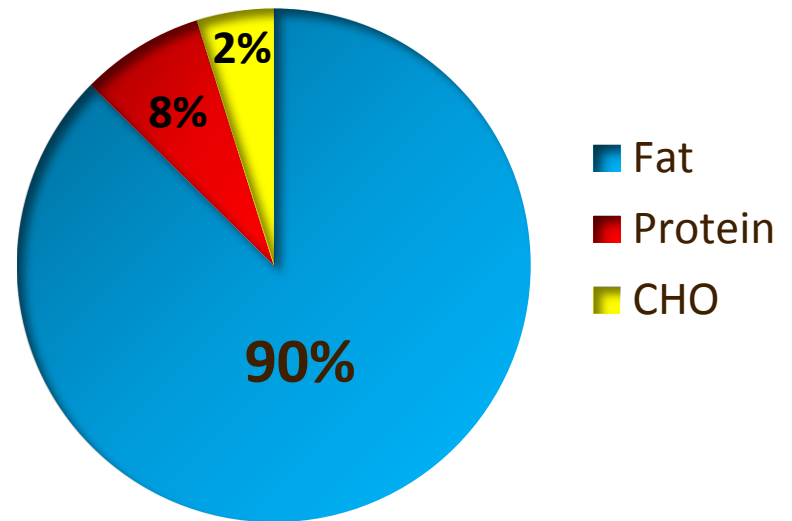
Ketogenic Diet (KD)

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

Standard Diet



Ketogenic Diet

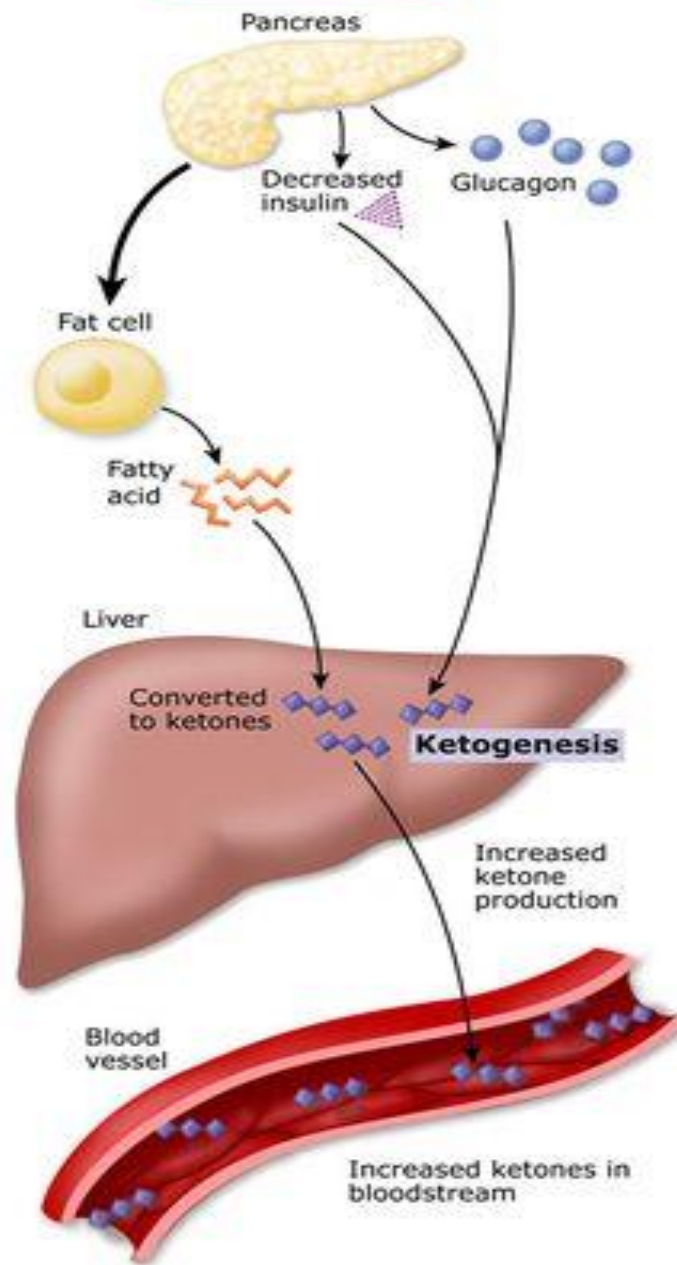


Ketogenic Diet → Ketosis

- Body switches from burning glucose to burning fat for energy.
- Carbohydrate restriction and fasting both 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.
- Normal cells can use ketone bodies as an energy source.
- Most cancer cells are not able to use ketone bodies to meet their high energy needs (rely on glucose).

Ketosis

Stimulated by fasting
or carbohydrate
restriction.



Testing for Ketosis

Urine Ketones

- ketone urine strips
- not very reliable
- influenced by hydration status
- inexpensive (<\$10 for 50 strips)

Breath Ketones

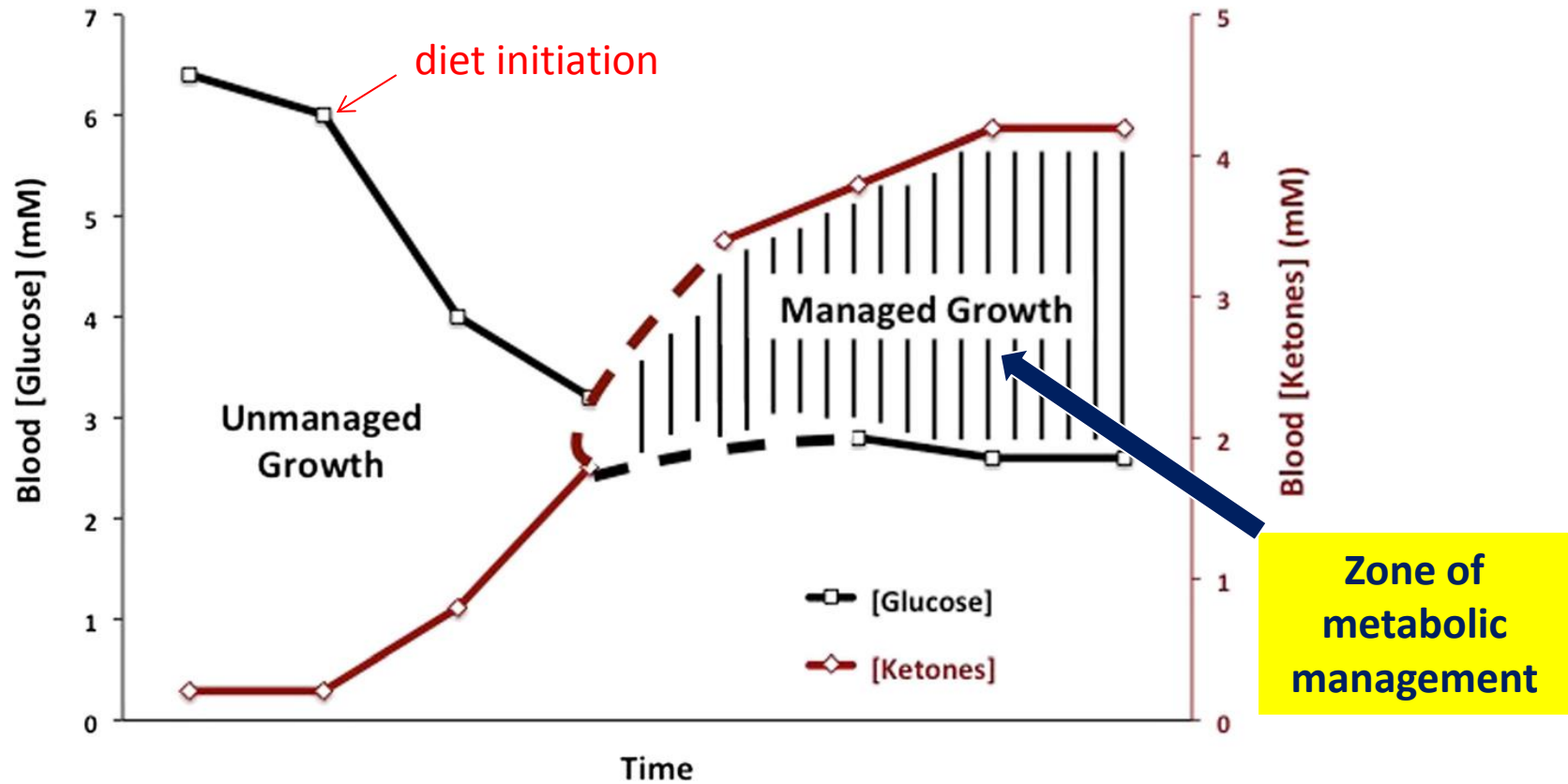
- ketone breath analyzer
- doesn't always correlate to blood ketones
- can be influenced by alcohol and water intake
- low long term cost

Blood Ketones

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

Testing for Ketosis⁵

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



Glucose/Ketone Index (GKI)⁵

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

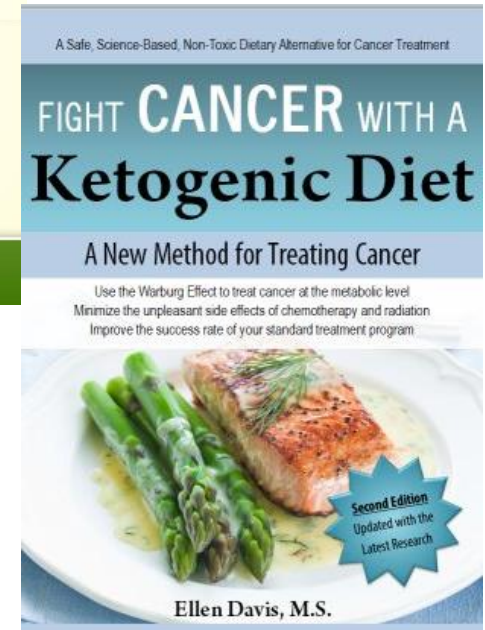
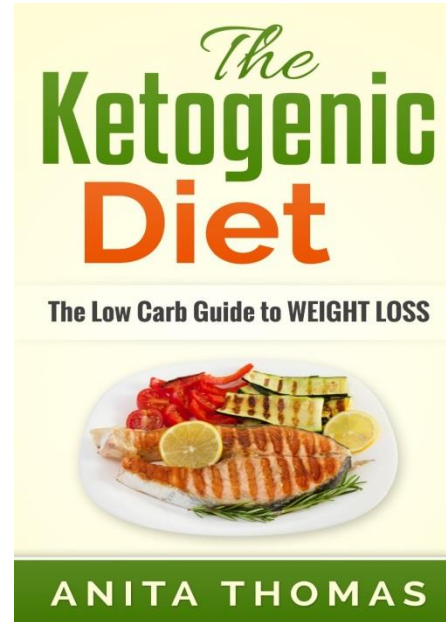
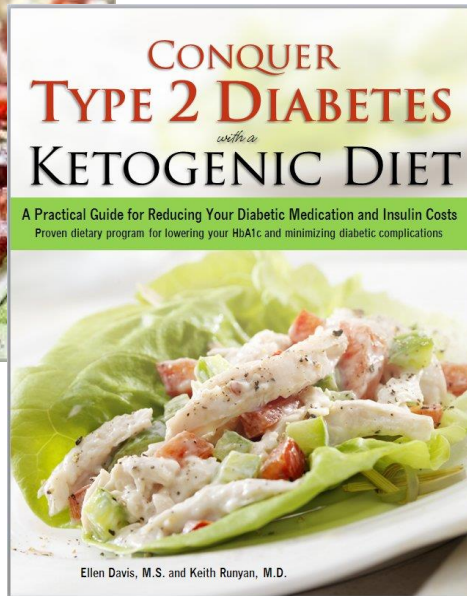
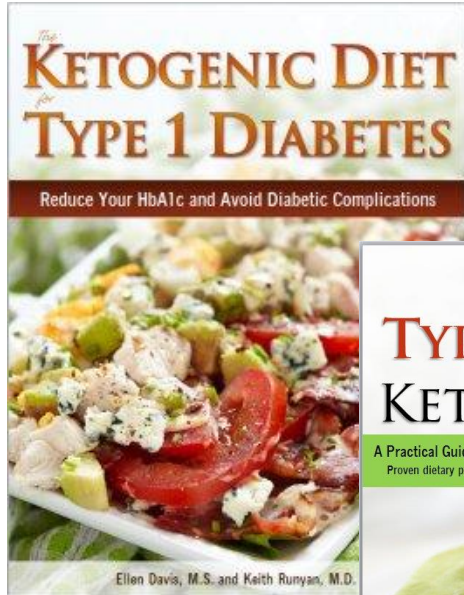
$$\text{GKI} = \frac{\text{Glucose (mmol/L)}}{\text{Ketones (mmol/L)}}$$

- 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 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 (medical supervision).
- KD are widely accepted in varying cultures and cuisines around the world.
- Other potential uses are being investigated or promoted (weight loss, type 2 diabetes, Alzheimer's, autism, Parkinson's).

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, vegetable oil, MCT, coconut oil, butter, mayo & avocado 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.

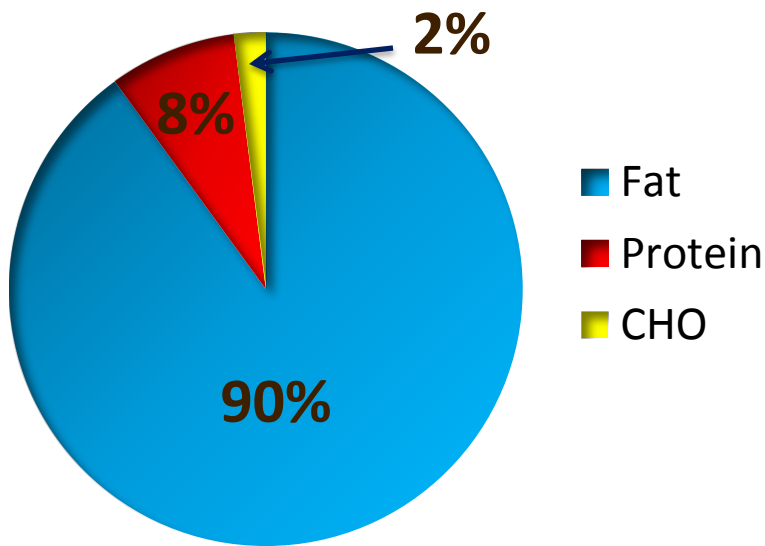
Modified Atkins Diet (1:1)

- 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;

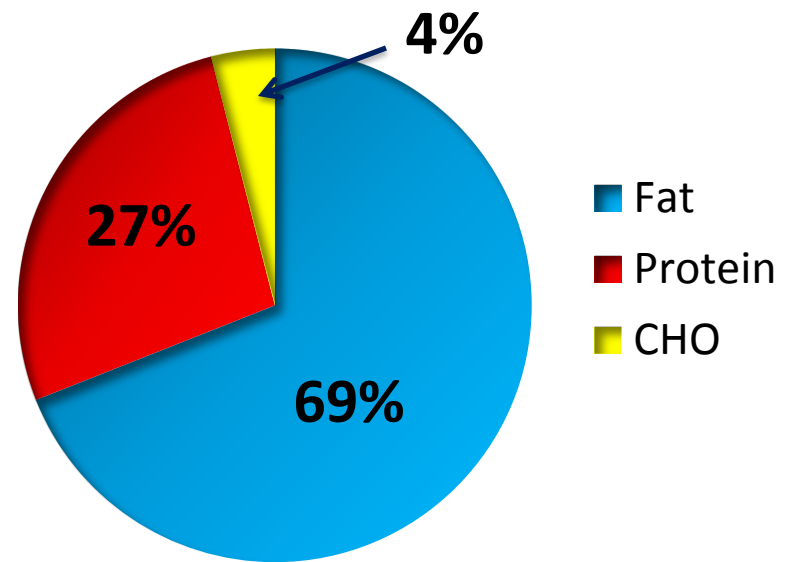
Fat	150 grams (69% of calories)
Carbohydrate	20 grams (4% of calories)
Protein	130 grams (27% of calories)

Energy Distribution

Classic 4:1 Diet



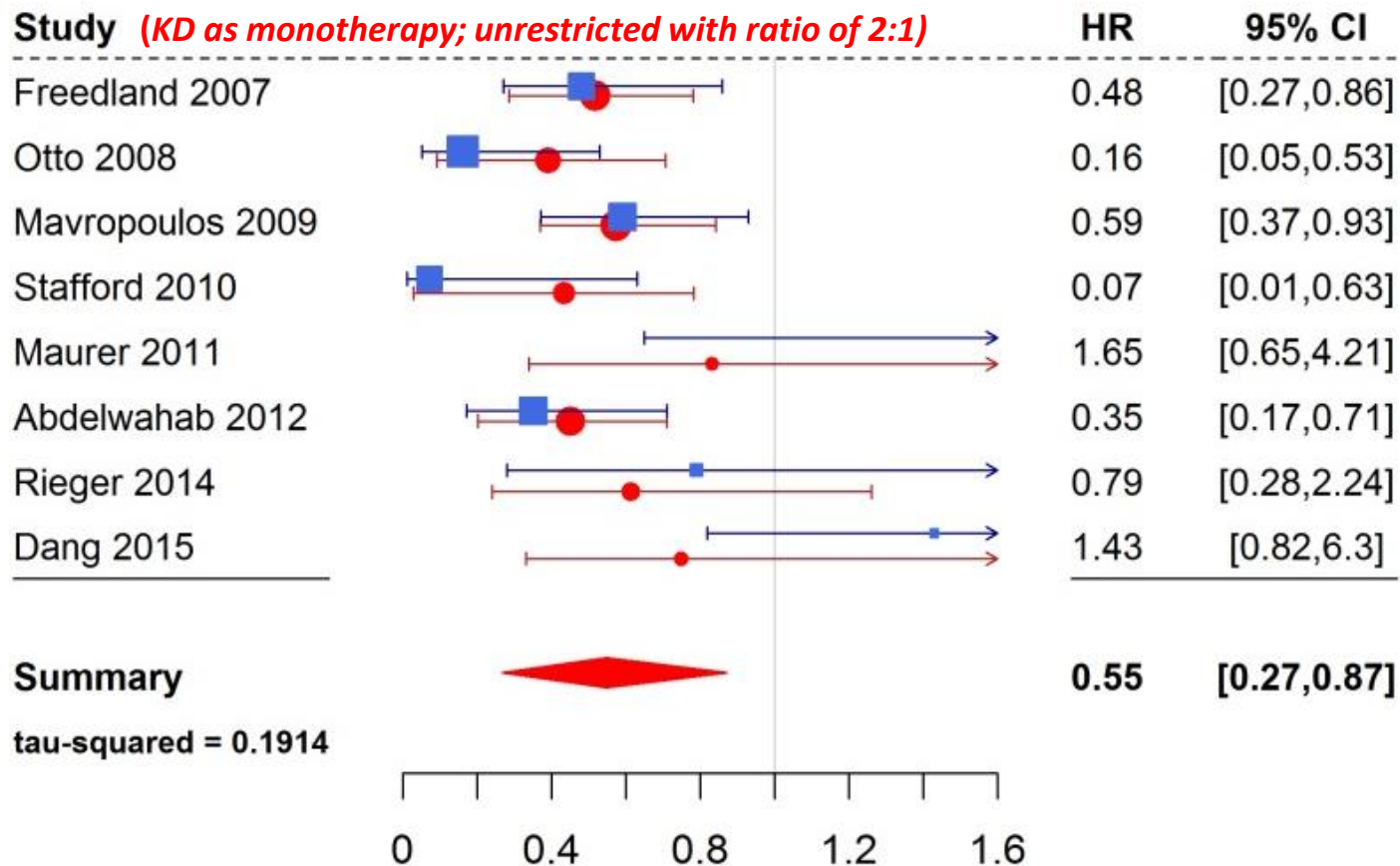
Modified Atkins 1:1



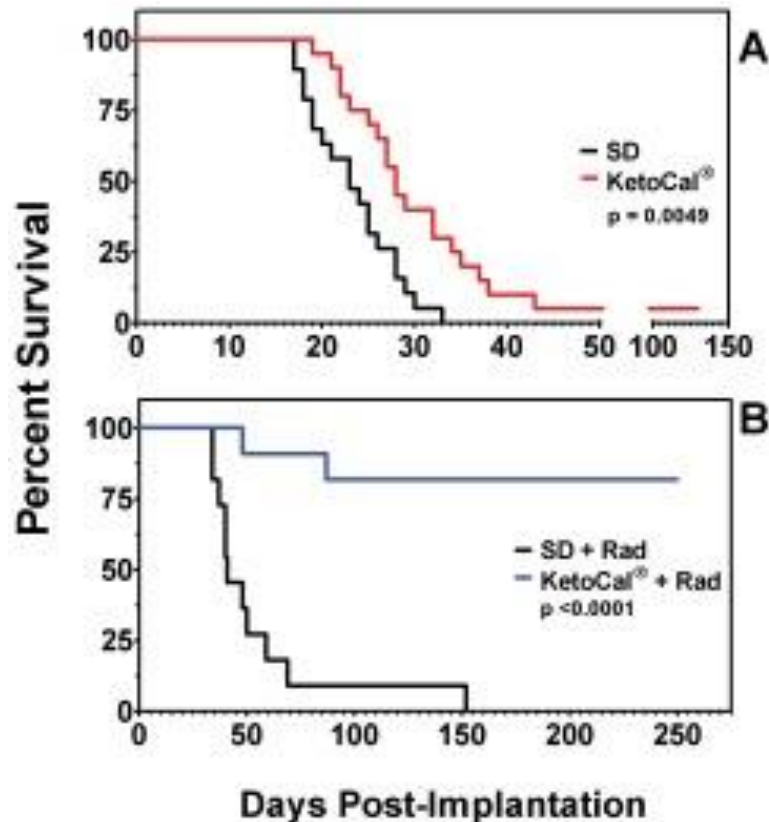
Managing Side Effects of the KD

- *Micronutrient deficiency* → daily multivitamin & mineral supplement, vitamin D, calcium.
- *Constipation* → OTC laxative is recommended.
- *High cholesterol* → diet should emphasize healthy fats, especially if pre-existing hypercholesterolemia.
- *Weight loss* → initially in the form of water bound to glycogen; weight maintenance can be achieved.
- *Renal calculi* → ensure adequate water intake.
- *Upset stomach* → take ¼ tsp baking soda with 6 to 8 ounces of water several times per day.

KD & Pre-Clinical Evidence⁶



KD & Pre-Clinical Evidence⁷



Treatment	Cohort Size	Median Survival (Days)
SD	19	23
KetoCal [®]	19	28
SD + Rad	11	41
KetoCal [®] + Rad	11	Undefined

Ketogenic Diet & Clinical Evidence⁸

- Narrative review of clinical trials published between 1988 and 2016.
- 14 studies conducted in humans;
 - average sample size N=15 (range of 1 to 78)
 - 5/14 studies → KD with treatment (1 CT; 4 CRT)
 - 5/14 studies → KD alone
 - 4/14 studies → not mentioned
 - diet duration was 5 days to 12 months

Ketogenic Diet & Clinical Evidence⁸

- 14 studies conducted in humans;
 - 6/14 studies → nutrition counseling (only 1 specified RD)
 - cancer types varied substantially among studies
 - mixed results in terms of disease progression → due to varying degrees of ketosis achieved?
 - majority of studies demonstrated diet tolerability & safety

Ketogenic Diet & Clinical Evidence

- Limitations → heterogeneity of study designs, timing of KD initiation, inconsistency in outcome measures (ketone testing), etc.
- Clinical studies often conducted in subjects with advanced stage cancer.
- 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).

Ketogenic Diet & Cancer Evidence

- Currently, 21 clinical trials listed at www.clinicaltrials.gov when searching “ketogenic diet and cancer”.
- Studies with various cancer types (most focusing on brain tumors).
- Assessing diet safety, tolerability, body composition changes, survival, blood parameters.

Benefits/Challenges with KDs

- KDs have a long safety record in epilepsy.
- Shown to be well-tolerated in case studies.
- Overall low toxicity profile (side effects can be effectively managed).
- Cost effective → inexpensive compared to current cancer therapies.
- Patients feel “a sense of control”.

Benefits/Challenges with KDs

- Comprehensive nutrition education & monitoring required (especially in early implementation).
- Important to monitor for weight loss.
- Some expense involved for patient (food scale, glucose/ketone meter and testing strips).
- Patients need to be highly motivated and have good social support.

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 this time, KDs are not currently being routinely prescribed in oncology but do show promise as a future metabolic nutritional therapy.
- 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.
- Emphasize the importance of good glycemic control for those patients with hyperglycemia.

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).

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