Ketogenic Nutrition
Emerging Applications for Chronic Diseases

Dominic P. D'Agostino, PhD
Associate Professor
Department of Molecular Pharmacology and Physiology
University of South Florida, Morsani College of Medicine

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They make research possible!

Disclaimer and Disclosure

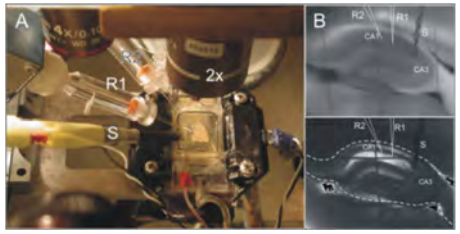
- Information presented is not medical or nutrition advice.
- Presentation includes data on ketone technologies patented by University of South Florida.
- I am an inventor on several patents that have been commercialized.
- Royalties from products support student research at USF..

Disclosures:

1. Dominic P. D'Agostino; Patrick Arnold; Jay B. Dean; Raffaele Pilla; "Ketone esters for prevention of CNS oxygen toxicity" (US Patent: 20140073693 A1)
2. Dominic P. D'Agostino; Patrick Arnold; "Composition and Methods for Producing Elevated and Sustained Ketosis" (US Patent No. 9,675,577)
3. Ari, C., Arnold P., D`Agostino, D.P. Technology Title: "Exogenous Ketone Supplements for Reducing Anxiety-Related Behavior" USF Ref. No. 16A007
4. Dominic P. D'Agostino; Angela M. Poff; Patrick Arnold; "Targeting Cancer with Metabolic Therapy and Hyperbaric Oxygen" (US Patent No. 9,801,903)
5. Co-owner of Ketone Technologies LLC

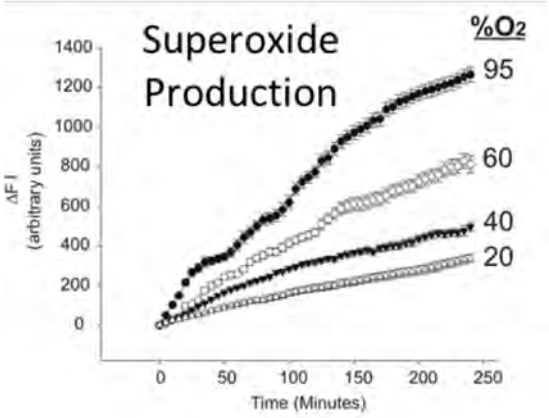
Presentation Outline

- Environmental Neuroscience and Physiology
- Ketosis 101: Fasting, Dietary, Supplemental
- Applications and Specific Examples
- Implementation Strategies
- Future Directions

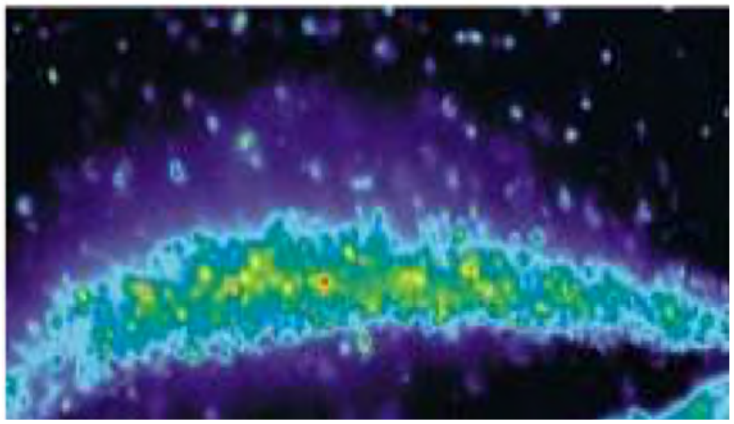


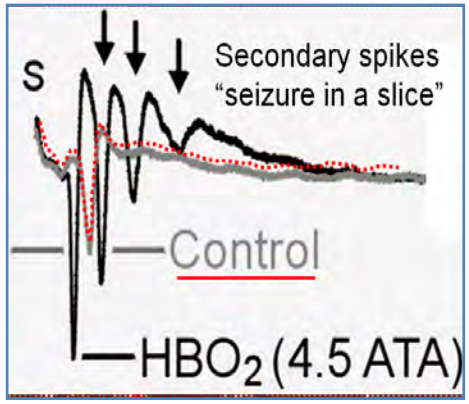
Environmental Neuroscience & Physiology

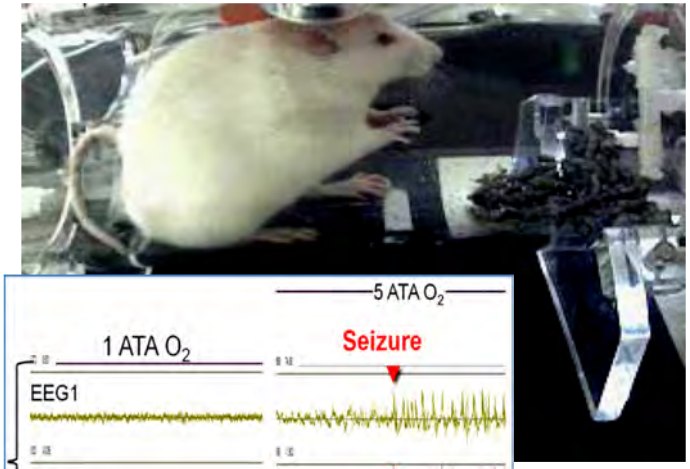
(Brain Cells to Human Performance)



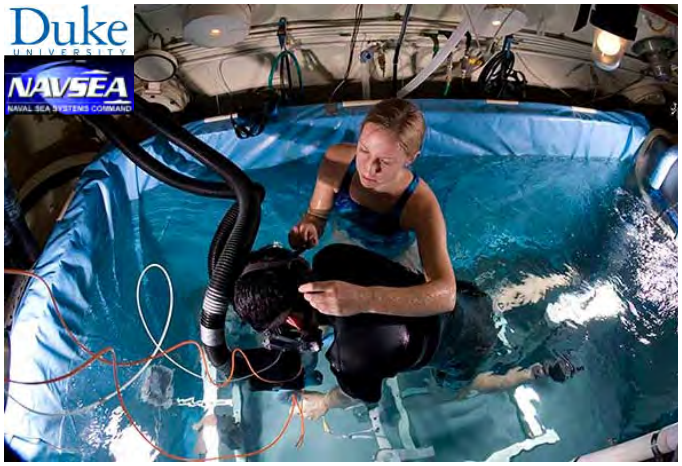
D'Agostino et al. Journal of Neurophysiology Aug.98(2):1030-41, 2007







D'Agostino et.al. AJP Reg, Int. and Comparative Physiology, 2013 May 15;304(10):R829-36.



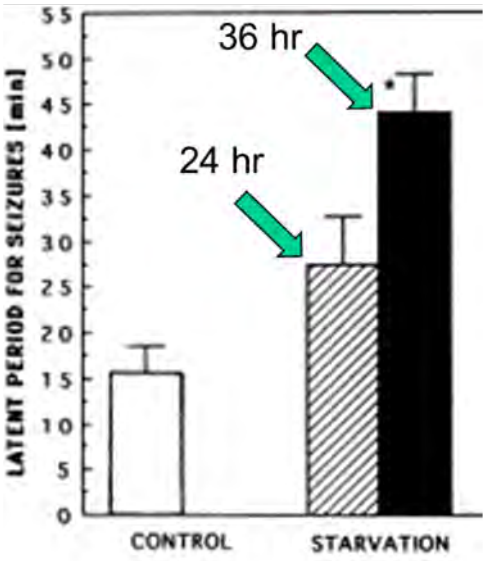
No way to Predict or Prevent Oxygen Toxicity

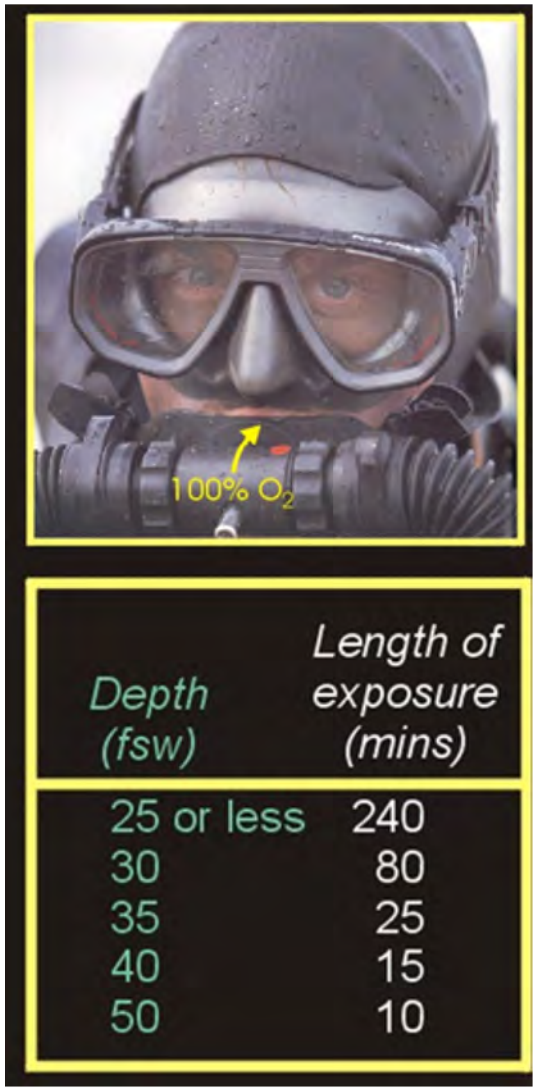
https://www.youtube.com/watch?v=z7Hi0HO24Vk

https://www.flickr.com/photos/40054892@N06/sets/72157683015049201

Preventing Oxygen Toxicity Seizures

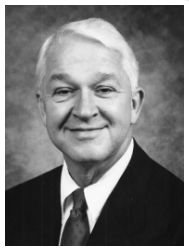
- Limit Exposure
- Antioxidants
- Drugs
- ✓ **Fasting Ketosis**





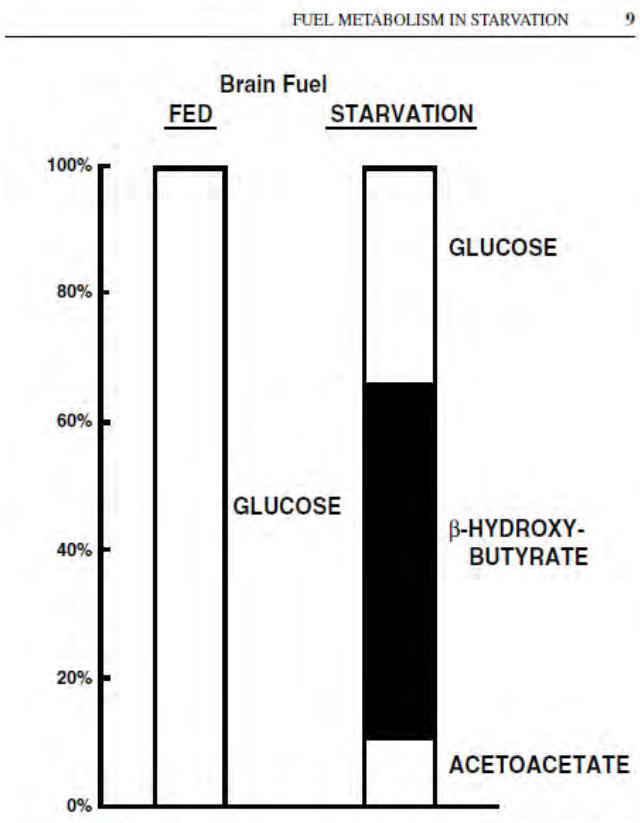
How Does Fasting Change Brain Metabolism?

Ketosis 101:
Shifting Metabolic Physiology



Oliver E. Owen, MD

George F. Cahill Jr., MD



Cahill GF Jr, Veech RL.
Ketoacids? Good medicine?
Trans Am Clin Climatol Assoc. 2003;114:149-61; discussion 162-3. Review.
PubMed PMID: 12813917; PubMed Central PMCID: PMC2194504.

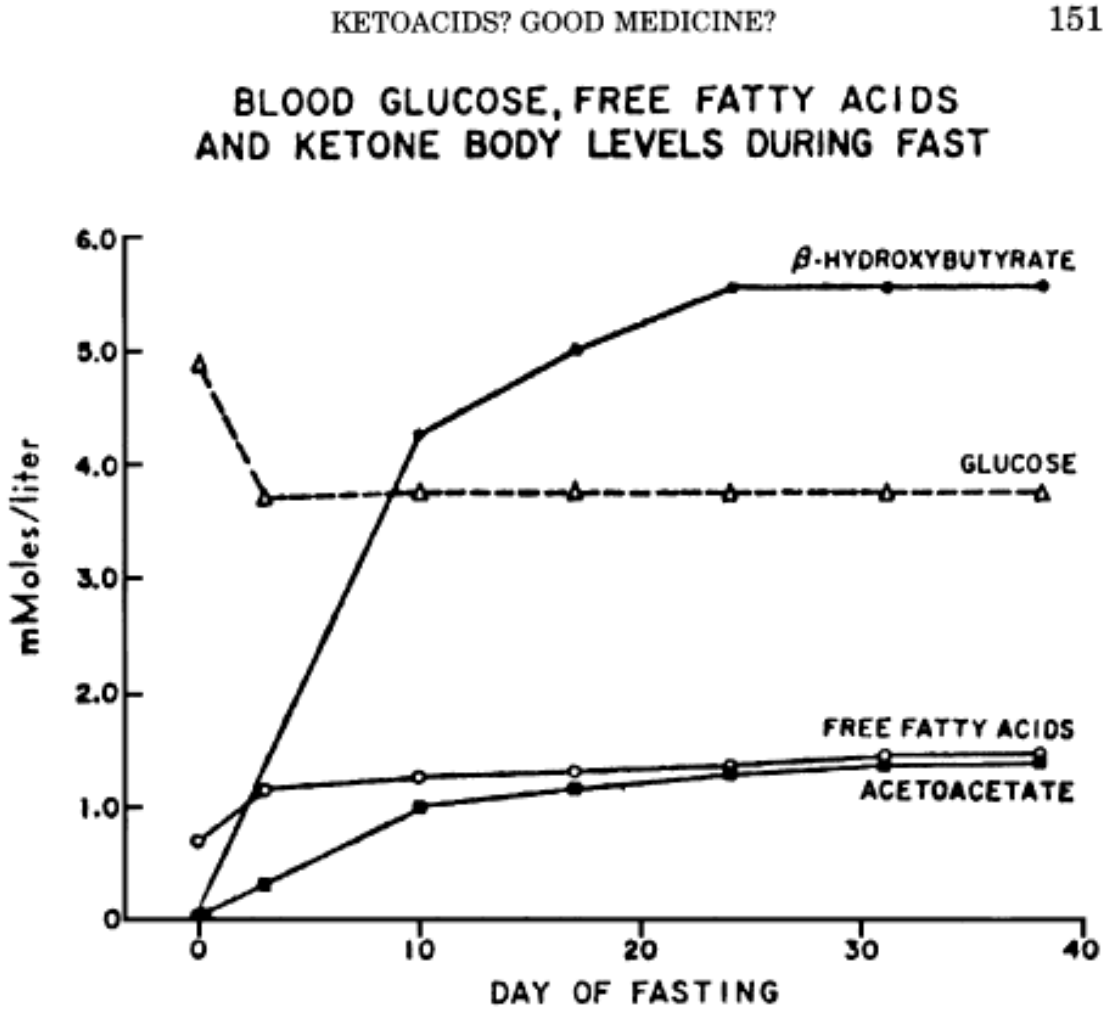
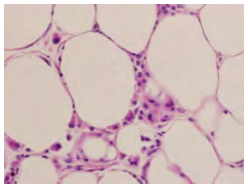


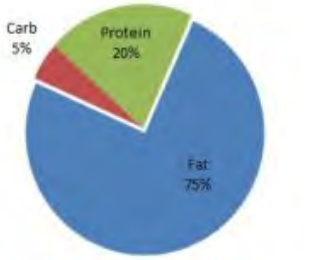
FIG. 2. Circulating concentrations of βOHB, glucose, free fatty acids and acetoacetate in obese but otherwise normal man fasting for 40 days (9).

Ketosis 101: Dietary and Supplemental

Starvation and Calorie Restriction (Adipose)

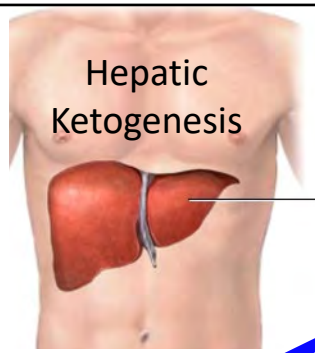


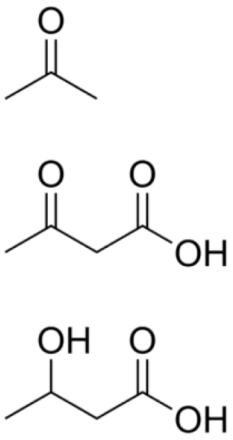
Ketogenic Diet



Difficult to sustain…

- Glucose
- Glycogen
- Insulin

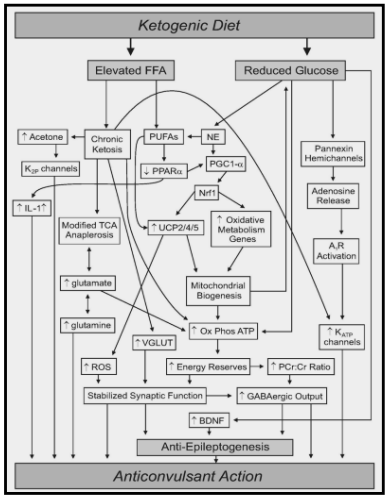




Alternative Fuel

Ketones

Brain Signaling



Ketogenic Fat (MCT) and Exogenous Ketones

Ketogenic Diet is used Clinically for Seizures

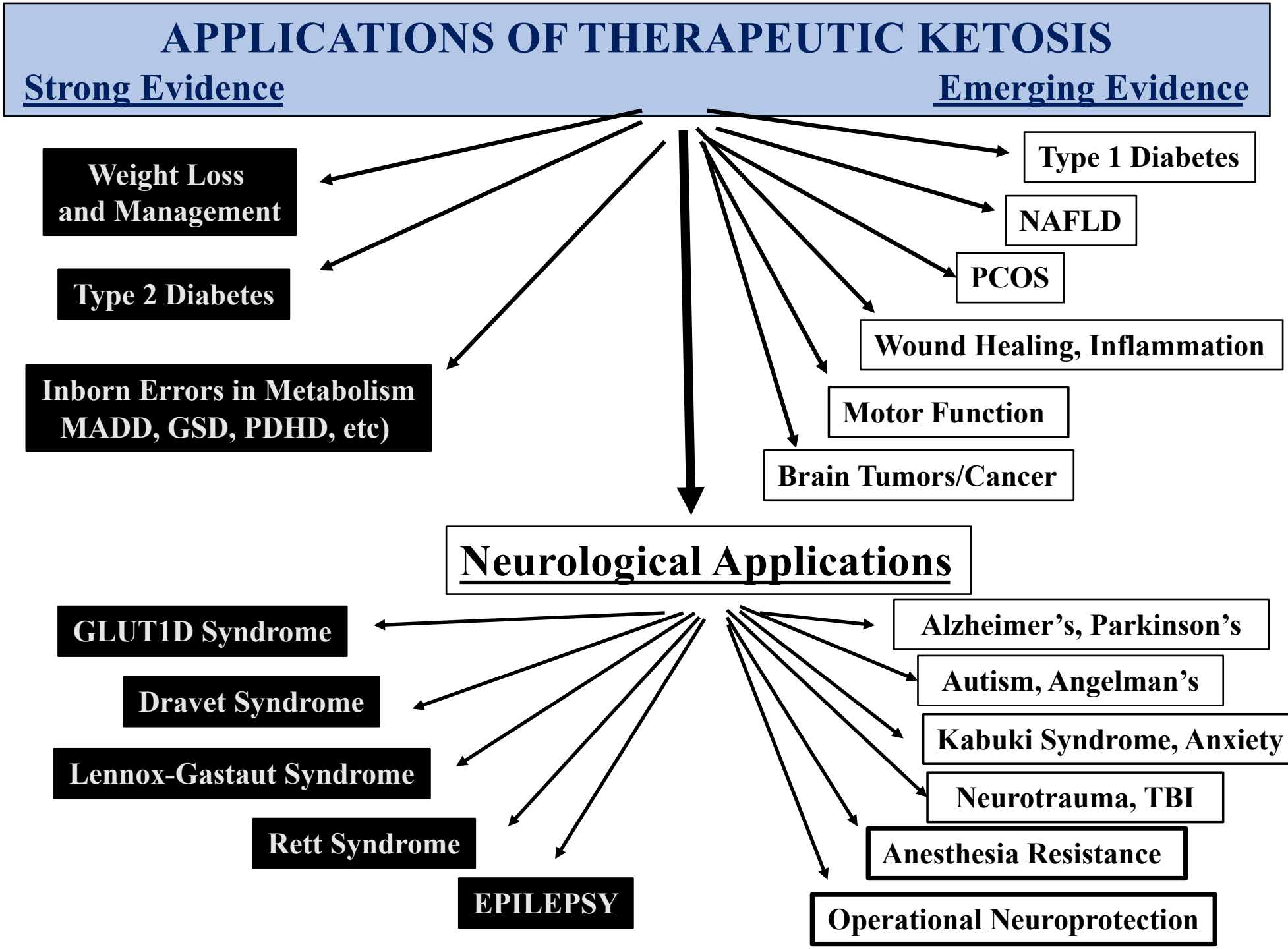
(independent of etiology)

- 2/3 of drug-refractory patients respond
- 33% will have a >90% seizure control
- 10-15% are "super-responders" – rapid, total, and permanent seizure control
- Can often stop off diet after 1-2 yrs

Kossoff, E. et al "The Ketogenic And Modified Atkins Diets – Treatments for Epilepsy and Other Disorders", 6th Edition (2016)

https://www.charliefoundation.org/

THE CHARLIE FOUNDATION


APPLICATIONS OF THERAPEUTIC KETOSIS
Strong Evidence
Emerging Evidence
Weight Loss and Management
Type 2 Diabetes
Inborn Errors in Metabolism MADD, GSD, PDHD, etc)
Type 1 Diabetes
NAFLD
PCOS
Wound Healing, Inflammation
Motor Function
Brain Tumors/Cancer
Neurological Applications
GLUT1D Syndrome
Dravet Syndrome
Lennox-Gastaut Syndrome
Rett Syndrome
EPILEPSY
Alzheimer's, Parkinson's
Autism, Angelman's
Kabuki Syndrome, Anxiety
Neurotrauma, TBI
Anesthesia Resistance
Operational Neuroprotection

Therapeutic ketosis with ketone ester delays central nervous system oxygen toxicity seizures in rats

Dominic P. D'Agostino,[1] Raffaele Pilla,[1] Heather E. Held,[1] Carol S. Landon,[1] Michelle Puchowicz,[2] Henri Brunengraber,[2] Csilla Ari,[3] Patrick Arnold,[4] and Jay B. Dean[1]

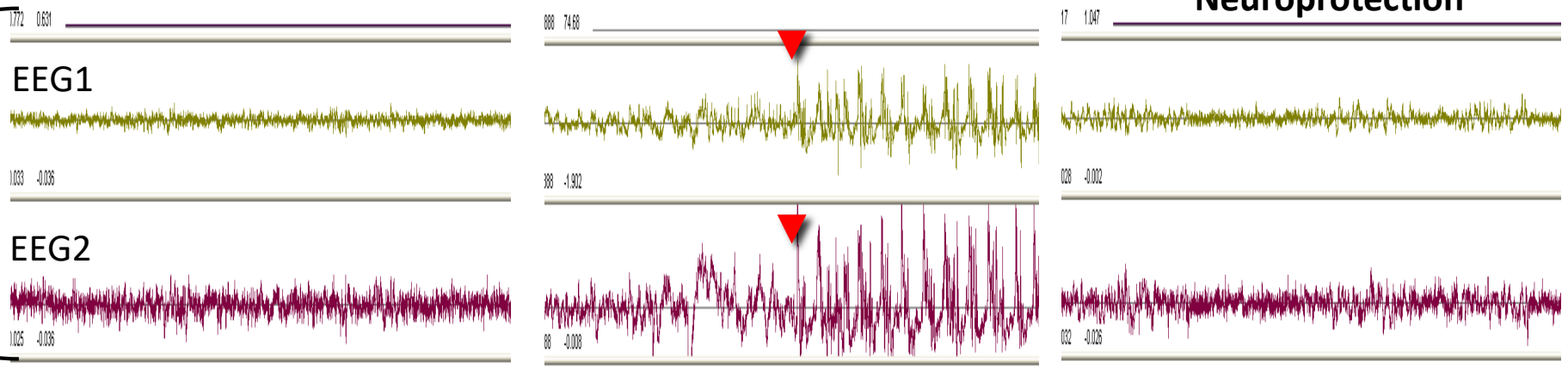
[1]Department of Molecular Pharmacology and Physiology, Hyperbaric Biomedical Research Laboratory, Morsani College of Medicine, University of South Florida, Tampa, Florida; [2]Department of Nutrition, Case Western Reserve University, Mouse Metabolic Phenotyping Center, Cleveland, Ohio; [3]Department of Molecular Medicine, USF Health Byrd Alzheimer's Institute, University of South Florida, Tampa, Florida; [4]Savind, Inc. Seymour, Illinios

Baseline
Air and 1 ATA O_2

5 ATA O_2
Control (water)

5 ATA O_2
Ketone Ester Neuroprotection

CNS



Neuroprotective Effect of Nutritional Ketosis

(Total Ketones: 2-5 mM)

D'Agostino et.al. *AJP Regulatory, Integrative and Comparative Physiology,* 2013 May 15;304(10):R829-36.

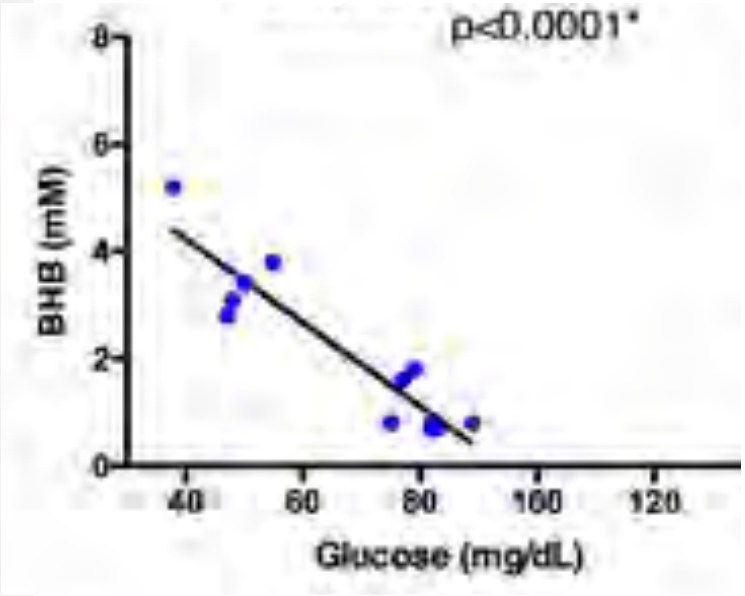
Anti-Seizure and Neuroprotective Effects of Ketones

(Independent of Dietary Chances)

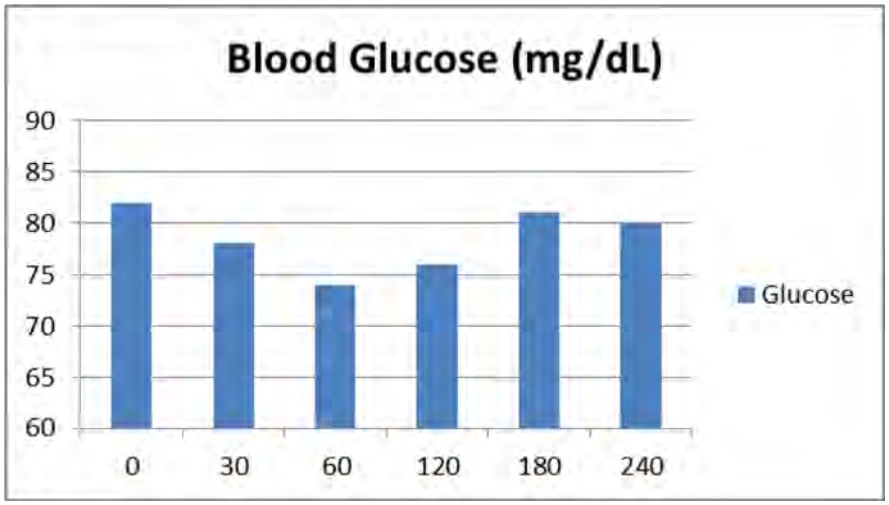
Authors	*Ketogenic Agent*	*Route of Admin*	*Species*	*Model System*	*Result*	*Ref*
Rho et al 2002	AcAc, ACE, D/L-BHB	i.p.	Mice	Frings audiogenic-induced Sz	↑Latency to Sz	#
Likhodii et al 2002	ACE	i.p. (acute) Oral in H2O (chronic)	Rat	PTZ-induced Sz	↑Sz threshold ↓Sz activity	#
Likhodii et al 2003	ACE	i.p.	Rat	Maximal Electroshock Test Amygdala Kindling Test AY-9944 Test	↑Sz threshold ↓Sz activity	#
Minlebaev et al 2011	DL-βHB	i.p.	Rat	Fluorthyl-induced Sz	↓Sz activity	#
Yum et al 2015	D-βHB	i.p. (acute & chronic)	Rat	NMDA-induced Sz	No effect (acute) ↓Sz frequency (chronic)	#
Kim et al 2015	βHB	s.c. (osmotic pump)	Mice	Kcna-null Mutant Mice	↓Sz frequency (*in vivo*) ↓Spontaneous Sz-like events (hippocampal slice)	#
D'Agostino et al 2013	BD-$AcAc_2$	Oral	Rat	Hyperbaric Hyperoxia-induced CNS-OT Sz	↑Latency to Sz	#
Viggiano et al 2015	BD-$AcAc_2$	Oral	Rat	PTZ-induced Sz	↑PTZ threshold for Sz induction	#
Kovács et al 2017	BD-$AcAc_2$ KS-MCT	Oral	Rat	WAG/Rjj rats, absent Sz	↓Spike Wave Discharges	#
Ciarlone et al 2017	BD-$AcAc_2$	Oral	Mice	Ube3a m-/p+ & WT mice Audiogenic-induced Sz Kanic acid-induced Sz	↑Latency to Sz ↓Sz Activity ↓Sz Severity	#

Blood Glucose Lowering Effect of Exogenous Ketones

(Mice, Rats, Human)



R,S-1,3-BD-AcAc$_2$ (30g)



Poff A, Ari C, Seyfried TN, D'Agostino DP. Ketone Supplementation Decreases Tumor Cell Viability and Prolongs Survival of Mice with Metastatic Cancer. *International Journal of Cancer*: 2014 Oct. 1;135(7):1711-20. DOI: 10.1002/ijc.28809

Kesl SL, Poff AM, Ward NP, Fiorelli TN, Ari C, Van Putten AJ, Sherwood JW, Arnold P, D'Agostino DP. (2015) Effects of exogenous ketone supplementation on blood ketone, glucose, triglyceride, and lipoprotein levels in Sprague–Dawley rats. *Nutrition and Metabolism*; 2016 Feb 4;13:9. doi: 10.1186/s12986-016-0069-y

Anti-Anxiety and Anti-Convulsant Effects

(mediated, in part, through adenosinergic mechanism)

frontiers in Molecular Neuroscience

Exogenous Ketone Supplements Reduce Anxiety-Related Behavior in Sprague-Dawley and Wistar Albino Glaxo/Rijswijk Rats

Csilla Ari[1], Zsolt Kovács[2], Gabor Juhasz[3], Cem Murdun[1], Craig R. Goldhagen[1], Andrew M. Koutnik[1], Angela M. Poff[1], Shannon L. Kesl[1] and Dominic P. D'Agostino[1]*

[1] Department of Molecular Pharmacology and Physiology, Hyperbaric Biomedical Research Laboratory, Morsani College of Medicine, University of South Florida, Tampa, FL, USA, [2] Department of Zoology, University of West Hungary, Szombathely, Hungary, [3] Proteomics Laboratory, Eotvos Lorand University, Budapest, Hungary

ORIGINAL RESEARCH ARTICLE
Front. Mol. Neurosci., 25 July 2017 | https://doi.org/10.3389/fnmol.2017.00235

Adenosine A1 Receptor Antagonism Abolished the Anti-seizure Effects of Exogenous Ketone Supplementation in Wistar Albino Glaxo Rijswijk Rats

Zsolt Kovács[1], Dominic P. D'Agostino[2], Arpád Dobolyi[3,4] and Csilla Ari[2,5]*

[1]Savaria Department of Biology, Eötvös Loránd University, Budapest, Hungary
[2]Hyperbaric Biomedical Research Laboratory, Department of Molecular Pharmacology and Physiology, Morsani College of Medicine, University of South Florida, Tampa, FL, United States
[3]Laboratory of Neuromorphology and Human Brain Tissue Bank, Department of Anatomy, Histology and Embryology, Semmelweis University, Budapest, Hungary
[4]Laboratory of Molecular and Systems Neurobiology, Department of Physiology and Neurobiology, Hungarian Academy of Sciences, Eotvos Loránd University, Budapest, Hungary
[5]Department of Psychology, University of South Florida, Tampa, FL, United States

frontiers in Behavioral Neuroscience

Anxiolytic Effect of Exogenous Ketone Supplementation Is Abolished by Adenosine A1 Receptor Inhibition in Wistar Albino Glaxo/Rijswijk Rats

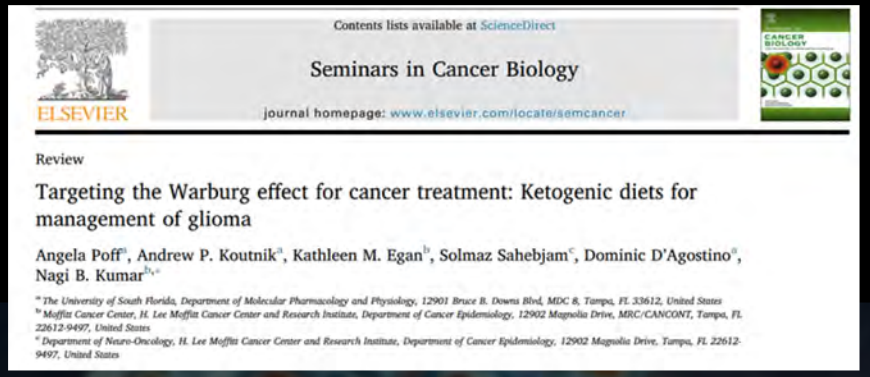
*Zsolt Kovács[1], Dominic P. D'Agostino[2,3] and Csilla Ari[2,4]**

[1] Savaria Department of Biology, Eötvös Loránd University (ELTE), Budapest, Hungary, [2] Department of Molecular Pharmacology and Physiology, Metabolic Medicine Research Laboratory, Morsani College of Medicine, University of South Florida, Tampa, FL, United States, [3] Institute for Human and Machine Cognition, Ocala, FL, United States, [4] Department of Psychology, Hyperbaric Neuroscience Research Laboratory, University of South Florida, Tampa, FL, United States

TARGETING CANCER:

BEYOND GLUCOSE

31 REGISTERED CLINICAL TRIALS



Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Review

Targeting the Warburg effect for cancer treatment: Ketogenic diets for management of glioma

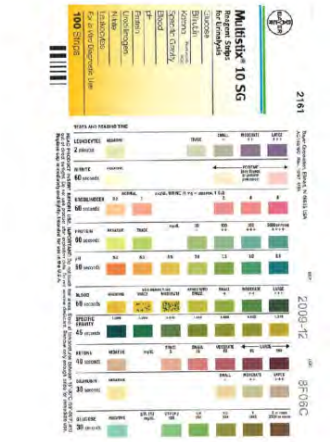
Angela Poff[a], Andrew P. Koutnik[a], Kathleen M. Egan[b], Solmaz Sahebjam[c], Dominic D'Agostino[a], Nagi B. Kumar[b,*]

[a] The University of South Florida, Department of Molecular Pharmacology and Physiology, 12901 Bruce B. Downs Blvd, MDC 8, Tampa, FL 33612, United States
[b] Moffitt Cancer Center, H. Lee Moffitt Cancer Center and Research Institute, Department of Cancer Epidemiology, 12902 Magnolia Drive, MRC/CANCONT, Tampa, FL 22612-9497, United States
[c] Department of Neuro-Oncology, H. Lee Moffitt Cancer Center and Research Institute, Department of Cancer Epidemiology, 12902 Magnolia Drive, Tampa, FL 22612-9497, United States

- Reduction in insulin & IGF signaling
- Enhance therapy-induced OxS in tumor
- Reduction in inflammation
- Altered gene expression (HDACi activity)
- Enhanced anti-tumor immunity
- Anti-cachexia
- Increase sensitivity to standard care therapies

Commercially Available Tools for Assessing Nutritional Ketosis

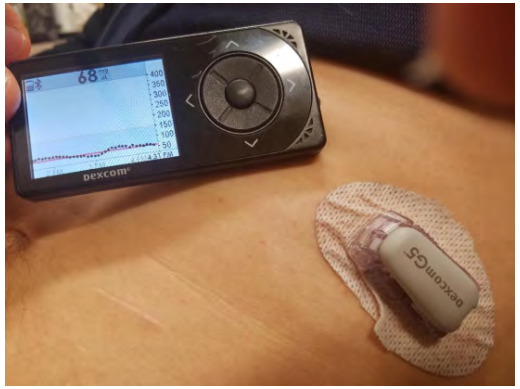
Urine
Acetoacetate
(AcAc)



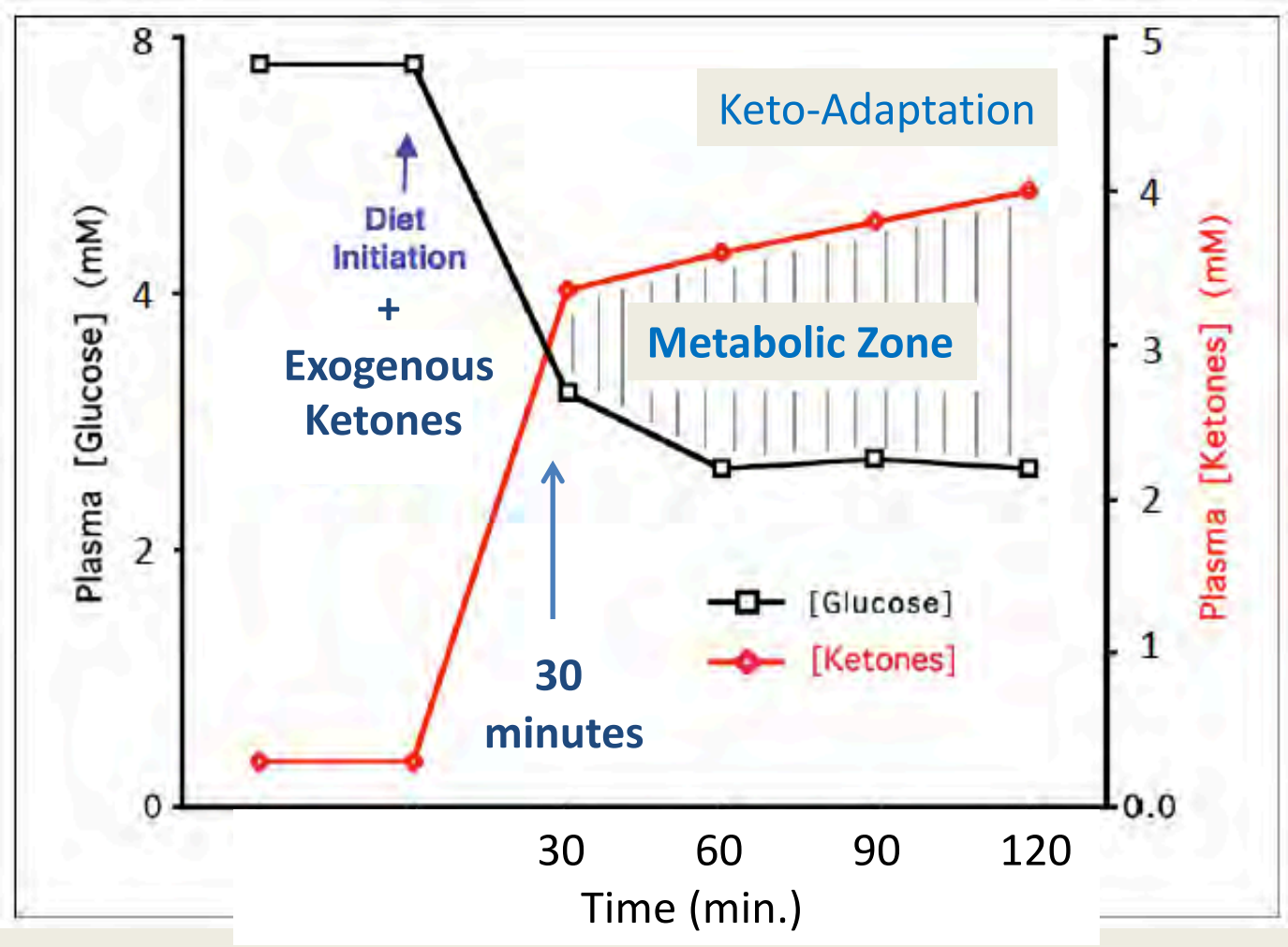
Breath
Acetone

Blood
(BHB)

Future Devices
Continuous BHB/AcAc
(*e.g.* Dexcom)



Practical Application for Patients
Metabolic Management of Disease

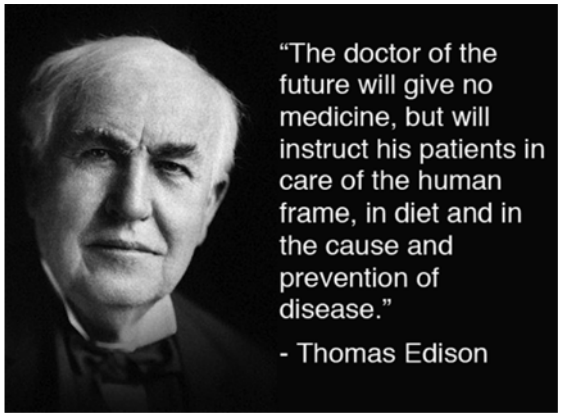


"Metabolic Zone"

Low Glucose (3.8 mM) **High Ketones**

Nutrition and Metabolism (Lond). 2010 Apr 22;7:33.
Carcinogenesis. 2014, Mar;35(3):515-27

Research Summary: Nutritional Ketosis (Past, Current and Future)



- ✓CNS O_2 Toxicity Seizures
- ✓Alzheimer's Disease
- ✓Angelman's Syndrome
- ✓Anxiety Behavior
- ✓Stress
- ✓GLUT1D Syndrome
- ✓Exercise Performance
- ✓NASA NEEMO 22, 23
- ✓Metabolomics
- ✓Pharmacokinetics
- ✓Glucose Regulation
- ✓Cancer Studies
- ✓Wound Healing
- ✓Inflammation
- ✓Longevity
- ✓Disease Prevention

Future Directions for Cancer Therapy

"Press"
Daily Routine

"Pulse"
Intermittent

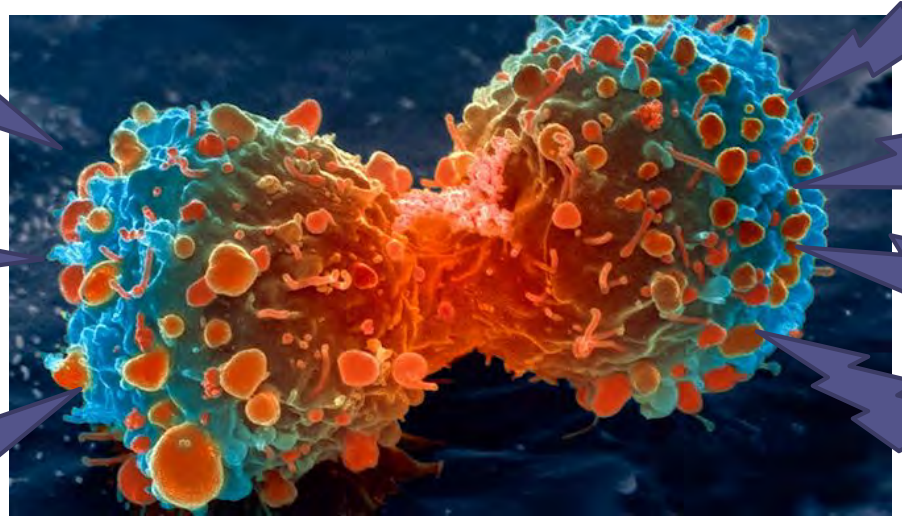
Ketogenic Therapies

↓ Glucose ↑Ketones

↓ Insulin

Metformin

Aerobic Exercise
Strength Training
Pro/Prebiotics
Meditation, etc.



Radiation Chemotherapies

Hyperbaric Oxygen

IV Vit. C

Metabolic Drugs (2-DG, 3-BP, Lonidamine, DCA, etc)

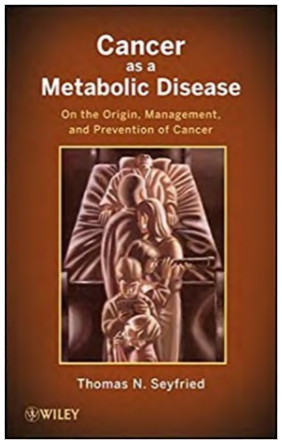
GKi = 1

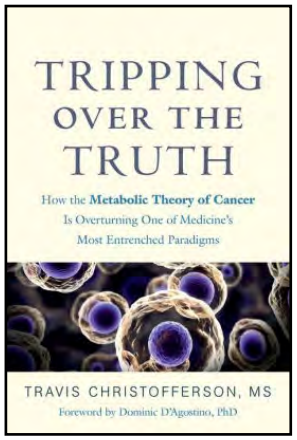
Seyfried TN, Maroon J, D'Agostino DP. Press-pulse: a novel therapeutic strategy for the metabolic management of cancer. *Nutr Metab (Lond)*. 2017 Feb 23;14:19. doi: 10.1186/s12986-017-0178-2

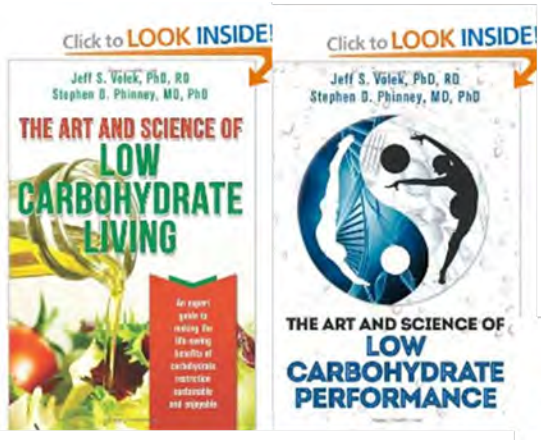
Suggested Resources

Resources Listed Here: KetoNutrition.org

Charliefoundation.org

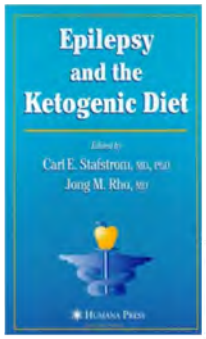






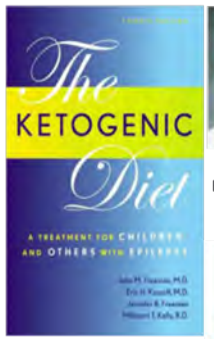
Jeff Volek PhD, RD
Ohio State
University

THE OHIO STATE
UNIVERSITY



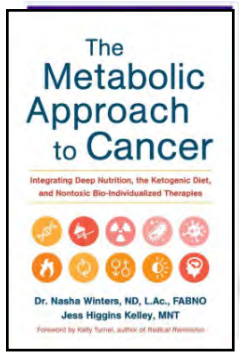
Jong Rho, MD
Chair Neurology
Univ. Calgary

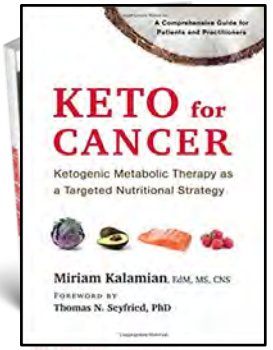
UNIVERSITY OF
CALGARY

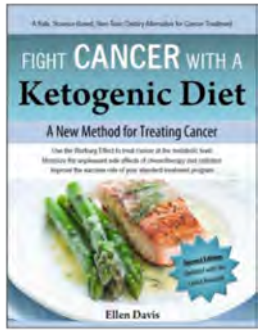


Eric Kossoff, MD
Neurology
Johns Hopkins

JOHNS HOPKINS
MEDICINE







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- Craig Goldhagen
- Dr. Nate Ward
- Andrew Koutnik
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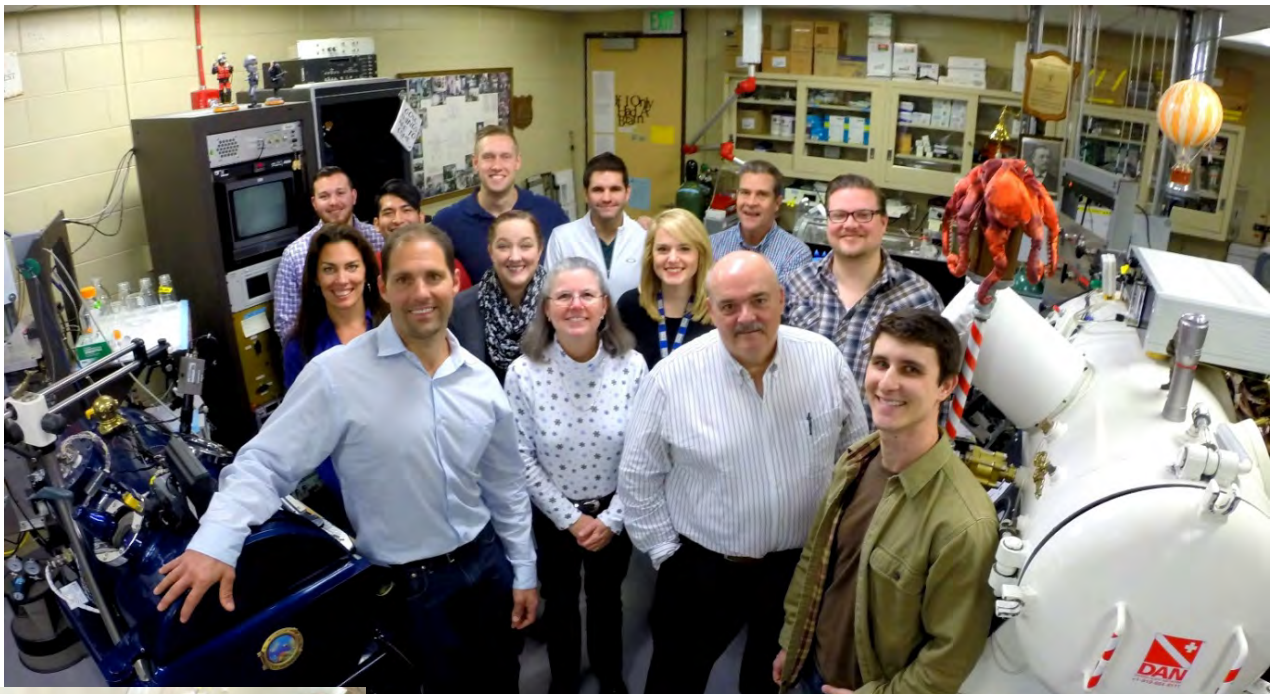
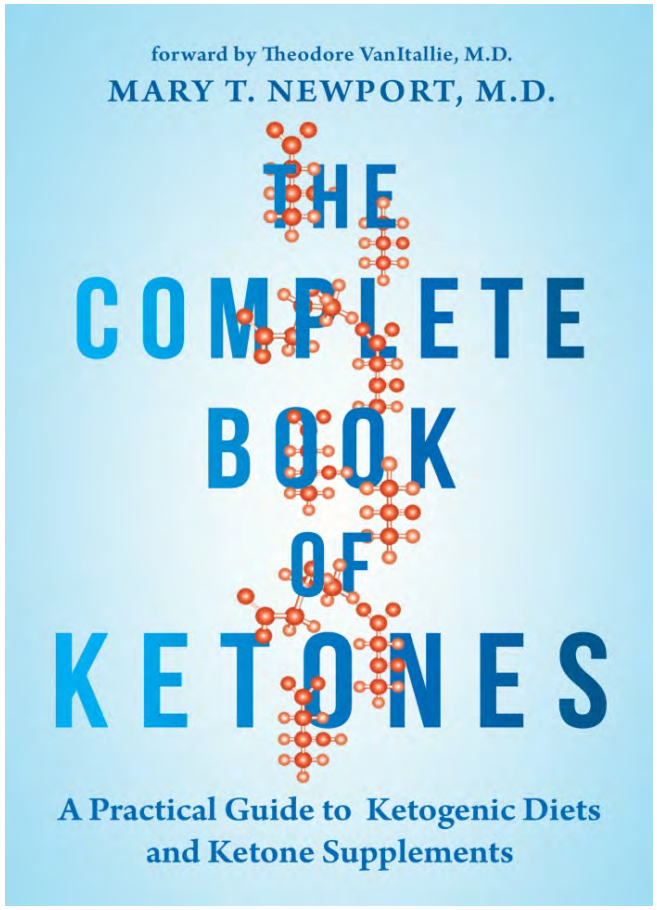


Hyperbaric Biomedical Research Lab

- Dr. Jay Dean
- Carol Landon
- Geoffrey Ciarlone
- Jacob Sherwood
- Chris Hinojo

Questions???



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The Complete Book of Ketones:

A Practical Guide to Ketogenic Diets and Ketone Supplements

By Mary T. Newport, M.D.

A comprehensive look at ketones and nutritional ketosis:

- The role of ketones in evolution.
- What ketones are and what they do.
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- A full list of resources and mouth-watering recipes round out the book and truly make this the complete book of ketones.

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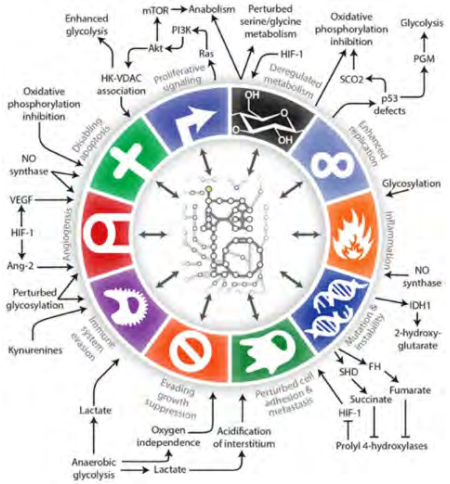
Review

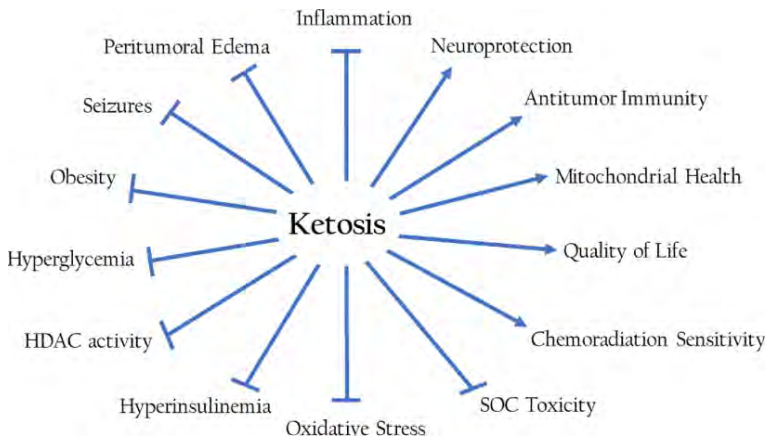
Targeting the Warburg effect for cancer treatment: Ketogenic diets for management of glioma

Angela Poff[a], Andrew P. Koutnik[a], Kathleen M. Egan[b], Solmaz Sahebjam[c], Dominic D'Agostino[a], Nagi B. Kumar[b,*]

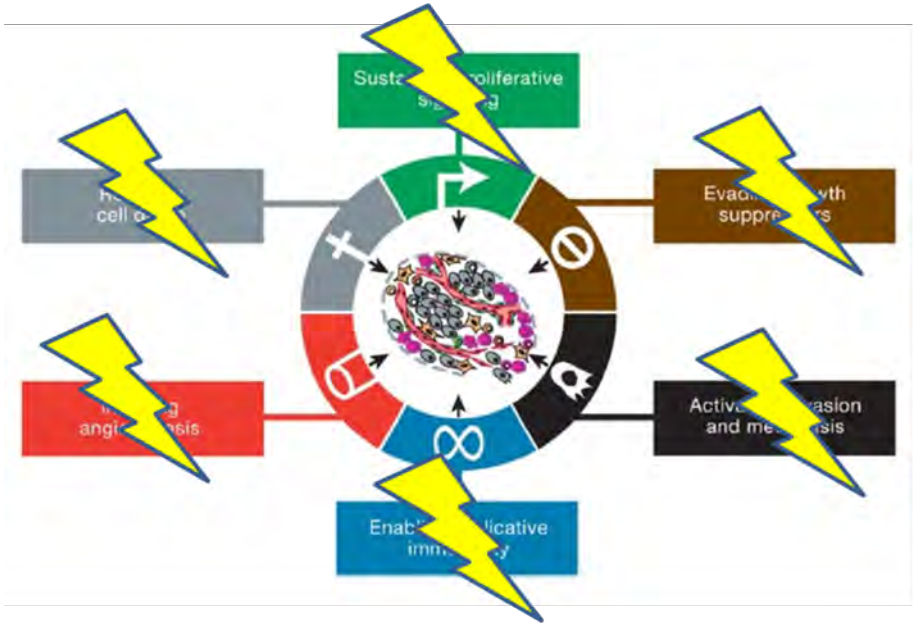
[a] The University of South Florida, Department of Molecular Pharmacology and Physiology, 12901 Bruce B. Downs Blvd, MDC 8, Tampa, FL 33612, United States
[b] Moffitt Cancer Center, H. Lee Moffitt Cancer Center and Research Institute, Department of Cancer Epidemiology, 12902 Magnolia Drive, MRC/CANCONT, Tampa, FL 22612-9497, United States
[c] Department of Neuro-Oncology, H. Lee Moffitt Cancer Center and Research Institute, Department of Cancer Epidemiology, 12902 Magnolia Drive, Tampa, FL 22612-9497, United States

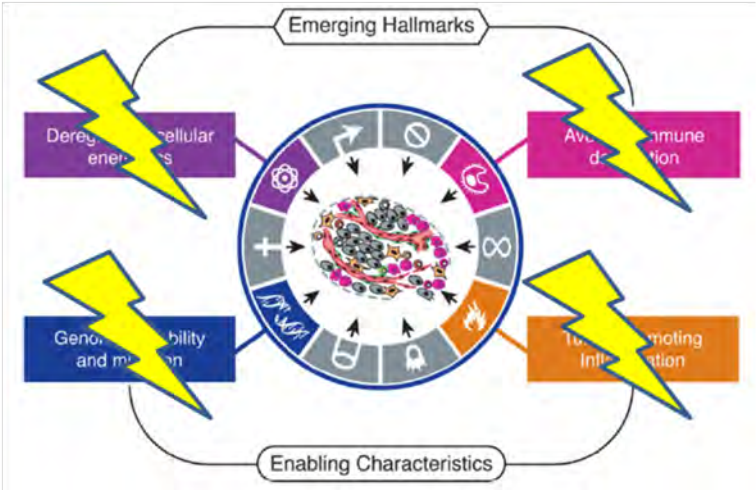
Interconnections between tumor metabolism

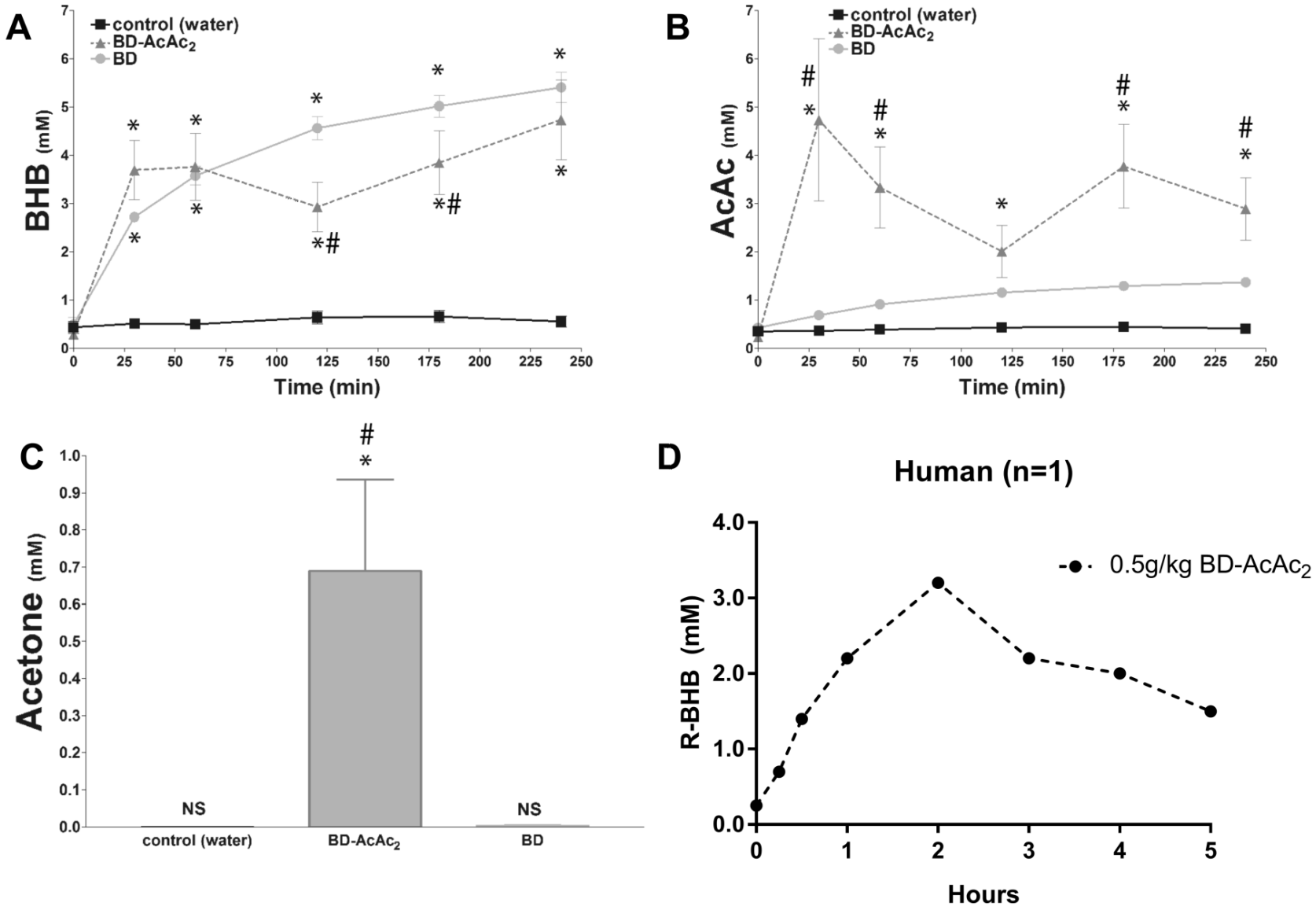




Therapeutic Ketosis Targets (directly/indirectly) The Hallmarks of Cancer






A
control (water)
BD-AcAc2
BD
BHB (mM)
Time (min)
B
control (water)
BD-AcAc2
BD
AcAc (mM)
Time (min)
C
Acetone (mM)
NS
NS
control (water)
BD-AcAc2
BD
D
Human (n=1)
0.5g/kg BD-AcAc2
R-BHB (mM)
Hours

Nutritional Ketosis (NK) 101

Diabetic Ketoacidosis (DKA) vs Nutritional Ketosis (NK)

Pathological **Therapeutic**

	Diabetic Ketoacidosis	Therapeutic Ketosis
Blood Ketones	8 - 30 mmol/L	1 - 3 mmol/L
Insulin	Dysregulated/Absent	Regulated/Low
Glycemia	High	Stable/Low
Renal Metabolism	Ketonuria, Glycosuria, Reduced GFR	Mild Diuresis
Acidosis	Very high	Normal
Inflammation	Elevated	Reduced
Pathology	Hypovolemia, Coma, Death	None

Metabolism of D-BHB and L-BHB