Exploiting Cancer Metabolism with Ketosis

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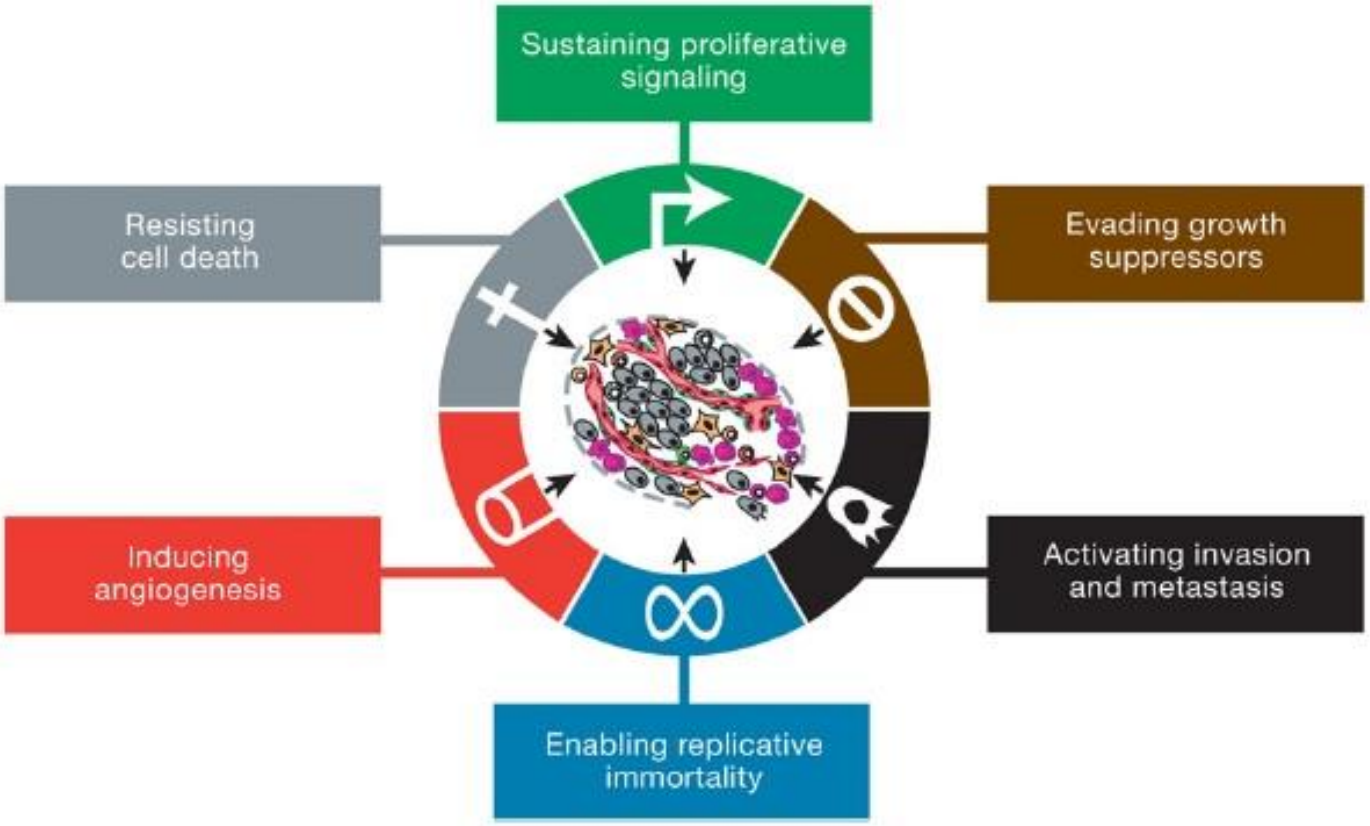
Disclosures:

- Scientific Consultant, Pruvit Venture
- Dominic P. D'Agostino; **Angela M. Poff**; Patrick Arnold; *"Targeting Cancer with Metabolic Therapy and Hyperbaric Oxygen"* (International Patent Application # PCT/US2013/072333)
- Dominic P. D'Agostino; **Angela M. Poff**; *"Ketone Esters and Suppression of Inflammation"* (Disclosure:#13A053, University of South Florida)

Disclaimer:

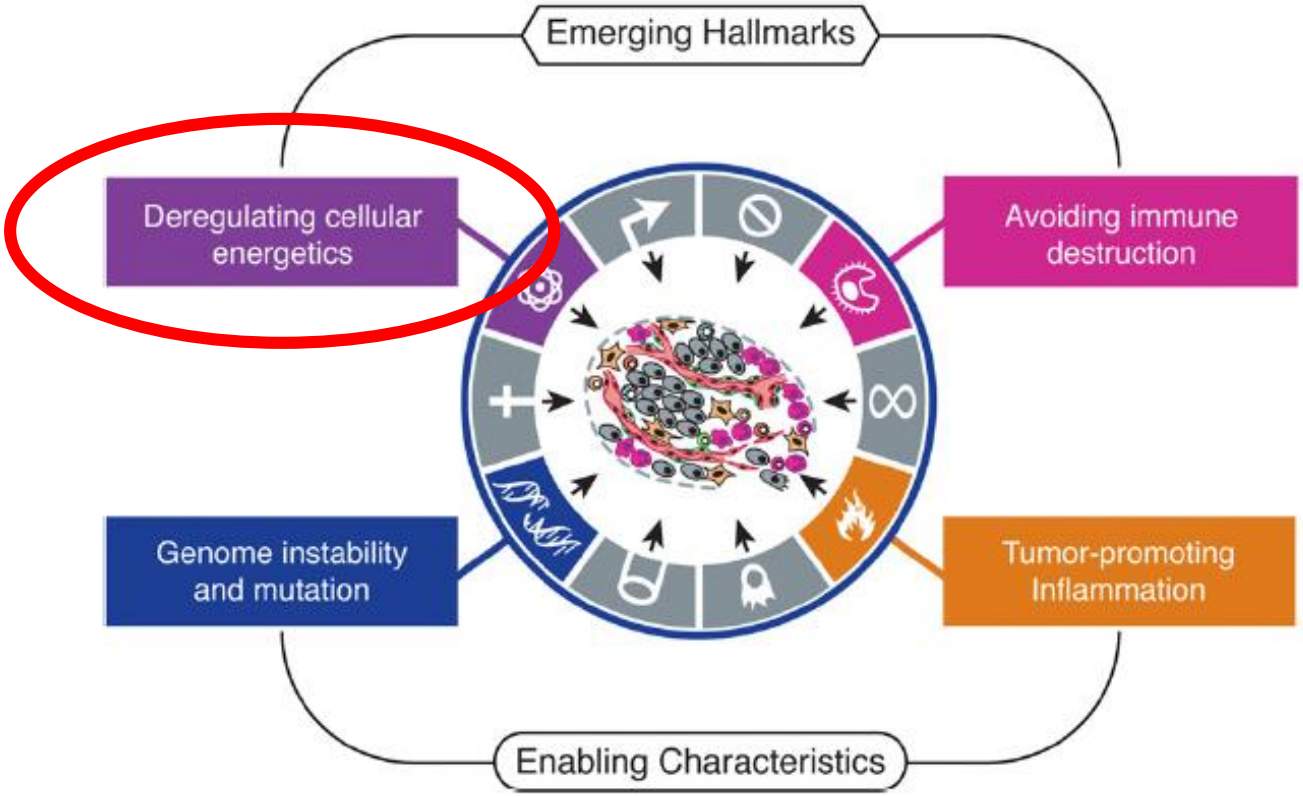
- The science being presented is in the investigatory stage and has not been fully tested in human clinical trials. I am not a physician, and this should not be considered medical advice.

What is Cancer?



- The Hallmarks of Cancer

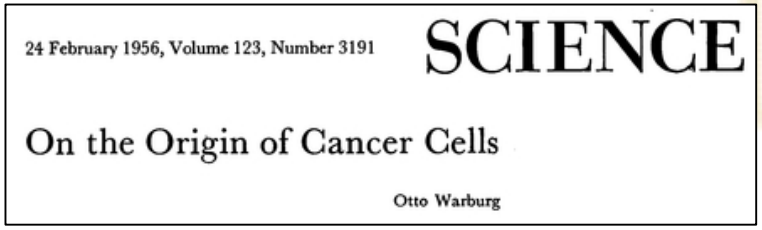
Hanahan and Weinberg, Cell, 2011

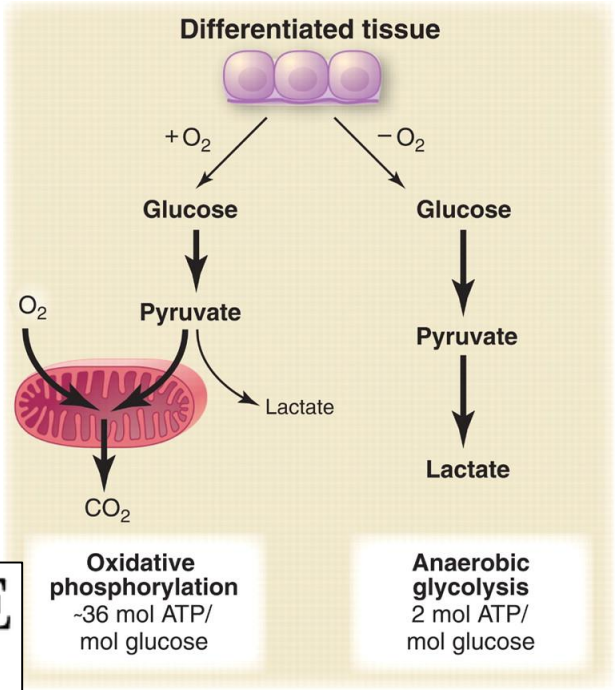


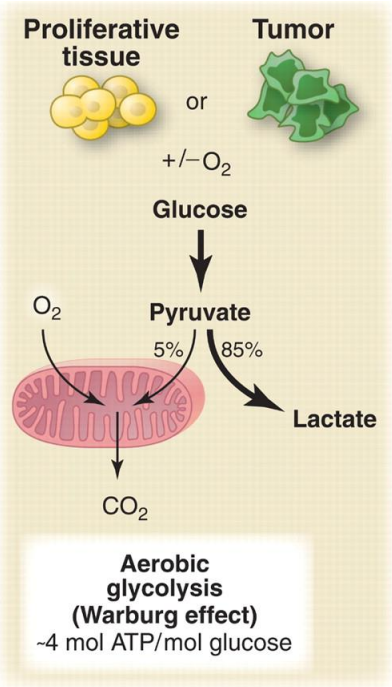
- In 2011, updated review proposed two enabling characteristics and two emerging hallmarks

Hanahan and Weinberg, Cell, 2011

Therapeutic Target: The Warburg Effect





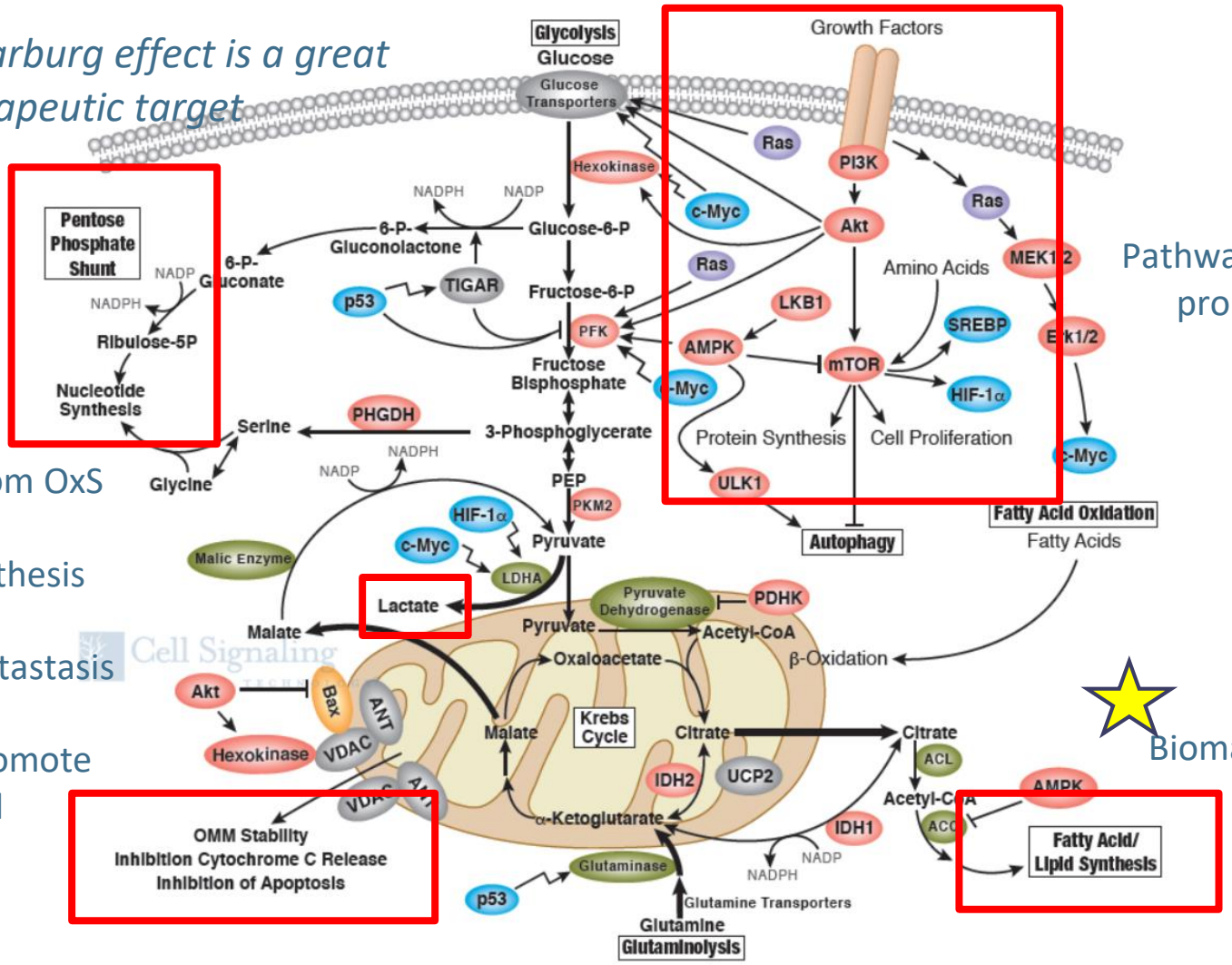


- Fermentation is a much less efficient mechanism of producing energy…. So why?

(Vander Heiden, Cantley et al. 2009)

Beneficial Consequences of the Warburg Effect

Thus, the Warburg effect is a great therapeutic target



Protection from OxS

Biomass synthesis

Invasion & metastasis

Pathways promote survival

Pathways stimulate proliferation

Biomass synthesis

- Glucose and insulin supply substrates to feed the Warburg effect and promoting tumor progression

Cell Signaling Technologies Image

^{18}F-FDG PET Scan

Metastatic Melanoma

- The Warburg Effect is a common feature of cancers and serves as the basis for one of the most important diagnostic tools in cancer treatment
- Radioactively-labeled glucose quickly taken up by cancer cells

http://www.nepetimaging.com/casemonth_february_05.html

Dietary carbohydrate intake is correlated cancer risk

Annals of Oncology **12**: 173–178, 2001.

Dietary glycemic load and colorectal cancer risk

S. Franceschi,[1,2] L. Dal Maso,[1] L. Augustin,[1,3] E. Negri,[4] M. Parpinel,[1] P. Boyle,[5] D. J. A. Jenkins[3] & C. La Vecchia[4,6]

Summary

Background: Insulin and insulin-like growth factors can stimulate proliferation of colorectal cells. High intake of refined carbohydrates and markers of insulin resistance are associated with colorectal cancer. To test the insulin/colon cancer hypothesis, we determined whether the dietary glycemic index and the glycemic load are associated with colorectal cancer risk.

Design: A case-control study on colorectal cancer conducted in Italy. Cases included 1125 men and 828 women with histologically confirmed incident cancer of the colon or rectum. Controls were 2073 men and 2081 women hospitalized for acute conditions. We calculated average daily dietary glycemic index and glycemic load, and fiber intake from a validated food frequency questionnaire.

Results: Direct associations with colorectal cancer risk emerged for glycemic index (odds ratio (OR) in highest vs. lowest quintile = 1.7; 95% confidence interval (CI): 1.4–2.0) and glycemic load (OR = 1.8; 95% CI: 1.5–2.2), after allowance for sociodemographic factors, physical activity, number of daily meals, and intakes of fiber, alcohol and energy. ORs were more elevated for cancer of the colon than rectum. Overweight and low intake of fiber from vegetables and fruit appeared to amplify the adverse consequences of high glycemic load.

Conclusions: The positive associations of glycemic index and load with colorectal cancer suggest a detrimental role of refined carbohydrates in the etiology of the disease.

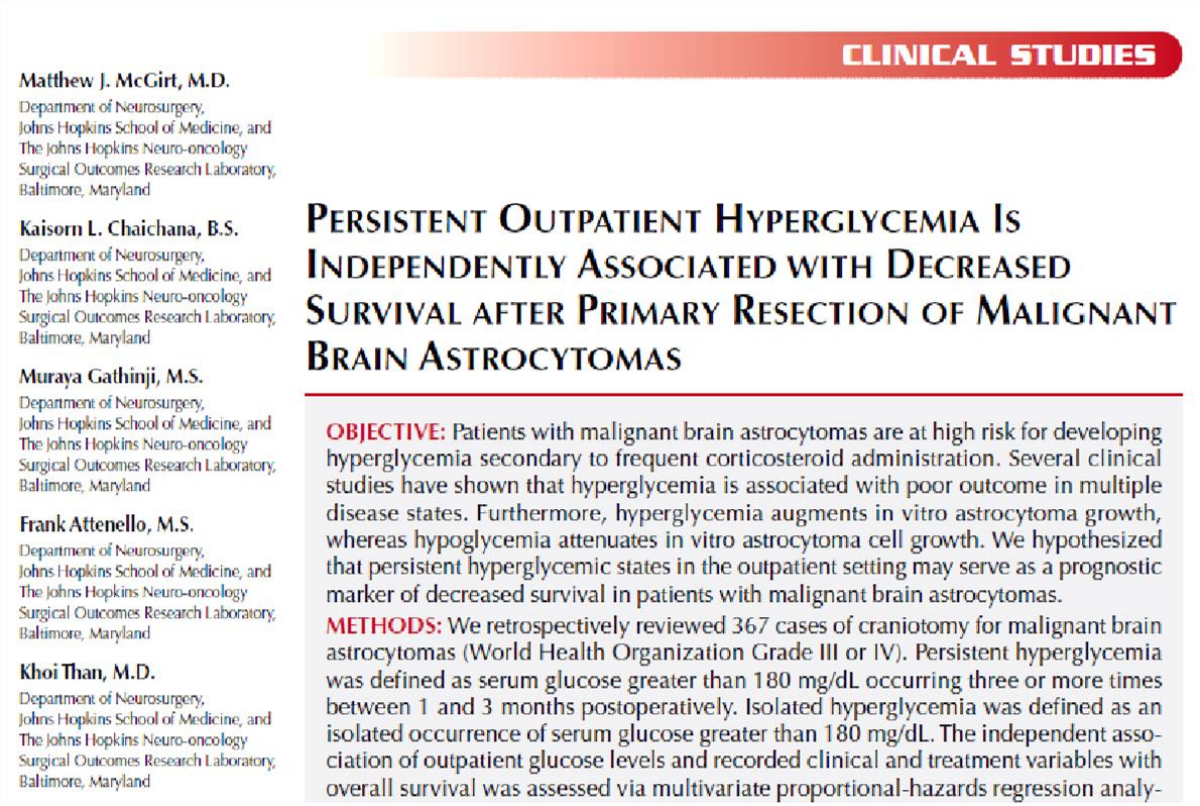
Key words: colon cancer, fiber, glycemic load, rectal cancer

The American Journal of
CLINICAL NUTRITION

Glycemic index, glycemic load, and cancer risk: a meta-analysis

Gnagnarella, et al; 2008

High blood glucose → poor clinical prognosis



CLINICAL STUDIES

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Frank Attenello, M.S.
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Department of Neurosurgery, Johns Hopkins School of Medicine, and The Johns Hopkins Neuro-oncology Surgical Outcomes Research Laboratory, Baltimore, Maryland

PERSISTENT OUTPATIENT HYPERGLYCEMIA IS INDEPENDENTLY ASSOCIATED WITH DECREASED SURVIVAL AFTER PRIMARY RESECTION OF MALIGNANT BRAIN ASTROCYTOMAS

OBJECTIVE: Patients with malignant brain astrocytomas are at high risk for developing hyperglycemia secondary to frequent corticosteroid administration. Several clinical studies have shown that hyperglycemia is associated with poor outcome in multiple disease states. Furthermore, hyperglycemia augments in vitro astrocytoma growth, whereas hypoglycemia attenuates in vitro astrocytoma cell growth. We hypothesized that persistent hyperglycemic states in the outpatient setting may serve as a prognostic marker of decreased survival in patients with malignant brain astrocytomas.

METHODS: We retrospectively reviewed 367 cases of craniotomy for malignant brain astrocytomas (World Health Organization Grade III or IV). Persistent hyperglycemia was defined as serum glucose greater than 180 mg/dL occurring three or more times between 1 and 3 months postoperatively. Isolated hyperglycemia was defined as an isolated occurrence of serum glucose greater than 180 mg/dL. The independent association of outpatient glucose levels and recorded clinical and treatment variables with overall survival was assessed via multivariate proportional-hazards regression analy-

Blood glucose is directly correlated to tumor growth

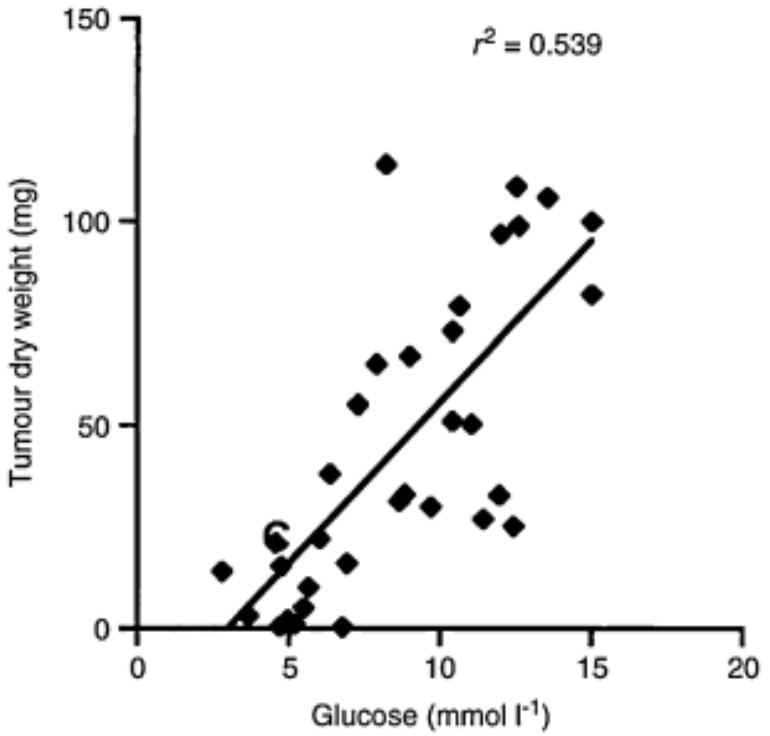
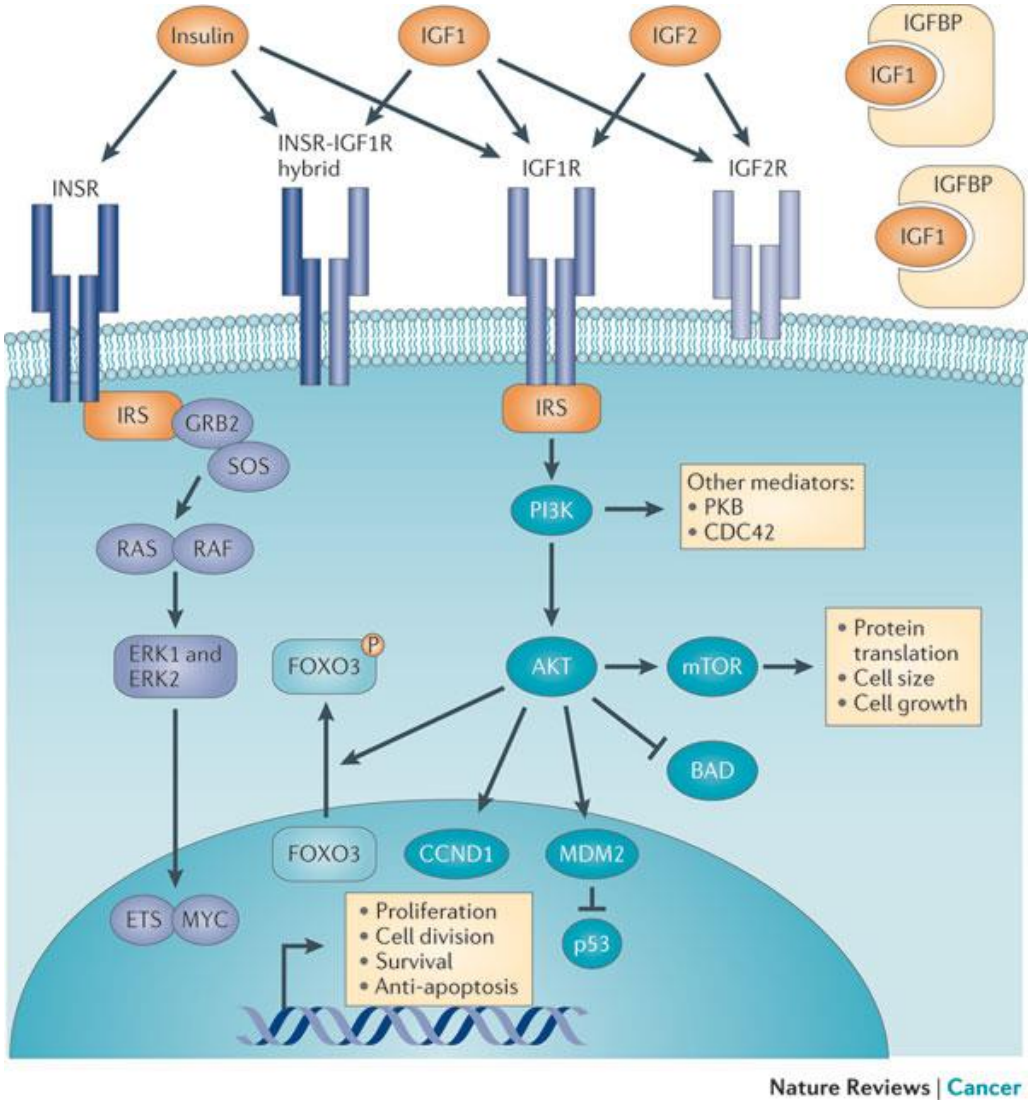


Figure 1 Linear regression analysis of plasma glucose and CT-2A tumor growth in C57BL/6 mice from both standard diet and KD dietary groups combined ($n = 34$). These analyses included the values for plasma glucose and tumor growth of individual mice from both food-restricted and unrestricted groups. The linear regression was highly significant ($^{*}P < 0.001$) and indicates that circulating glucose levels are highly predictive of tumor growth rate (Seyfried et al., 2003).
With permission from British J. Cancer.

Seyfried et al. *British Journal of Cancer (2003) 89, 1375 – 1382*

Insulin, IGF-1 and Cancer

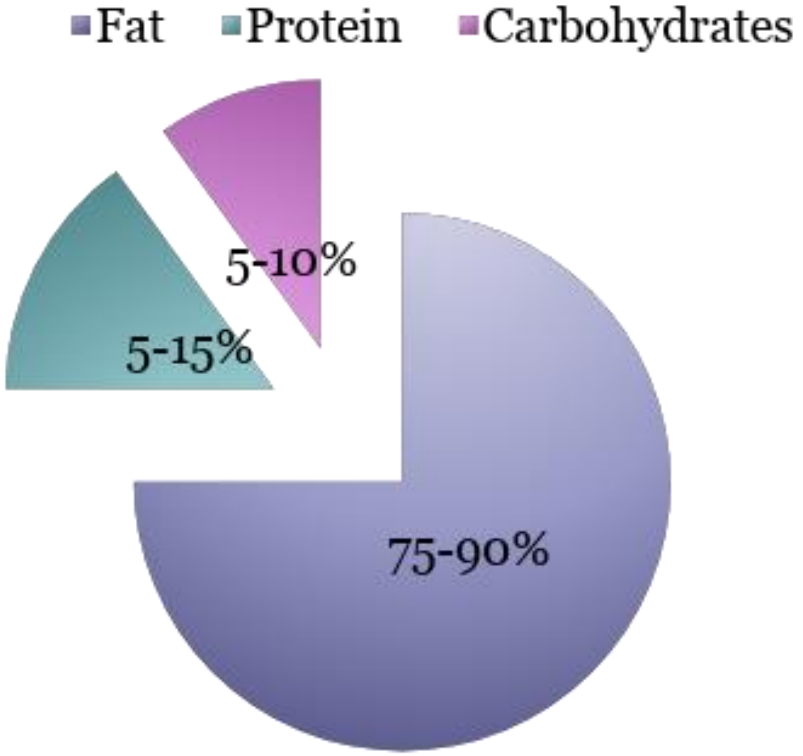


How can we lower glucose and insulin to the tumor?

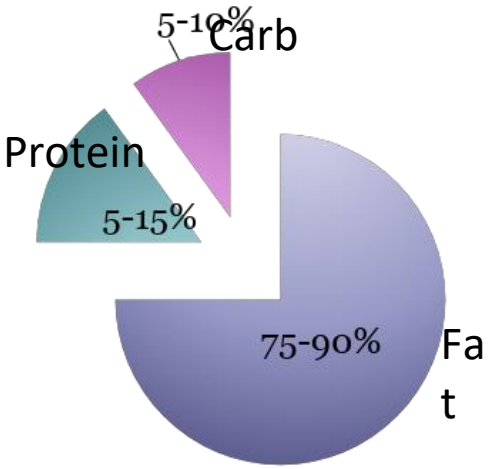
Ketogenic Diet

- 4:1 Fat:Protein+Carb
  - 75-90% Fat
    - Coconut Oil Butter, Olive Oil, Nuts, Fatty Fish, Medium Chain Triglycerides
  - 5-15% Protein
    - Fatty Animal Meats and Fish, Cheese
  - 5-10% Carbohydrates
    - Green Leafy Plants (high fiber)
- Induces physiological state of ketosis

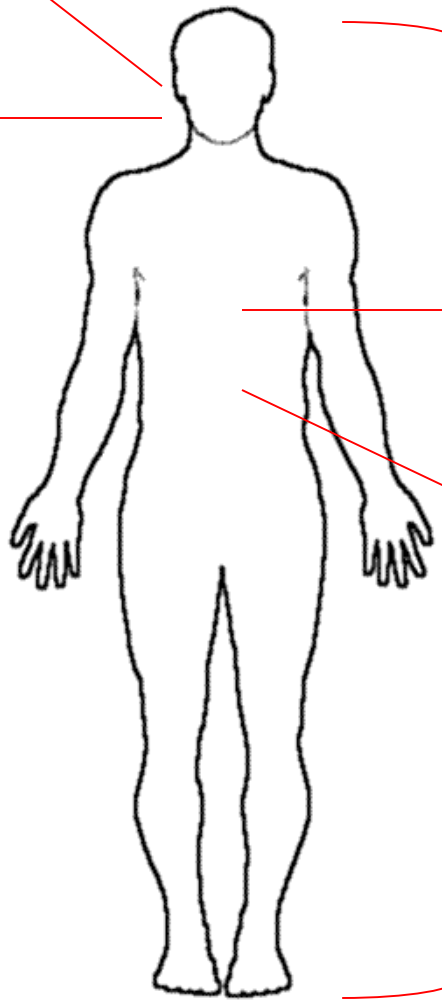
Glucose
Insulin



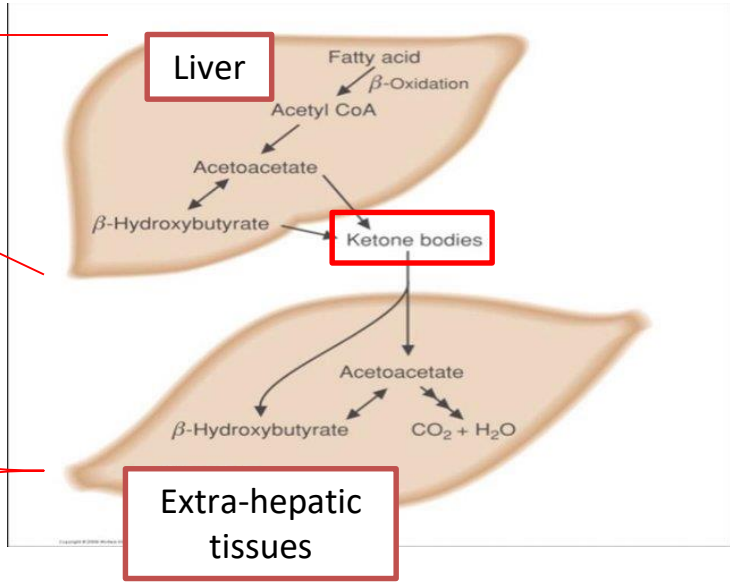
Ketosis



- β-hydroxybutyrate and acetoacetate
- Water-soluble fat molecules
- Alternate energy source for tissues, including brain
- Replace glucose as primary fuel for brain during fasting or starvation



When glucose and insulin are low, acetyl-CoA generated from fatty-acid β-oxidation fuels hepatic ketogenesis



The Diet which Mimics Fasting

FASTING AS EPILEPSY CURE.

Osteopaths Hear That 22 Days on Water Usually End Fits.

LOS ANGELES, July 5.—Epilepsy may be cured by fasting, Dr. Hugh Conklin told the twenty-sixth annual convention of the American Osteopathic Association, now in session here. Epilepsy, according to Dr. Conklin, is caused by the improper functioning of certain glands in the bowels. By fasting for twenty-two days, taking only water, a cure may be effected, he said.

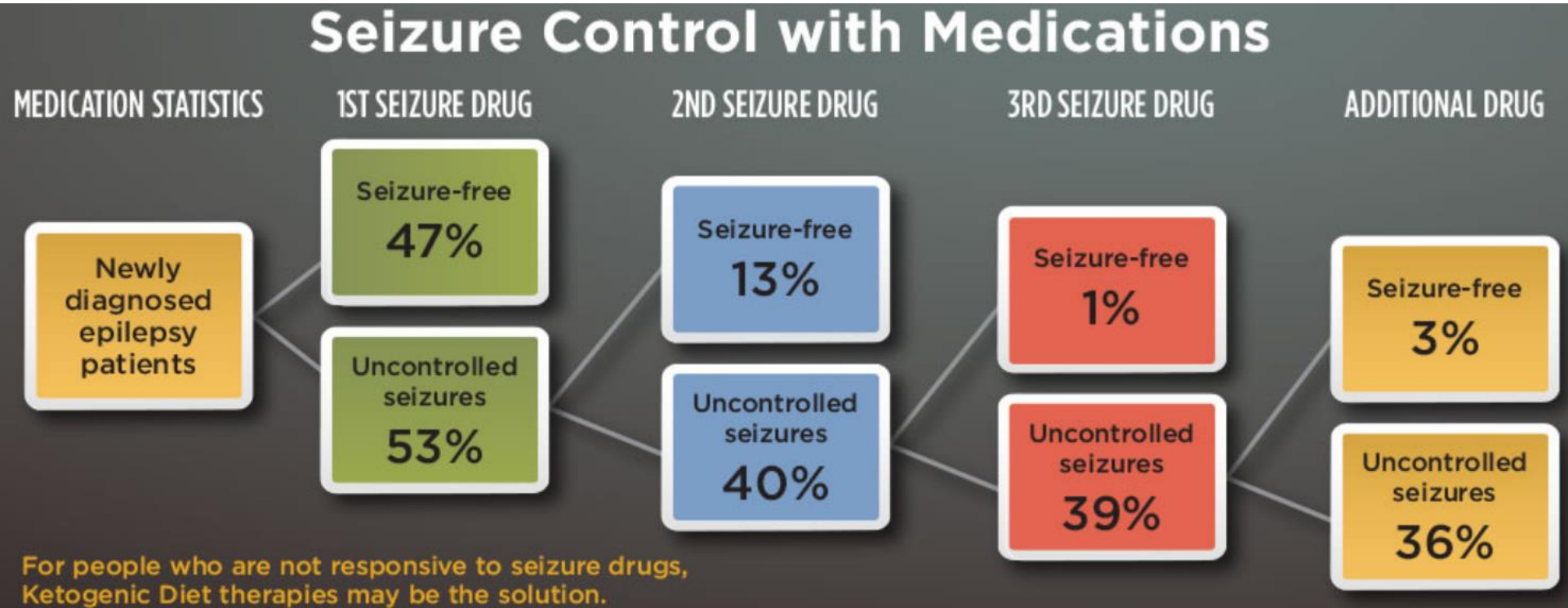
"Many people," added Dr. Conklin, "fast thirty days and are never afflicted by fits again. The longest fast which any patient ever took under my direction lasted sixty days. Out of thirty-seven tests in which children were used as patients, only two still are affected by the disease. The children all were under the age of 11 years, but we effect cures in older patients in from 50 to 60 per cent. of the cases we undertake."

- Fasting has long been known to cure epileptic seizures
- Earliest reports 400 BC
- ← 1922 report
- 1920s, Mayo Clinic – proposed a high fat, very low carbohydrate diet to mimic fasting, *The Ketogenic Diet*
  - 1g/kg protein
  - Carbs 10-15g/d
  - Remainder fat
  - Caloric requirement: BMR + 50%

- First 17 pts, 59% seizure free, 23% marked improvement, remainders lost to follow up or discontinued

History of the Ketogenic Diet

- Robust effectiveness continued to be reported through the decades that followed
- Discovery of anti-epileptics caused diet to fall out of favor, but still used in some circles
- Renaissance of the KD since 1990s with increased awareness of effectiveness and relative safety to AEDs (adverse side effects)
- Under active investigation for large variety of disorders



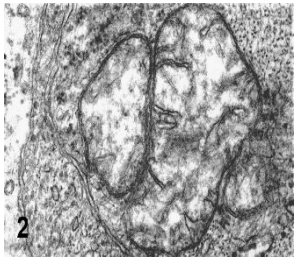
Ketones are an efficient energy source for healthy cells, but maybe not for some cancers

Journal of Electron Microscopy **57(1)**: 33–39 (2008)
doi: 10.1093/jmicro/dfm038

Ultrastructural mitochondrial pathology in human astrocytic tumors: potentials implications pro-therapeutics strategies

Gabriel J. Arismendi-Morillo* and Alan V. Castellano-Ramirez

Laboratorio de Microscopía Electrónica, Instituto de Investigaciones Biológicas, Facultad de Medicina, Universidad del Zulia, Maracaibo-Estado Zulia, Apartado Postal 526, Venezuela



Gaude and Frezza *Cancer & Metabolism* 2014, **2**:10
http://www.cancerandmetabolism.com/content/2/1/10

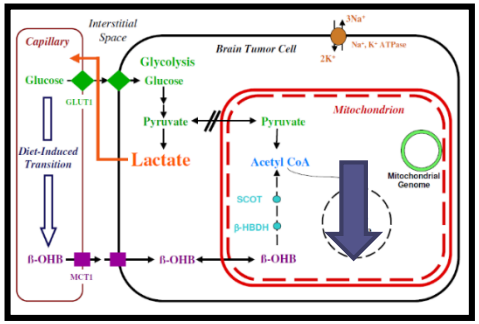
Cancer & Metabolism

REVIEW Open Access

Defects in mitochondrial metabolism and cancer

Edoardo Gaude and Christian Frezza*

- Ketones are metabolized exclusively in the mitochondria



Seyfried, et. Al, 2010

Maurer *et al. BMC Cancer* 2011, **11**:315
http://www.biomedcentral.com/1471-2407/11/315

BMC Cancer

RESEARCH ARTICLE Open Access

Differential utilization of ketone bodies by neurons and glioma cell lines: a rationale for ketogenic diet as experimental glioma therapy

Gabriele D Maurer[1], Daniel P Brucker[1], Oliver Bähr[1], Patrick N Harter[2], Elke Hattingen[3], Stefan Walenta[4], Wolfgang Mueller-Klieser[4], Joachim P Steinbach[1] and Johannes Rieger[1*]

- Ketones saved healthy brain cells from glucose withdrawal-induced death, but did not protect 5 different types of brain cancer cells.
- These brain cancer cells expressed the enzymes necessary for ketone utilization; however, they were insufficient to provide energy

Chang *et al. Nutrition & Metabolism* 2013, **10**:47
http://www.nutritionandmetabolism.com/content/10/1/47

Nutrition&Metabolism

RESEARCH Open Access

Ketolytic and glycolytic enzymatic expression profiles in malignant gliomas: implication for ketogenic diet therapy

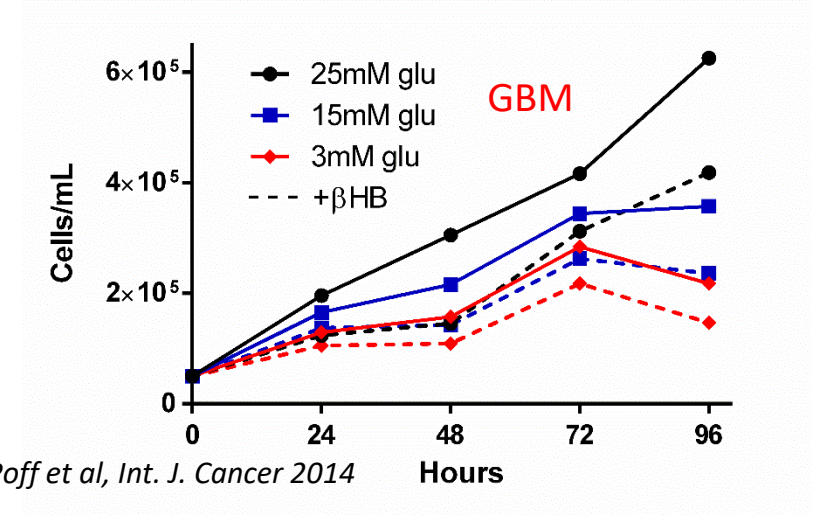
Howard T Chang[1,2*], Lawrence Karl Olson[3] and Kenneth A Schwartz[4]

- Pt biopsies: Ketolytic enzymes significantly ↓ in 14 of 17 GBMs; Glycolytic enzymes ↑ in 13 of 17 GBMs.

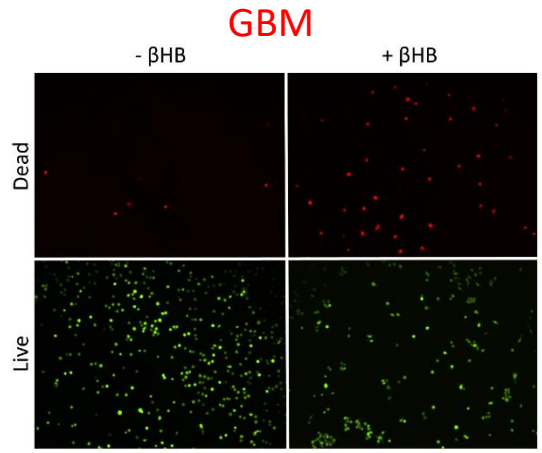
(Maurer, Brucker et al. 2011)

Ketones appear to have direct anti-cancer effects in some models

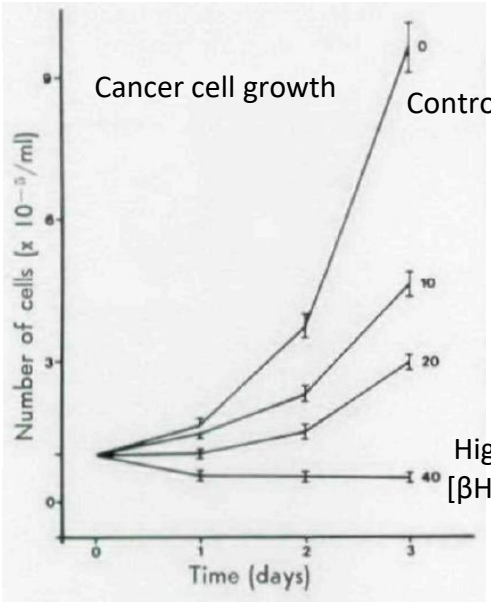
- Ketones inhibit cancer cell proliferation independently of glucose restriction
  - Shown in lymphoma, melanoma, & brain, kidney, cervical, colon, and breast cancer cell lines
- Ketones reduce GBM cell viability



Poff et al, Int. J. Cancer 2014



In presence of 25mM glucose



Magee et al, 1979

Cancer Cell International

Primary research

Open Access

Acetoacetate reduces growth and ATP concentration in cancer cell lines which over-express uncoupling protein 2

Eugene J Fine*[1,2], Anna Miller[3], Edward V Quadros[2,3], Jeffrey M Sequeira[2,3] and Richard D Feinman[3]

PLOS ONE

RESEARCH ARTICLE

Anti-Tumor Effects of Ketogenic Diets in Mice: A Meta-Analysis

Rainer J. Klement[1]*, Colin E. Champ[2], Christoph Otto[3], Ulrike Kämmerer[4]

- Since the 80s, numerous pre-clinical studies have reported therapeutic effects of the KD in a variety of model systems
- Brain – most well-studied
- Prostate
- Breast
- Lung
- Melanoma
- Pancreatic
- Colon
- Metastatic cancer

PLOS ONE

RESEARCH ARTICLE

Roles of Caloric Restriction, Ketogenic Diet and Intermittent Fasting during Initiation, Progression and Metastasis of Cancer in Animal Models: A Systematic Review and Meta-Analysis

Mengmeng Lv[1,2☯], Xingya Zhu[3,4☯], Hao Wang[4], Feng Wang[4], Wenxian Guan[4*]

Thematic Review Series: Calorie Restriction and Ketogenic Diets

The ketogenic diet for the treatment of malignant glioma

Eric C. Woolf and Adrienne C. Scheck[1]

Neuro-Oncology Research, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, AZ 85013

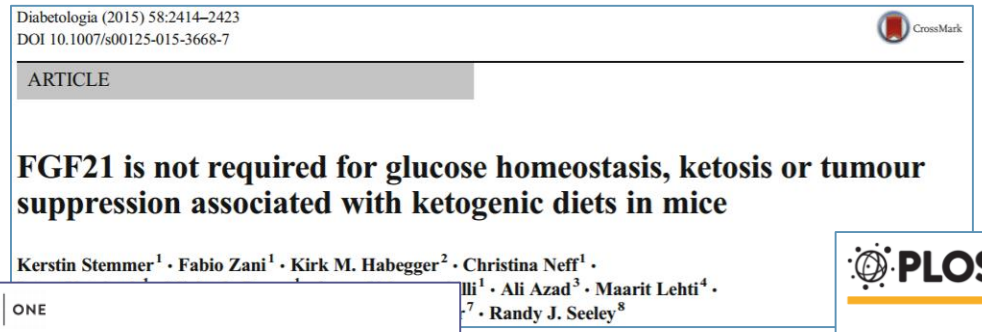
- **How widespread is applicability? More studies in varied model tumor types needed.**

Pre-clinical studies
Beyond efficacy: Important questions

- Mechanisms
- Importance of calories
- Level of carbohydrate restriction
- Understanding ketone metabolism in tumors
- Anti-cancer effects of ketones?
- Coupling with standard of care or other adjuvant therapies
- Importance of fat composition
- Developing tools for implementation
- Contraindications
- Prevention

How does it work? Narrowing in on Mechanisms

2010s-present

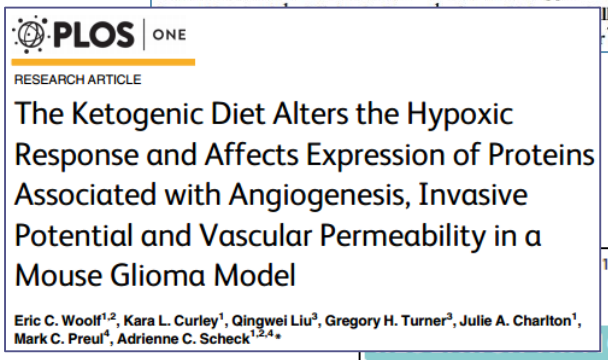


Diabetologia (2015) 58:2414–2423
DOI 10.1007/s00125-015-3668-7

ARTICLE

FGF21 is not required for glucose homeostasis, ketosis or tumour suppression associated with ketogenic diets in mice

Kerstin Stemmer[1] · Fabio Zani[1] · Kirk M. Habegger[2] · Christina Neff[1] · … lli[1] · Ali Azad[3] · Maarit Lehti[4] · … -7 · Randy J. Seeley[8]

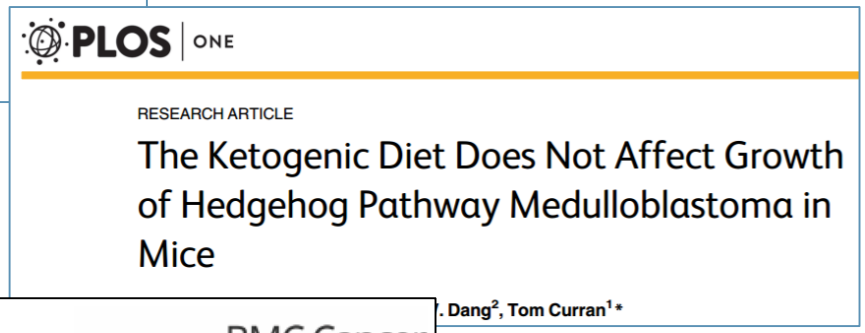


PLOS ONE

RESEARCH ARTICLE

The Ketogenic Diet Alters the Hypoxic Response and Affects Expression of Proteins Associated with Angiogenesis, Invasive Potential and Vascular Permeability in a Mouse Glioma Model

Eric C. Woolf[1,2], Kara L. Curley[1], Qingwei Liu[3], Gregory H. Turner[3], Julie A. Charlton[1], Mark C. Preul[4], Adrienne C. Scheck[1,2,4]*

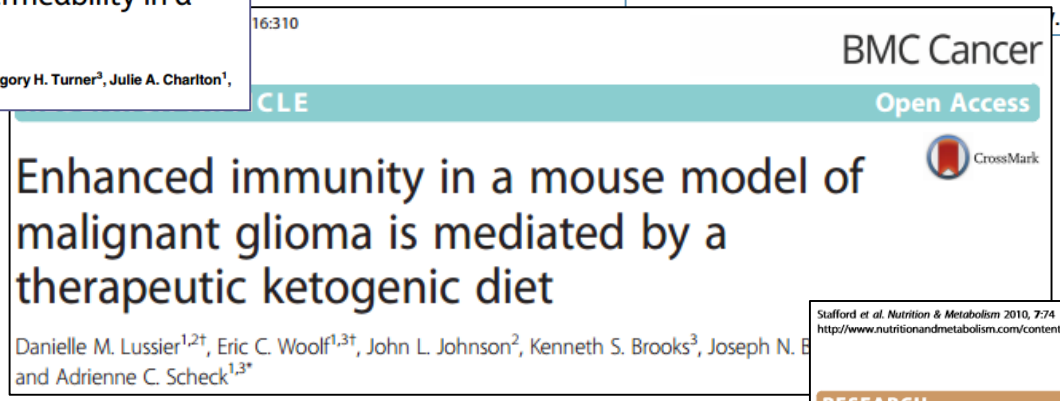


PLOS ONE

RESEARCH ARTICLE

The Ketogenic Diet Does Not Affect Growth of Hedgehog Pathway Medulloblastoma in Mice

. Dang[2], Tom Curran[1]*



16:310

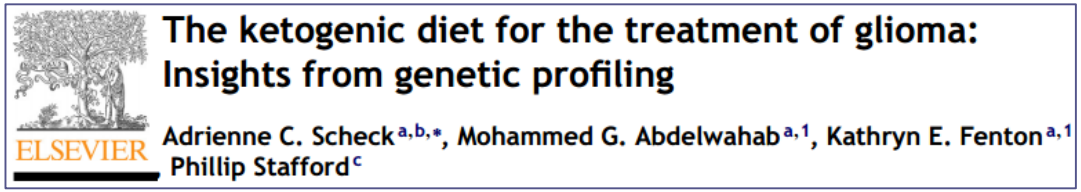
BMC Cancer

CLE Open Access

CrossMark

Enhanced immunity in a mouse model of malignant glioma is mediated by a therapeutic ketogenic diet

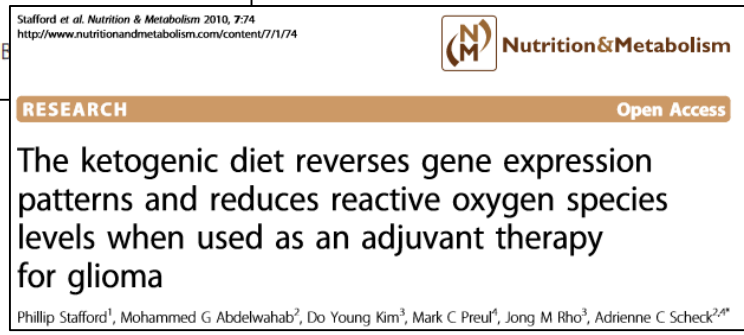
Danielle M. Lussier[1,2†], Eric C. Woolf[1,3†], John L. Johnson[2], Kenneth S. Brooks[3], Joseph N. B… and Adrienne C. Scheck[1,3*]



ELSEVIER

The ketogenic diet for the treatment of glioma: Insights from genetic profiling

Adrienne C. Scheck[a,b,*], Mohammed G. Abdelwahab[a,1], Kathryn E. Fenton[a,1] Phillip Stafford[c]



Stafford *et al. Nutrition & Metabolism* 2010, 7:74
http://www.nutritionandmetabolism.com/content/7/1/74

Nutrition&Metabolism

RESEARCH Open Access

The ketogenic diet reverses gene expression patterns and reduces reactive oxygen species levels when used as an adjuvant therapy for glioma

Phillip Stafford[1], Mohammed G Abdelwahab[2], Do Young Kim[3], Mark C Preul[4], Jong M Rho[3], Adrienne C Scheck[2,4*]

Potential mechanisms

- Signaling molecules *(Newman and Verdin 2014)*
- Lower blood glucose, insulin *(Veech 2004)*
- Inhibit glycolytic enzymes *(Wu and Thompson 1988)*
- Reduce basal oxidative stress, increase OxS in response to SOC *(Shimazu, Hirschey et al. 2013)*
- Endogenous histone deacetylase inhibitor *(Shimazu, Hirschey et al. 2013)*
- Alter gene expression *(Stafford, Abdelwahab et al. 2010)*
- Inhibit inflammation (potential decrease in peritumoral edema) *(Youm, Nguyen et al. 2015)*
- Enhance anti-tumor immunity *(Scheck al. 2016)*
- Muscle sparing *(Shukla, Gebregiworgis et al. 2014)*

Synergy with Standard of Care?

OPEN ACCESS Freely available online

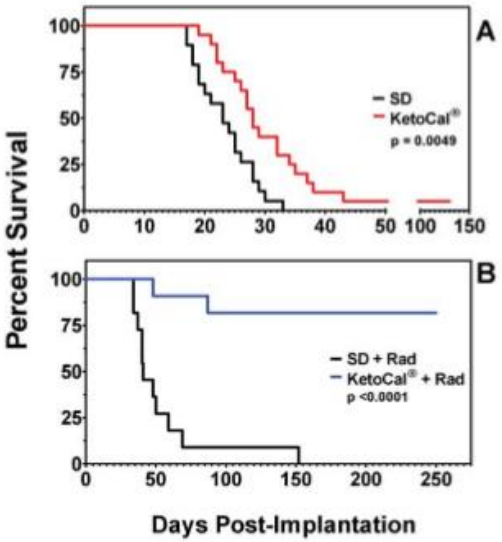
PLoS one

The Ketogenic Diet Is an Effective Adjuvant to Radiation Therapy for the Treatment of Malignant Glioma

Mohammed G. Abdelwahab[1], Kathryn E. Fenton[1], Mark C. Preul[2], Jong M. Rho[3¤], Andrew Lynch[4], Phillip Stafford[5], Adrienne C. Scheck[1,2*]

1 Neuro-Oncology Research, Barrow Neurological Institute® of St. Joseph's Hospital and Medical Center, Phoenix, Arizona, United States of America, **2** Neurosurgery Research, Barrow Neurological Institute® of St. Joseph's Hospital and Medical Center, Phoenix, Arizona, United States of America, **3** Pediatric Epilepsy Research, Barrow Neurological Institute® of St. Joseph's Hospital and Medical Center, Phoenix, Arizona, United States of America, **4** Nutricia Advanced Medical Nutrition, Danone Research, Centre for Specialised Nutrition, Liverpool, United Kingdom, **5** AZ Biodesign, Center for Innovations in Medicine, Arizona State University School of Life Sciences, Tempe, Arizona, United States of America

- GL-261 glioma model
- SD, KD, Rad, KD+Rad
- KD, Rad, and KD+Rad prolong survival
- Potent synergy KD+Rad– 81% of mice exhibit total and permanent remission
- 100 days tx, 200 days SD, sac'd no tumor evident

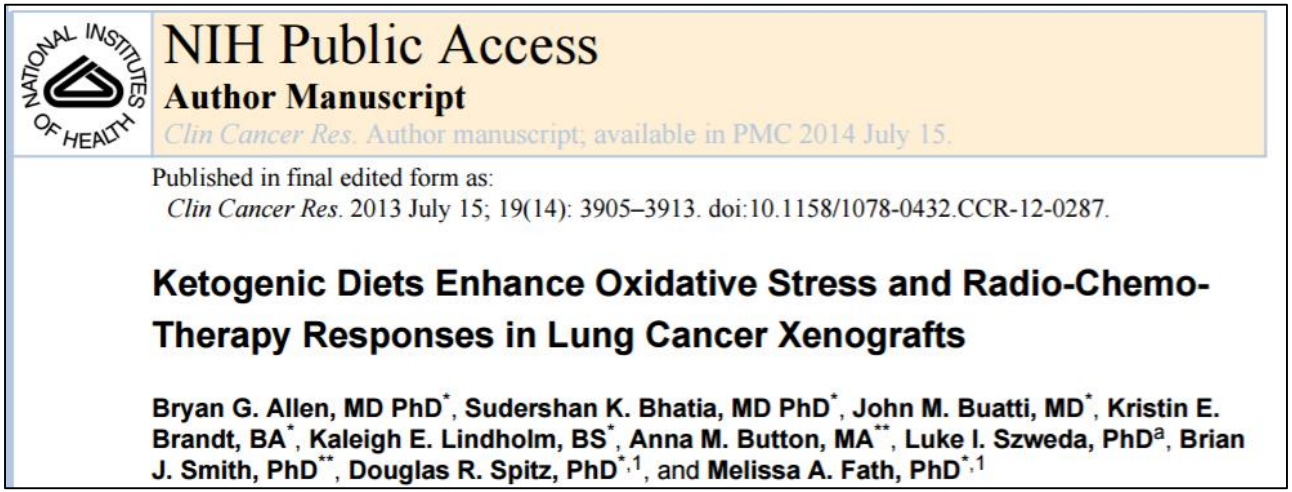


C

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

KD may enhance efficacy of SOC – must investigate in this context for clinical translatability

Synergy with Standard of Care?



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Clin Cancer Res. 2013 July 15; 19(14): 3905–3913. doi:10.1158/1078-0432.CCR-12-0287.

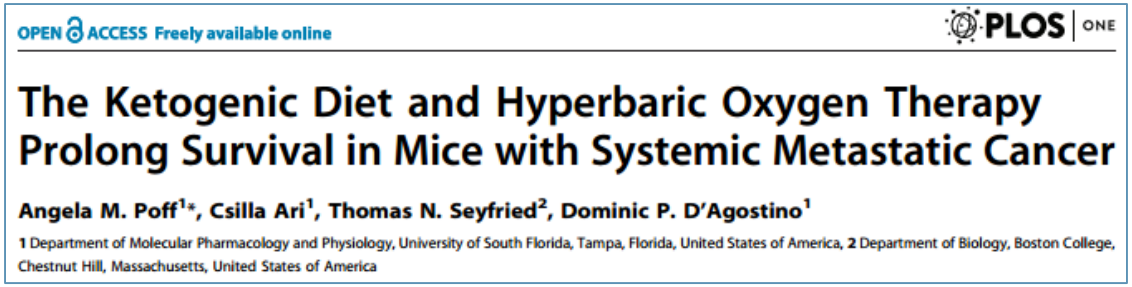
Ketogenic Diets Enhance Oxidative Stress and Radio-Chemo-Therapy Responses in Lung Cancer Xenografts

Bryan G. Allen, MD PhD[*], Sudershan K. Bhatia, MD PhD[*], John M. Buatti, MD[*], Kristin E. Brandt, BA[*], Kaleigh E. Lindholm, BS[*], Anna M. Button, MA[**], Luke I. Szweda, PhD[a], Brian J. Smith, PhD[**], Douglas R. Spitz, PhD[*,1], and Melissa A. Fath, PhD[*,1]

- NCI-H292 and A549 lung xenograft models
- KD, Rad+Carboplatin, KD+RCT
- KD+RCT slower tumor growth than RCT alone
- KD+RCT increased lipid and protein oxidation in tumors, decreased proliferation marker PCNA

KD may enhance efficacy of SOC – must investigate in this context for clinical translatability

Synergy with Other Metabolic Therapies?



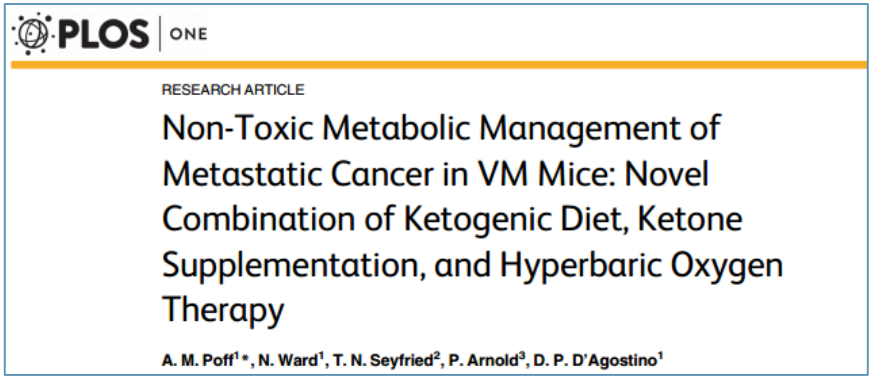
OPEN ACCESS Freely available online

PLOS ONE

The Ketogenic Diet and Hyperbaric Oxygen Therapy Prolong Survival in Mice with Systemic Metastatic Cancer

Angela M. Poff[1]*, Csilla Ari[1], Thomas N. Seyfried[2], Dominic P. D'Agostino[1]

1 Department of Molecular Pharmacology and Physiology, University of South Florida, Tampa, Florida, United States of America, 2 Department of Biology, Boston College, Chestnut Hill, Massachusetts, United States of America

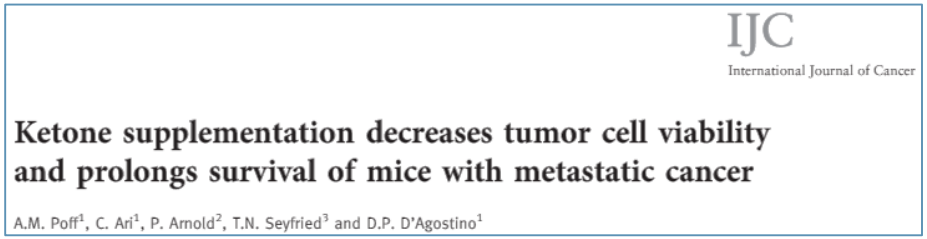


PLOS ONE

RESEARCH ARTICLE

Non-Toxic Metabolic Management of Metastatic Cancer in VM Mice: Novel Combination of Ketogenic Diet, Ketone Supplementation, and Hyperbaric Oxygen Therapy

A. M. Poff[1]*, N. Ward[1], T. N. Seyfried[2], P. Arnold[3], D. P. D'Agostino[1]



IJC

International Journal of Cancer

Ketone supplementation decreases tumor cell viability and prolongs survival of mice with metastatic cancer

A.M. Poff[1], C. Ari[1], P. Arnold[2], T.N. Seyfried[3] and D.P. D'Agostino[1]

- KD-UR slows tumor growth and prolongs survival in VM-M3 metastatic model
- Exogenous ketone supplementation shows similar therapeutic effect
- Ketones reduce viability and proliferation of VM-M3 cells in culture in presence of high glucose
- Potent synergy with hyperbaric oxygen therapy *in vitro* and *in vivo*

Non-toxic adjuvants could offer safe tx

What's optimal admin of these? Pre/during/post SOC?

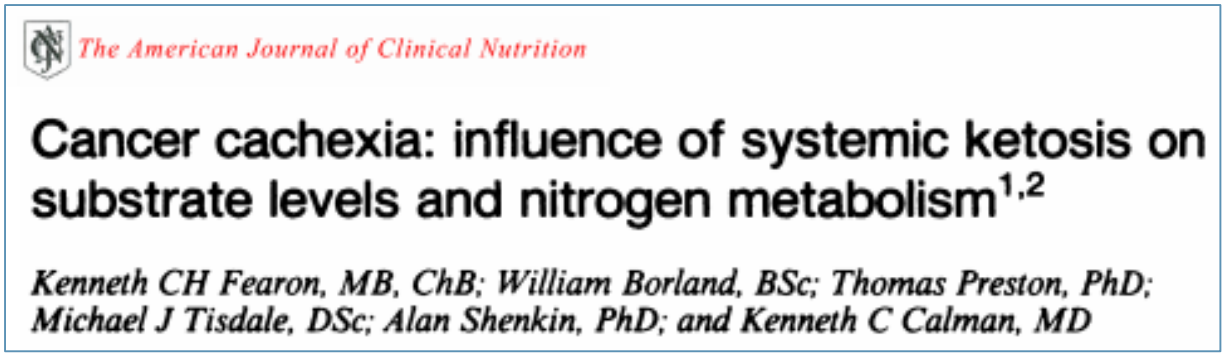
But what about in humans?

Trials are limited

- Slow mainstream acceptance
- Funding
- Compliance
- Feasibility (provision of diet to pts more complicated than pill)
- Currently, the human literature largely consists of case reports and small safety and feasibility trials

Early studies in humans – late stage disease and cachexia

1988



The American Journal of Clinical Nutrition

Cancer cachexia: influence of systemic ketosis on substrate levels and nitrogen metabolism[1,2]

Kenneth CH Fearon, MB, ChB; William Borland, BSc; Thomas Preston, PhD; Michael J Tisdale, DSc; Alan Shenkin, PhD; and Kenneth C Calman, MD

- Cachexic pts with metastatic disease
- KD via NG tube for 7 days
- Goal: to determine if KD would decrease nitrogen loss in pts
- Blood ketones elevated, blood glu, lactate, and pyruvate decreased
- No affect on N-balance, whole-body protein synthesis, degradation, or turnover

Lessons from Humans
Case reports in brain cancer

1995

Clinical and Laboratory Pearl

Effects of a Ketogenic Diet on Tumor Metabolism and Nutritional Status in Pediatric Oncology Patients: Two Case Reports

Linda C. Nebeling, PhD, MPH, RD, Floro Miraldi, MD, PhD, Susan B. Shurin, MD, and Edith Lerner, PhD, LD, FACN

Nutrition Department (L.C.N., E.L.), Case Western Reserve University, School of Medicine; Departments of Nuclear Radiology (F.M.) and Pediatrics (S.B.S.), Division of Hematology/Oncology, University Hospitals of Cleveland, Cleveland, Ohio

But glucose levels still relatively normal on KD… So does it really reduce glucose availability to tumor?

PERSPECTIVES IN PRACTICE

Implementing a ketogenic diet based on medium-chain triglyceride oil in pediatric patients with cancer

LINDA C. NEBELING, PhD, MPH, RD; EDITH LERNER, PhD

- Pts: 2 female children with non-resectable advanced stage brain tumors (anaplastic astrocytoma stage IV and cerebellar astrocytoma stage III), prior chemo & radiation
- Goal: determine if ketosis could decrease availability of glucose to tumor.
- Result: ~22% reduction in glucose uptake via PET imaging and long-term tumor management

KD reduces glucose availability to tumor

Lessons from Humans
Case reports in brain cancer

Zuccoli *et al. Nutrition & Metabolism* 2010, **7**:33
http://www.nutritionandmetabolism.com/content/7/1/33

Nutrition&Metabolism

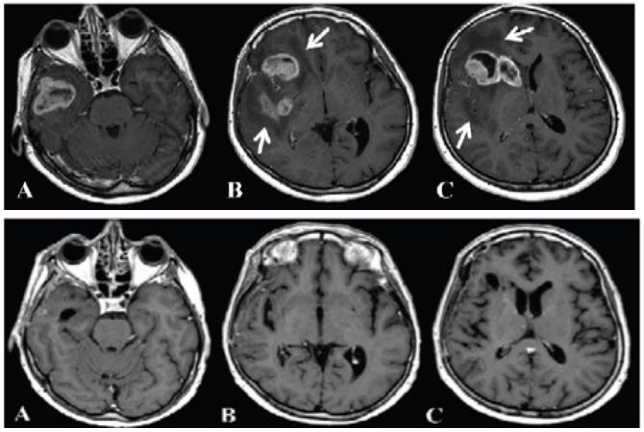
BRIEF COMMUNICATION Open Access

Metabolic management of glioblastoma multiforme using standard therapy together with a restricted ketogenic diet: Case Report

Giulio Zuccoli*[1,5], Norina Marcello[2], Anna Pisanello[2], Franco Servadei[3], Salvatore Vaccaro[4], Purna Mukherjee[6] and Thomas N Seyfried*[6]

2010

- GBM pt – Incomplete surgical debulking → KD-R + Rad + TMZ
- Results: After 2 months tx, no discernable brain tumor tissue was detected using either FDG-PET or MRI imaging.
- MRI evidence of tumor recurrence was found 10 weeks after suspension of strict diet therapy.



How long will pts need to be on diet therapy?

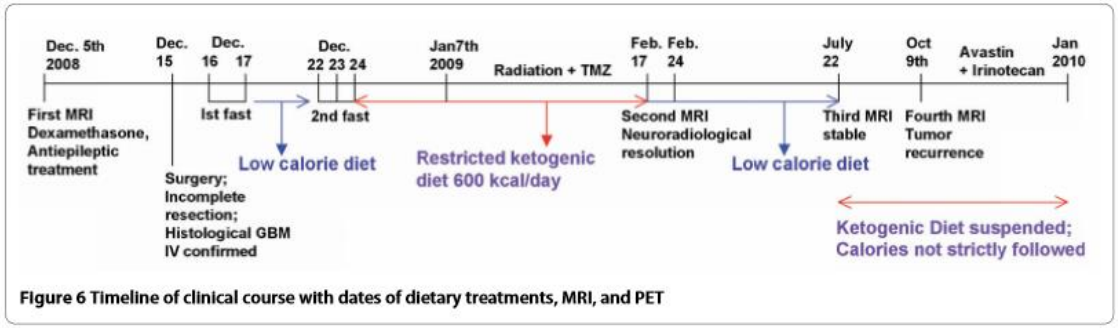


Figure 6 Timeline of clinical course with dates of dietary treatments, MRI, and PET

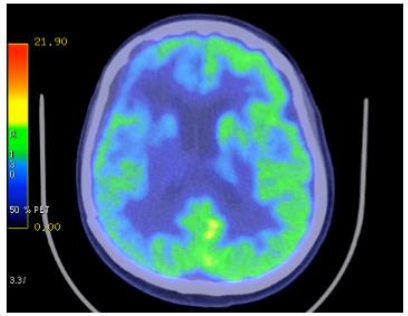


Figure 5 Positron emission tomography with fluoro-deoxy-glucose (FDG-PET) imaging showing no evidence of recurrent tumor.

Lessons from Humans: Safety & Feasibility Trials

2011

Schmidt *et al. Nutrition & Metabolism* 2011, **8**:54
http://www.nutritionandmetabolism.com/content/8/1/54

Nutrition&Metabolism

RESEARCH Open Access

Effects of a ketogenic diet on the quality of life in 16 patients with advanced cancer: A pilot trial

Melanie Schmidt, Nadja Pfetzer, Micheal Schwab, Ingrid Strauss and Ulrike Kämmerer*

- Advanced metastatic cancer pts, post-tx
  - Various types (ovarian, breast, granulosa cell, parotis carcinoma, osteosarcoma, oesophageal, pancreatic, thyroid, colon, endometrial, lung, stomach), post-treatment
- <70g/d carb KD, 3 months
- 5/16 pts completed the 3 month treatment period; others dropped out for personal reasons, or disease progression

Lessons from Humans: Safety & Feasibility Trials

2011

Schmidt *et al. Nutrition & Metabolism* 2011, **8**:54
http://www.nutritionandmetabolism.com/content/8/1/54

Nutrition&Metabolism

RESEARCH Open Access

Effects of a ketogenic diet on the quality of life in 16 patients with advanced cancer: A pilot trial

Melanie Schmidt, Nadja Pfetzer, Micheal Schwab, Ingrid Strauss and Ulrike Kämmerer*

- Concluded KD was safe and feasible
  - Of the 5 pts that completed the whole 3 month treatment period, none experienced further tumor progression while on the diet (all stable disease)
  - Side Effects: Temporary constipation, fatigue; No adverse effects of blood parameters or lipids
- QOL assessments revealed improved emotional functioning, less insomnia

KD may improve some Quality of Life measures for pts – importance of this should not be understated. Personal contribution to outcome.

Lessons from Humans: Safety & Feasibility Trials

2012

Nutrition 28 (2012) 1028–1035

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Targeting insulin inhibition as a metabolic therapy in advanced cancer: A pilot safety and feasibility dietary trial in 10 patients

- 10 patients with advanced, incurable (post-treatment), progressive metastatic disease
  - Breast, fallopian tube, colorectal, lung, esophageal, ovarian
- <5% carb diet (high fat, high protein) → 28 days
- 6/10 had stable disease or partial remission (FDG-PET)

BG unchanged. Outcome strongly correlated to relative ketosis

Lessons from Humans: Safety & Feasibility Trials

2013

Original Articles

Decline of Lactate in Tumor Tissue After Ketogenic Diet: In Vivo Microdialysis Study in Patients with Head and Neck Cancer

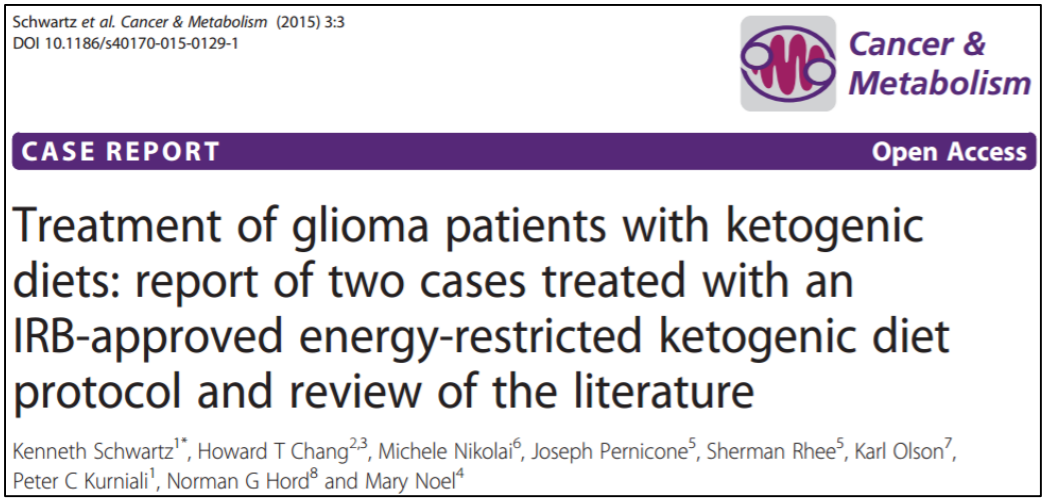
U. Schroeder , B. Himpe , R. Pries , R. Vonthein , S. Nitsch & B. Wollenberg

Pages 843-849 | Received 23 Mar 2012, Accepted 02 May 2013, Published online: 02 Aug 2013

- Tumor lactate production observed during western diet vs. up to 4 days of ketogenic diet
- After 3 days, mean lactate declined in both normal and tumor tissue, but to a greater extent in the tumor
- Supports idea that KD can reduce glycolytic metabolism of tumors in humans

Lessons from Humans: Safety & Feasibility Trials

2015



Schwartz *et al. Cancer & Metabolism* (2015) 3:3
DOI 10.1186/s40170-015-0129-1

Cancer & Metabolism

CASE REPORT Open Access

Treatment of glioma patients with ketogenic diets: report of two cases treated with an IRB-approved energy-restricted ketogenic diet protocol and review of the literature

Kenneth Schwartz[1*], Howard T Chang[2,3], Michele Nikolai[6], Joseph Pernicone[5], Sherman Rhee[5], Karl Olson[7], Peter C Kurniali[1], Norman G Hord[8] and Mary Noel[4]

- Case report and literature review
- Both pts showed tumor progression on KD-R monotherapy
  - Tumors did express at least 1 of 2 ketolytic enzymes SCOT or BHBDH
- Most of reports in literature KD was not monotherapy, with varying responses.
- KD safe and feasible

Safety & Feasibility Trials

2014

J Neurooncol (2014) 117:125–131
DOI 10.1007/s11060-014-1362-0

CLINICAL STUDY

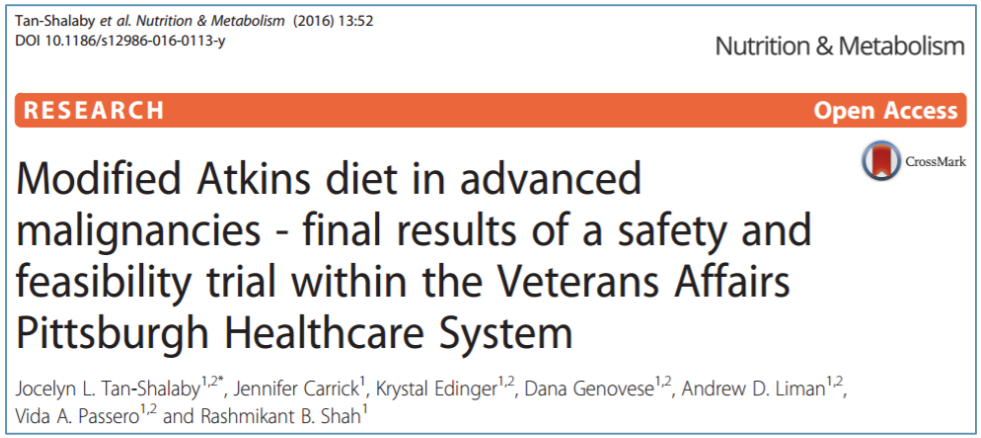
Targeting metabolism with a ketogenic diet during the treatment of glioblastoma multiforme

Colin E. Champ · Joshua D. Palmer · Jeff S. Volek · Maria Werner-Wasik · David W. Andrews · James J. Evans · Jon Glass · Lyndon Kim · Wenyin Shi

- 20 pts with recurrent glioblastoma
- LCKD with plant oils
- Urine ketosis achieved in 92% of pts
- No serious adverse events
- 3 pts discontinued due to compliance issues
- 1 pt minor response (partial remission)
- 2 pts stable disease
- KD safe and feasible but probably minimally effective in this pt group as a monotherapy

Safety & Feasibility Trials

2016



Tan-Shalaby *et al. Nutrition & Metabolism* (2016) 13:52
DOI 10.1186/s12986-016-0113-y

Nutrition & Metabolism

RESEARCH Open Access

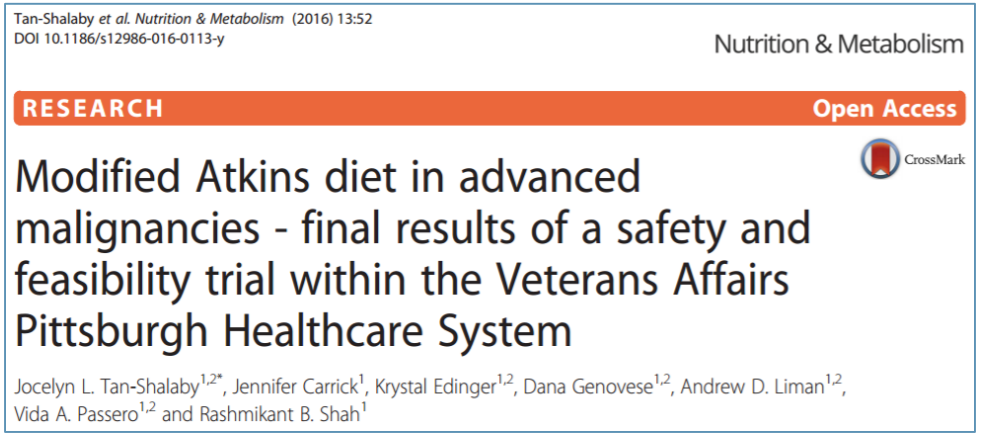
Modified Atkins diet in advanced malignancies - final results of a safety and feasibility trial within the Veterans Affairs Pittsburgh Healthcare System

Jocelyn L. Tan-Shalaby[1,2*], Jennifer Carrick[1], Krystal Edinger[1,2], Dana Genovese[1,2], Andrew D. Liman[1,2], Vida A. Passero[1,2] and Rashmikant B. Shah[1]

- MAD (20-40g carb/d) in advanced cancer patients of diverse cancer types
- QOL scores improved
- Dietary compliance difficulty – 3/17 pts continued diet past 16 weeks
- Response not correlated to serum glucose, ketones, or lipids
- Responders lost more weight than non-responders. Pts who lost >10% of body weight responded best.

Safety & Feasibility Trials

2016



Tan-Shalaby *et al. Nutrition & Metabolism* (2016) 13:52
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Nutrition & Metabolism

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Jocelyn L. Tan-Shalaby[1,2*], Jennifer Carrick[1], Krystal Edinger[1,2], Dana Genovese[1,2], Andrew D. Liman[1,2], Vida A. Passero[1,2] and Rashmikant B. Shah[1]

- Improvements in insulin requirements and renal fx in a few pts
- Concluded MAD safe and feasible in advanced cancer
- Potential survival benefit in melanoma and lung cancer pts
- Of the 4 pts who did well until 16 weeks, 3 had melanoma and exceeded their projected lifespan of 3 months (1 was BRAF V600E positive)

Safety & Feasibility Trials

2016

Klement and Sweeney *BMC Res Notes (2016) 9:143*
DOI 10.1186/s13104-016-1959-9

BMC Research Notes

RESEARCH Open Access

CrossMark

Impact of a ketogenic diet intervention during radiotherapy on body composition: I. Initial clinical experience with six prospectively studied patients

Rainer J. Klement* and Reinhart A. Sweeney

- 6 pts, self administered KD + RT
- No adverse diet-related side effects
- Tumor regression in 5 pts with early disease
- 1 pt with metastatic lung cancer exhibited slight progression during KD+RCT, which progressed rapidly after ending KD

2017

Med Oncol (2017)34:72
DOI 10.1007/s12032-017-0930-5

REVIEW ARTICLE

Systematic review: isocaloric ketogenic dietary regimes for cancer patients

N. Erickson[1] · A. Boscheri[2] · B. Linke[3] · J. Huebner[4]

Authors conclude:

- The studies are limited by their sample sizes, lack in homogeneity of type, location, and cancer stage
- Do not use standardized diet protocols
- Most studies not powered to look at efficacy, rather test safety & tolerability
- Low adherence
- Concern over weight loss

2017

Med Oncol (2017) 34:108
DOI 10.1007/s12032-017-0968-4

LETTER TO THE EDITOR

Need for new review of article on ketogenic dietary regimes for cancer patients

Rainer J. Klement[1] · Richard D. Feinman[2] · Elena C. Gross[3] · Colin E. Champ[4] · Dominic P. D'Agostino[5] · Eugene J. Fine[2,6] · Ulrike Kämmerer[7] · Angela Poff[5] · Jong M. Rho[8] · Thomas N. Seyfried[9] · Adrienne C. Scheck[10]

Authors conclude:

- Erickson paper failed to portray balanced review
- Evaluate KD as if it's an established therapy, not in early stages of clinical investigation
- Lack of mention of multiple proposed mechanisms in literature
- Attributes side effects from trials to KD, when known effects of SOC
- List effects observed in pediatric epilepsy pts which are known to be much less risk in adults
- Weight loss in overweight or obese pts – maybe not negative

Clinical Trials

- Several recruiting or ongoing
- Brain, Head & Neck, Pancreatic, Lung, Metastatic, Breast, Lymphoma, Pancreaticobiliary

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

20 studies found for: ketogenic diet cancer
Modify this search | How to Use Search Results

List | By Topic | On Map | Search Details

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Only show open studies

Rank	Status	Study
1	Completed Has Results	Ketogenic Diet in Advanced Cancer **Condition:** Cancer **Intervention:** Other: Ketogenic Diet
2	Recruiting	Ketogenic Diet Phase 1 for Head & Neck Cancer **Condition:** Head and Neck Neoplasms **Intervention:** Dietary Supplement: Ketogenic diet
3	Suspended	Ketogenic Diet With Concurrent Chemoradiation for Pancreatic Cancer **Condition:** Pancreatic Neoplasms **Intervention:** Dietary Supplement: Ketogenic diet
4	Suspended	Ketogenic Diet With Chemoradiation for Lung Cancer (KETOLUNG) **Condition:** Carcinoma, Non-Small-Cell Lung **Intervention:** Dietary Supplement: Ketogenic diet
5	Recruiting	Pilot Study of a Metabolic Nutritional Therapy for the Management of Primary Brain Tumors **Condition:** Glioblastoma **Intervention:** Other: Energy restricted Ketogenic Diet (ERKD) (Metabolic Nutritional Therapy)
6	Unknown †	The Effect of Ketogenic Diet on Malignant Tumors- Recurrence and Progress **Condition:** Malignant Tumors **Interventions:** Other: Nutritional support with Standard diet; Other: Nutritional intervention with the Ketogenic diet
7	Completed	Ketogenic Or LOGI Diet In a Breast Cancer Rehabilitation Intervention (KOLIBRI) **Condition:** Quality of Life **Interventions:** Other: Standard diet (SD); Other: Experimental 1: Ketogenic diet (KD).; Other: Experimental 2: "Low glycämic and insulinemic" diet (LOGI)
8	Recruiting	Impact of a Ketogenic Diet Intervention During Radiotherapy on Body Composition **Condition:** Neoplasms **Interventions:** Dietary Supplement: Ketogenic breakfast; Dietary Supplement: Ketogenic diet; Radiation: Radio(chemo)therapy
9	Not yet recruiting	Comparison of Healthy Diets on Breast Cancer Markers **Condition:** Breast Neoplasms **Interventions:** Other: Low carbohydrate diet; Other: Low fat diet
10	Not yet recruiting	Ketogenic Diet Adjunctive to HD-MTX Chemotherapy for Primary Central Nervous System Lymphoma **Condition:** Primary Central Nervous System Lymphoma **Interventions:** Dietary Supplement: ketogenic diet; Dietary Supplement: Routine diet
11	Not yet recruiting	Development and Clinical Validation of Ketogen-based Therapeutic Diet for Pancreaticobiliary Cancer Patients **Conditions:** Ketogen-based Therapeutic Diet; Pancreaticobiliary Cancer **Interventions:** Dietary Supplement: Ordinary Diet; Dietary Supplement: Modified Atkin's Diet; Dietary Supplement: Ketogenic Diet
12	Recruiting	Ketogenic Diet Adjunctive to Salvage Chemotherapy for Recurrent Glioblastoma:a Pilot Study **Condition:** Glioblastoma Multiforme **Interventions:** Dietary Supplement: Ketogenic diet; Dietary Supplement: Standard diet
13	Recruiting	Ketogenic Diet as Adjunctive Treatment in Refractory/End-stage Glioblastoma Multiforme: a Pilot Study **Condition:** Glioblastoma Multiforme **Intervention:** Other: ketogenic diet
14	Recruiting	Calorie-restricted, Ketogenic Diet and Transient Fasting During Reirradiation for Patients With Recurrent Glioblastoma **Condition:** Recurrent Glioblastoma **Interventions:** Dietary Supplement: calorie-restricted ketogenic diet and transient fasting; Dietary Supplement: standard nutrition
15	Recruiting	Ketogenic Diet Treatment Adjunctive to Radiation and Chemotherapy in Glioblastoma Multiforme: a Pilot Study **Condition:** Glioblastoma Multiforme of Brain **Interventions:** Other: Ketogenic Diet; Other: Standardized Diet
16	Active, not recruiting	Ketogenic Diet With Radiation and Chemotherapy for Newly Diagnosed Glioblastoma **Condition:** Glioblastoma (GBM) **Interventions:** Dietary Supplement: Ketogenic Diet; Radiation: Radiation therapy; Drug: Temozolomide
17	Recruiting	Glioma Modified Atkins-based Diet in Patients With Glioblastoma **Condition:** Glioblastoma Multiforme **Intervention:** Other: Diet modification
18	Terminated	Pilot Study of the Modified Atkins Diet for Tourette Syndrome **Condition:** Tourette Syndrome **Intervention:** Dietary Supplement: Modified Atkins diet
19	Completed Has Results	Ketogenic Diet for Recurrent Glioblastoma **Condition:** Recurrent Glioblastoma **Intervention:** Dietary Supplement: TAVARLIN

Questioning recommended dietary guidelines for pts

Review Article

Weight Gain, Metabolic Syndrome, and Breast Cancer Recurrence: Are Dietary Recommendations Supported by the Data?

Colin E. Champ,[1] Jeff S. Volek,[2] Joshua Siglin,[1] Lianjin Jin,[1] and Nicole L. Simone[1]

- Review article examining link between metabolic syndrome, breast cancer recurrence, and poor prognosis
- Current guidelines include LFD with supplemental calories from fruit, grains, and vegetable carbohydrates
- Since LCHF diets are effective at mitigating multiple components of metabolic syndrome, such diets should be investigated in this pt population

Investigating scenarios where KD may be ineffective or detrimental

Cell Metabolism

Cell PRESS

Available online 12 January 2017

Article

Prevention of Dietary-Fat-Fueled Ketogenesis Attenuates BRAF V600E Tumor Growth

Siyuan Xia[1], Ruiting Lin[1], Lingtao Jin[1], Liang Zhao[1], Hee-Bum Kang[1], Yaozhu Pan[1], Shuangping Liu[1], Guoqing Qian[1], Zhiyu Qian[1], Evmorfia Konstantakou[1], Baotong Zhang[1], Jin-Tang Dong[1], Young Rock Chung[3], Omar Abdel-Wahab[3], Taha Merghoub[3], Lu Zhou[4], Ragini R. Kudchadkar[1], David H. Lawson[1], Hanna J. Khoury[1], Fadlo R. Khuri[1], Lawrence H. Boise[1], Sagar Lonial[1], Benjamin H. Lee[5], Brian P. Pollack[6, 7], Jack L. Arbiser[6, 7], Jun Fan[2], Qun-Ying Lei[4], Jing Chen[1, 8]

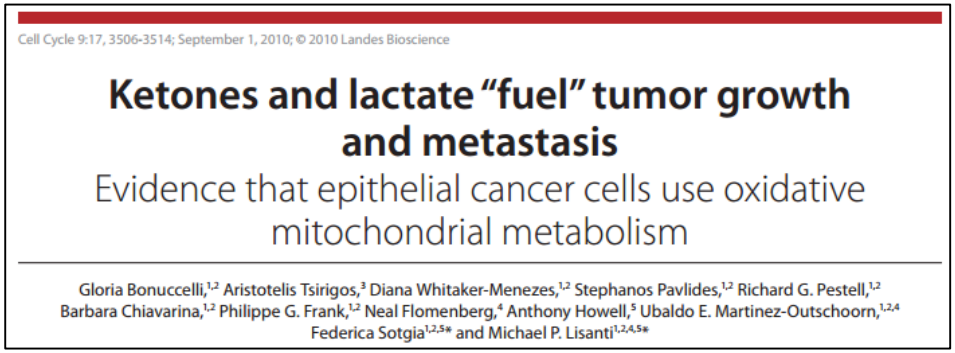
SCIENTIFIC REPORTS

OPEN

Long-term High Fat Ketogenic Diet Promotes Renal Tumor Growth in a Rat Model of Tuberous Sclerosis

Arkadiusz D. Liśkiewicz[1,2], Daniela Kasprowska[3,4], Anna Wojakowska[5], Krzysztof Polański[6], Joanna Lewin–Kowalik[1], Katarzyna Kotulska[7] & Halina Jędrzejowska–Szypułka[1]

- Handful of pre-clinical studies showing that ketosis and/or KD promote tumor growth
- Need close attention



Cell Cycle 9:17, 3506-3514; September 1, 2010; © 2010 Landes Bioscience

Ketones and lactate "fuel" tumor growth and metastasis

Evidence that epithelial cancer cells use oxidative mitochondrial metabolism

Gloria Bonuccelli,[1,2] Aristotelis Tsirigos,[3] Diana Whitaker-Menezes,[1,2] Stephanos Pavlides,[1,2] Richard G. Pestell,[1,2] Barbara Chiavarina,[1,2] Philippe G. Frank,[1,2] Neal Flomenberg,[4] Anthony Howell,[5] Ubaldo E. Martinez-Outschoorn,[1,2,4] Federica Sotgia[1,2,5]* and Michael P. Lisanti[1,2,4,5]*

Absolute Contraindications

- Carnitine deficiency (primary)
- Carnitine palmitoyltransferase (CPT) I or II deficiency
- Carnitine translocase deficiency
- ß-oxidation defects
  - Medium-chain acyl dehydrogenase deficiency (MCAD)
  - Long-chain acyl dehydrogenase deficiency (LCAD)
  - Short-chain acyl dehydrogenase deficiency (SCAD)
  - Long-chain 3-hydroxyacyl-CoA deficiency
  - Medium-chain 3-hydroxyacyl-CoA deficiency
- Pyruvate carboxylase deficiency
- Porphyria

Relative Contraindications

- Inability to maintain adequate nutrition
- Parent or caregiver noncompliance
- Liver disorders, including liver cancer
- Pancreatitis
- Gall bladder disease
- Kidney disorders

List adapted from: Kossoff, E. et al "The Ketogenic And Modified Atkins Diets – Treatments for Epilepsy and Other Disorders", 6th Edition

Complications and Side Effects of cKD

- Constipation
  - Due to reduced bulk and fiber consumption
  - Addition of fibrous vegetables or MCT oil help
  - Laxatives
- Gastroesophageal Reflux
  - OTC acid blockers used
- Changes in Weight
  - Gain or loss – specific diet assistance necessary
- Hunger
  - Physical bulk of food is smaller which can lead to hunger, especially in first 1-2 weeks. With increased ketosis, this typically goes away

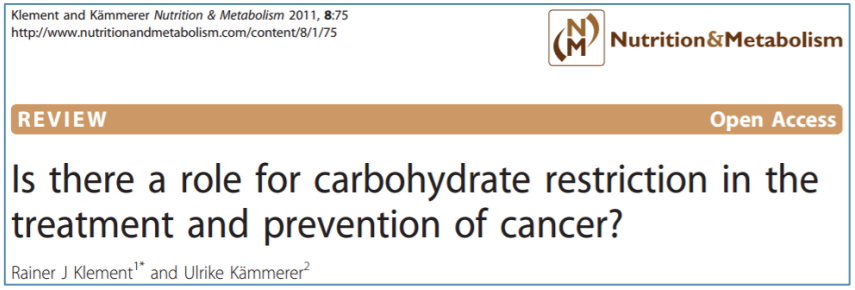
Complications and Side Effects of cKD

- Vitamin and Mineral Deficiency
  - Calcium, selenium, zinc, copper, vitamin D, others, may be deficient in cKD
  - Requires monitoring and possibly supplementation
- Kidney Stones
  - Potassium citrate reduces risk
- High Cholesterol and Other Lipid Abnormalities
  - Typically transient
  - Require monitoring
- Carnitine Deficiency
  - May require supplementation
- Bone Metabolism (esp. in children)
  - May require vitamin D supplements
- Growth Retardation in children
  - Proper monitoring and supplementation critical

Cancer-specific side effects or concerns?

- Known side effects from healthy or epilepsy population
- Drug interactions
- Unacceptable weight loss – cancer cachexia
- Compliance issues, esp. in late stage patients

Turning sights towards prevention

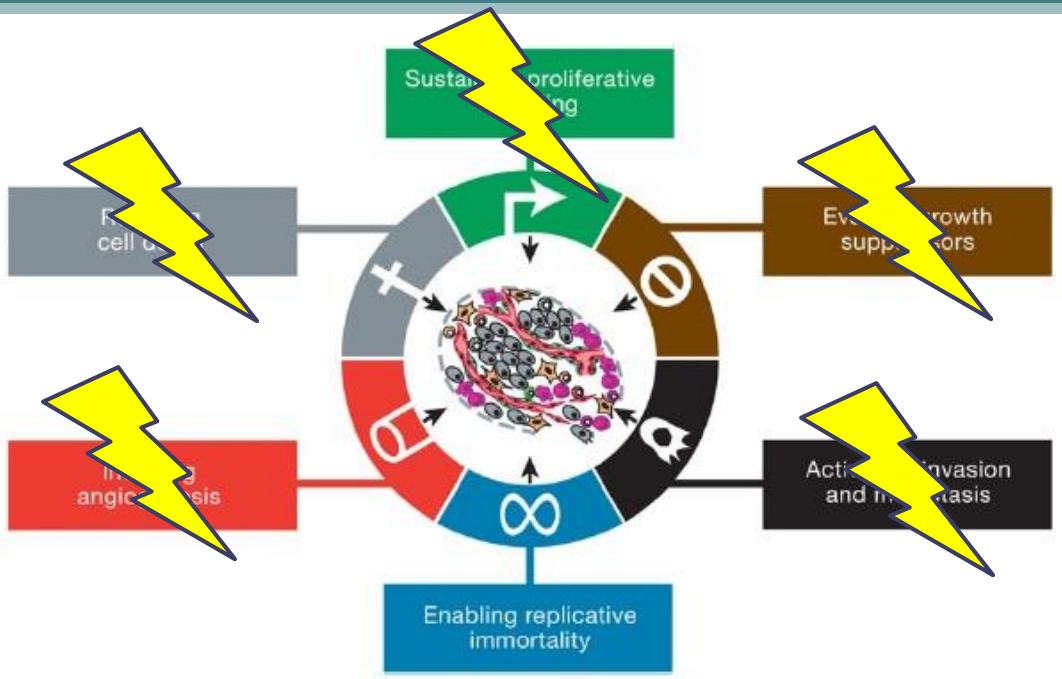


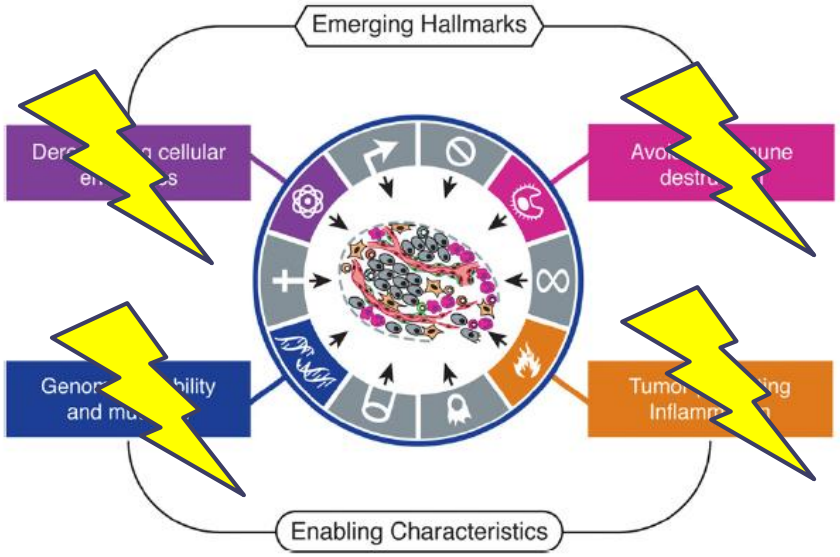
Largely theoretical – need more studies!

Epidemiological suggestions:

- Cancer is considered by some to be a disease of civilization, and is rare among hunter-gatherer societies
  - Two key differences from Western diet: 1) strong reliance on animal foods (45-65% of energy) and 2) consumption of low GI plant foods
  - → Lower carbohydrate intake

↓Hyperglycemia
↓Insulin
↓Obesity
↓Inflammation
↓Oxidative Stress
↑Anti-tumor Immunity





Ketosis targets nearly **all** Hallmarks of Cancer

- Extremely encouraging preliminary results as a potential new cancer therapy.
- More animal work and human clinical trials are crucial to determine its place in the treatment of cancer.

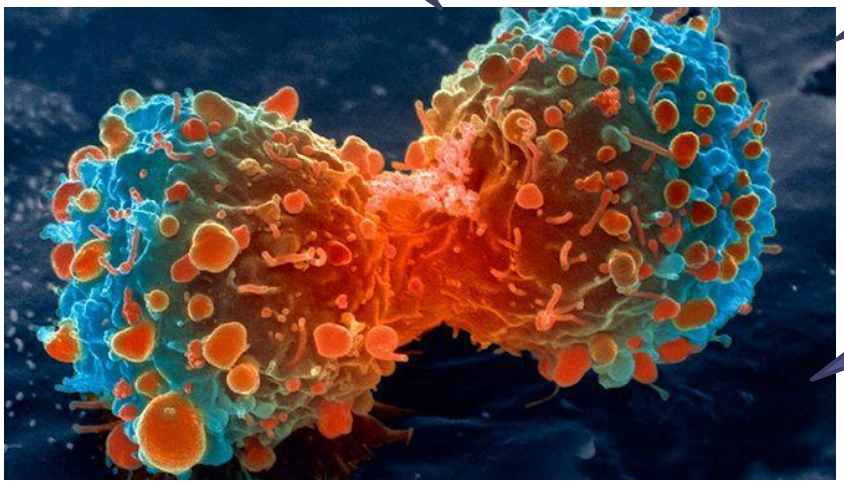
Multifaceted Approach:

A promising piece to the puzzle

Metabolic therapies
- Ketosis
- HBOT
- Metabolic Drugs

Immunotherapies

Targeted gene therapies



Neutraceuticals

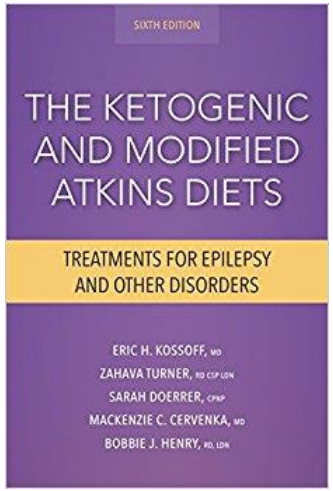
Cytotoxic chemotherapies

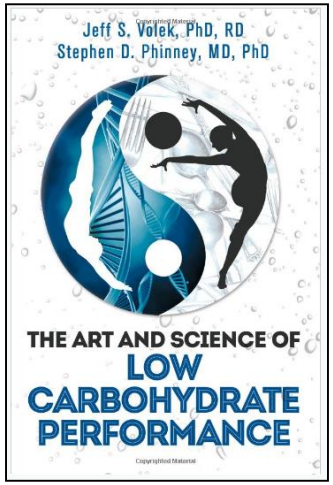
Supportive health
- Nutrition
- Exercise
- Mental health

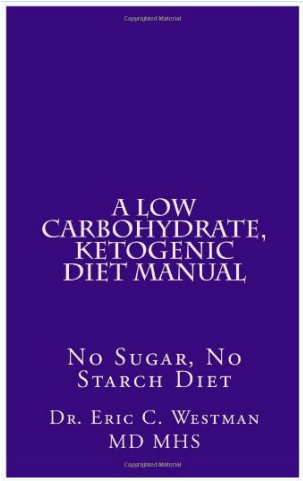
Radiation

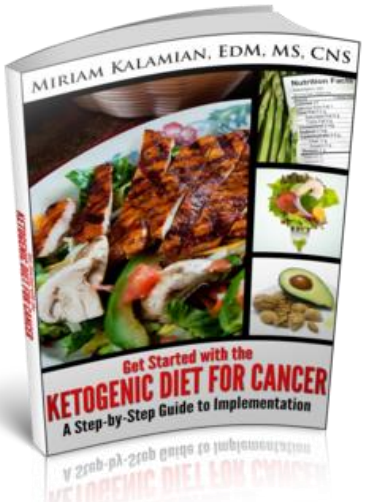
Practical Guidelines for Implementing Nutritional Ketosis

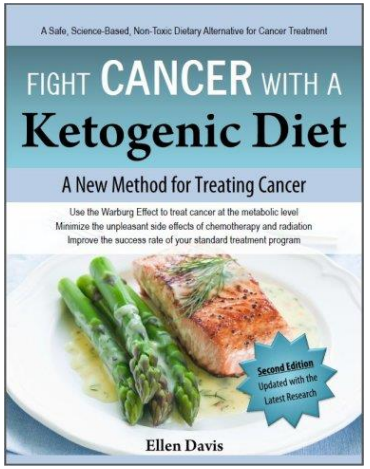
* Patients should be monitored by their own physician, while working closely with the Registered Dietitian



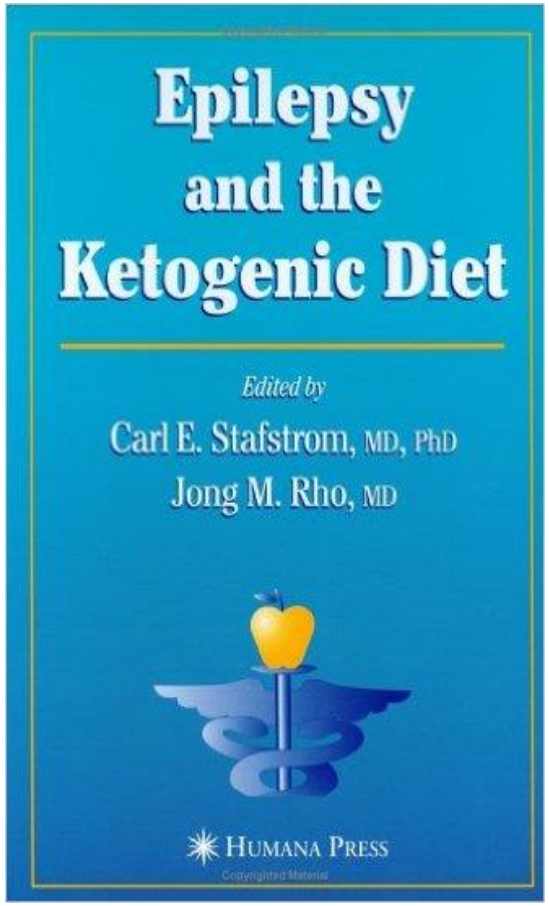








Suggested Resources:
Basic Science and Clinical Application



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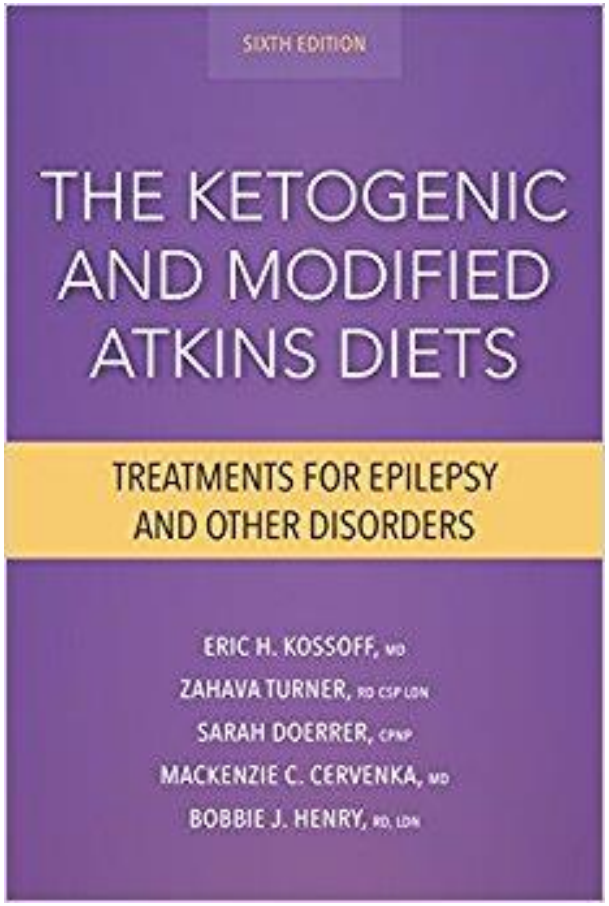

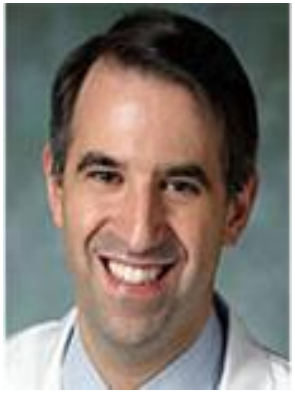

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Thank You!

Patent: *"Targeting Cancer with Metabolic Therapy and Hyperbaric Oxygen"*
(International Patent Application # PCT/US2013/072333)

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