Nutrition Research Virtual 2020 Webinar

Ketone ester applications & clinical updates

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Office of Naval Research (ONR) Project: CNS Oxygen Toxicity

Seizures that result from breathing $O_2$ at hyperbaric pressures (>2.4 atmospheres $O_2$)

Hyperbaric Oxygen Therapy

Diving with Re-breathers
Central Nervous System Oxygen Toxicity Seizures

2.8 atmospheres absolute in pure oxygen
**Undersea Medicine**

**Hypothesis**—
The pattern of respiration that precedes onset of CNS O₂ toxicity is a reliable biomarker of an impending seizure.

**In vitro (Cellular)**
- Rat Brain
- Brain slices
  - Solitary Complex
  - Cardio-Respiratory Neurons

**In vivo (Whole Animal)**
- Hyperbaric Radio-Telemetry (awake, unrestrained rat)

**Electrophysiology**

**Goal:** Time on HBO₂

**Single depth O₂ exposure limits used by USN**

<table>
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<tr>
<th>Depth (fsw)</th>
<th>Exposure (min)</th>
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<td>25 or less</td>
<td>240</td>
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<td>30</td>
<td>80</td>
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Seizure onset in rats: tonic/clonic movements of forelimbs and head

at rest

during seizures

Air (surface)

5 ATA O₂
(132 ft; 40 m)
A potential early physiological marker for CNS oxygen toxicity: hypoxic hyperpnea precedes seizure in unanesthetized rats breathing hyperbaric oxygen

Raffaele Pilla, Carol S. Landon, and Jay B. Dean
Department of Molecular Pharmacology & Physiology, Hyperbaric Biomedical Research Laboratory, University of South Florida, Morsani College of Medicine, Tampa, Florida
Submitted 1 November 2012; accepted in final form 15 February 2013
Strategies to prevent CNS $O_2$ toxicity seizures

- Antioxidants
- Anti-epileptic drugs
- Starvation ketosis

Do ketone esters show any anticonvulsant effects against seizures?
Nutritional Ketosis challenging to sustain!

Dietary Fat

Sustained

Glucose

Insulin

Body Fat

Acetone

AcAC

βHB

Liver

Ketogenic Diet

Carb

Protein

Fat

75%

20%

5%
What level of Ketosis is optimal?

Blood Ketones (millimolar)

- Optimal Ketone Zone
- Post-Exercise Ketosis
- Starvation Ketosis
- Nutritional Ketosis Begins
- Ketoacidosis

Optimal Fuel Flow for Brain and Muscles

Page 91: The Art and Science of Low Carbohydrate Performance
Jeff S. Volek and Stephen D. Phinney
Metabolic Benefits:
- Decreased Central Fatigue
- Enhanced Brain Metabolism
- Decreased ROS
- Mitochondrial biogenesis
- Anti-Catabolic/Protein sparing
- Increased insulin sensitivity
- Less lactate

Volek et al
Strength & Condition J. 32:42-47, 2010
How Does Fasting Change Brain Metabolism?

1922

Fasting Seizure Cure.

Osteopathic students那人22 days on water usually end fits.

LOS ANGELES, July 5.—Epilepsy may

Fuel Metabolism in Starvation

George F. Cahill, Jr.*
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email: gcahill1@cheshire.net

Key Words: starvation, ketosis, β-h

Abstract: This article, which prizes a life in academic medicine. It is and then to academic and research teaching of human biology to college undergraduates. In 1953, treating a youngsters in diabetes, the controls in human fuel metabolism

known, insulin could not be measured, which was difficult to measure, was central role of insulin and the metabolism of this

and pyruvate, combined with insulin.

Due to its use by brain, D-β-hydroxybutyrate to survive prolonged starvation, but a greater efficiency in providing cellular content.

Fatigue.
Seizure Protection

Ketones preserve brain metabolism extreme metabolic demands

Conclusions:
KE, but not BD, increased latency to seizure by 574% compared to control

574 % increase in latency to seizure in “rat divers”
Conclusions:

Ketone Esters:

- induced sustained elevation of blood BHB, AcAc and acetone
- did not modify blood glucose levels
Rat model of epilepsy

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

Seizure 35 (2016) 45–49

Contents lists available at ScienceDirect

Seizure

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

Different calorie restriction treatments have similar anti-seizure efficacy

Andrea Viggiano a, *, Raffaele Pilla b,c, Patrick Arnold d, Marcellino Monda e, Dominic D’Agostino b, Pio Zeppa a, Giangennaro Coppola a,f
Neuroprotective effect of ketones

Ketogenic diet mimics starvation

Reported positive effects of ketosis/ketogenic diet:

• Weight loss (Atkins diet)
• Alzheimer's disease
  Nutr Metabolism 2009 Aug 10;6:31
• Parkinson's disease
• Lou Gehrig's disease (ALS)
  BMC Neurosci. 2006 Apr 3;7:29
• Traumatic brain injury
  J Neurotrauma. 2011 Sep;28(9):1813-25
• Glioblastoma
  Nutr Metabolism. 2007 Feb 21;4:5.
• Epilepsy
Clinical & Nutritional Collaborations

Dr. Cristina Perillo, RD

Mrs. Marisa Gamberi
Le Gamberi Ketogenic Foods

Dr. Stefania Pacini, MD, PhD
Dolce Vita LLC-Gilbert, AZ, USA
Keto-Social Networking...

Ketogenic diet definition & Instructions

Glut1 Deficiency how to proceed
The Ketogenic Diet Approach as Metabolic Treatment for a Variety of Diseases

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Ketosis as a treatment for multiple metabolic and neurodegenerative pathologies

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Special Medical Purposes Food

- authorization obtained from the Ministry of Health according to EU regulations

- soon will be fully covered by Public Health System
Patient 1: Marco C., 63 y.o.

- Diagnosis: prostate cancer with multiple rib metastases
- Treated with surgery → removal of prostate cancer and part of 2 ribs
- Conventional therapy → Leuprolelin acetate (hormone therapy)
- 1st month on a strict 3:1 KD → adjustment
- KD implemented with Le Gamberi products → ease of compliance
- 2nd month on a KD → Prostate Specific Antigen (PSA) from 1.62 to below 1.00
- > 2 years on a KD → PSA below 1.00
  - no radiotherapy
  - PET scan: no evidence of cancer recurrence
- Stable blood glucose (75 mg/dl) and ketones (2.5 mMol)
Patient 2: *Mario C.*: 66 y.o.

- Diagnosis: **Pancreatic intraductal papillary mucinous neoplasm** with infiltrations and lymph node metastasis
- Treated with surgery → partial removal of duodenum and pancreas
- 1\textsuperscript{st} month on a strict 4:1 **KD** → adjustment
- KD implemented with **Le Gamberi** products → increase of compliance
- **Cancer antigen** (CA) at start → 43.69 U/ml
- CA after 6 months → 9.84 U/ml
- > 2.5 years on a KD → PET scan: **no evidence** of cancer recurrence
- **Stable blood glucose** (63-77 mg/dl) and **ketones** (1.5-2.9 mMol)
Patient 3: Michele M., 47 y.o.

• Diagnosis: **2 high grade glial lesions** (WHO grade III)
  – below supratentorial area, in left cerebellum
  – over right frontal supratentorial area

• Previous treatment → standard radio and chemo-therapy

• 1 year and 2 months on a strict **4:1 KD → stable** blood ketones (between 0.8 and 2.0 mM)

• KD implemented with *Le Gamberi* products → increase of compliance

• MRI after 9 months on a KD → consistent **reduction** of
  – glial lesions’ extension
  – tumor mass
  – perilesional edema
Patient 4: Matteo T., 45 y.o.

- Diagnosis: **stage IV colon adenocarcinoma** with liver and lung metastases
- 1\textsuperscript{st} treatment $\rightarrow$ Selective Internal Radiation Therapy (S.I.R.T.) on liver and surgery for metastases removal
- 2\textsuperscript{nd} treatment $\rightarrow$ cyberknife intervention on lung lesions
- 1 year and 3 months on a strict **4:1 KD**
  - Ketosis was stable ($\sim$4 mM)
- KD implemented with *Le Gamberi* products $\rightarrow$ increase of compliance
- Computerized Axial Tomography (CAT) scan after 10 months on a KD $\rightarrow$ consistent **reduction** of adenocarcinoma lesions
Patient 5: Luca R., 25 y.o.

• Diagnosis: **glycogenosis**
  glycogen storage disease caused by enzyme deficit in muscle and liver which affects **glycogen synthesis** and **glycolysis**
  – stopped working & exercising
  – muscle pain and spasms

• 1 year and 2 months on a strict 3:1 KD
  – Ketosis was stable (~2 mM)
  – CPK (creatine phosphokinase) decreased from ~500 to ~250U/L

• KD implemented with *Le Gamberi* products → increase of compliance

• Clear results:
  – back to work & exercising
  – no more spasms or pain
Patient 6: Giancarlo V., 43 y.o.

- Diagnosis: **Glioblastoma Multiforme**
- 1\textsuperscript{st} treatment → *Depatuxizumab Mafodotin* (ABT-414 - *Abbvie*) investigational anti-epidermal growth factor receptor
  - only releases cytotoxic agent once inside targeted cancer cells
- 1 year on a strict **4:1 KD**
  - Ketosis was stable (~2.5 mM)
- KD implemented with *Le Gamberi* products → increase of compliance
- Computerized Axial Tomography (CAT) scan after 8 months on a KD → **No evidence of tumor mass**
Long-term (6+ months) ketogenic diet in Italy is quite challenging as most people still refer to the Mediterranean diet, rich in carbohydrates. Thus compliance is often low, especially in families with multiple kids.
Neuroprotective and disease-modifying effects of the ketogenic diet

Maciej Gasior\textsuperscript{a}, Michael A. Rogawski\textsuperscript{a}, and Adam L. Hartman\textsuperscript{a,b}

\textsuperscript{a}Epilepsy Research Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda

\textsuperscript{b}The John M. Freeman Pediatric Epilepsy Center, Johns Hopkins Hospital, Baltimore, Maryland, USA

- KD and caloric restriction induce resistance against neurotoxin MPTP (degeneration of mesencephalic dopamine neurons)
- BHB is neuroprotective in MPTP models
- BHB $\uparrow$ mitochondrial ATP synthesis
The ketogenic diet as a treatment paradigm for diverse neurological disorders

Carl E. Stafstrom¹,² and Jong M. Rho³,⁴ *

¹ Department of Neurology, University of Wisconsin, Madison, WI, USA
² Department of Pediatrics, University of Wisconsin, Madison, WI, USA
³ Department of Pediatrics, University of Calgary Faculty of Medicine, Calgary, AB, Canada
⁴ Department of Clinical Neurosciences, University of Calgary Faculty of Medicine, Calgary, AB, Canada

• BHB administration ameliorated the mitochondrial respiratory chain damage
• Anti-inflammatory effects on MPTP-induced neurotoxicity
• Interest: test commercially available treatments increasing ketonemia (MCT-based formulations) on PD patients
Literature: KD Vs. Parkinson’s disease

Thematic Review Series: Calorie Restriction and Ketogenic Diets

Ketone body therapy: from the ketogenic diet to the oral administration of ketone ester

Sami A. Hashim and Theodore B. VanItallie
Department of Medicine, St. Luke’s-Roosevelt Hospital and Columbia University College of Physicians and Surgeons, New York, NY 10025

- BHB confers protection against dopaminergic neurodegeneration and motor deficits induced by the neurotoxin MPTP
- 3GHB ketone ester (glyceryl-tris-3-hydroxybutyrate) neuroprotects against MPTP in a dose-dependent manner
- Exogenous ketons protect against oxidative stress in neocortical neurons
- Ketone bodies protect against neuronal synaptic dysfunction induced by respiratory complex inhibitors
Impact of Ketogenic Diet on Parkinson Patients @ Villa Margherita Neurological Institute

Dr. A. Ciarimboli
Dr. G. Matarazzo
Dr. A. Vardaro
Unified Parkinson’s Disease Rating Scale
UPDRS (motory)

- Speaking abilities
- Facial expressions
- General tremor at rest
- Postural hand tremor
- Rigidity
- Hand mobility
- Rapid & alternate hand movements
- Leg agility
- Capability of standing up from sitting on a chair
- Posture/walk typology
- Postural stability
- Bradykinesia and hypokinesia
Non-motor Symptoms Scale

non-motor Symptoms in PD

Autonomic dysfunctions
- Orthostatic hypotension
- Urologic dysfunctions
- Gastro-intestinal disorders

Sleep troubles
- Insomnia
- Daily drowsiness
- Nocturia
- Night akinesia
- REM phase disorders/nightmares

Neuro-psychiatric disturbances
- Depression
- Anxiety
- Panic attacks
- Psychotic disorders
- Cognitive and behavioral disturbances

Others
- Respiratory troubles
- Falling
- Pain
- Surgical interventions
Movement analysis

G-Walk BTS

time up & go (with torsion)

10-meter walking test
Neurocognitive tests

- Minimental state examination (MMSE)
- Attention/concentration tests
  - Memory:
    - digit span
    - course test
    - learning word association test
  - Logic:
    - Raven's Progressive Matrices
- Frontal functions:
  - phonemic fluency
  - Semantic fluency
  - Frontal Assessment Battery (FAB)
OBJECTIVE (3 months)

Evaluation of KD impact on:

- cognitive performances
- cognitive decline
- motor conditions
  - autonomy
  - self-confidence
- non-motor conditions
Low-Fat Versus Ketogenic Diet in Parkinson’s Disease: A Pilot Randomized Controlled Trial

Matthew C.L. Phillips, MSc, FRACP,1* Deborah K.J. Murtagh,2 Linda J. Gilbertson, BLitComm, PGCert(Nursing),1 Fredrik J.S. Asztely, PhD, FRACP1,3 and Christopher D.P. Lynch, MD, FRACP1

1Department of Neurology, Waikato Hospital, Hamilton, New Zealand
2Healthy Kitchen Christchurch Ltd, Hamilton, New Zealand
3Institute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden

- randomized 47 patients
  - 44 commenced the diets
  - 38 completed the study (86%)
- decrease in
  - urinary problems
  - pain
  - fatigue
  - daytime sleepiness
  - cognitive impairment
- safe for patients to maintain a low-fat or ketogenic diet for 8 weeks
- both groups significantly improved in motor and non-motor symptoms
  - KD showed greater improvements in non-motor symptoms
RUN FOR PARKINSON’S 2018

"Passeggiata per sensibilizzare i cittadini sulla malattia di Parkinson"

PAGO VEIANO
19 MAGGIO 2018
dalle ore 15,00 alle ore 17,00

Partenza: Piazza Municipio
Arrivo: Piazza Roma

Run for Parkinson’s
Parkinson Sannio Association
Next step...
RareConnect.org
Connecting rare disease patients globally

Search and join a community | Search or start a discussion | JOIN NOW

Connecting rare disease patients globally
START A COMMUNITY FOR A RARE DISEASE IN PARTNERSHIP WITH US.

JOIN NOW (it takes 30s) | SEE HOW IT WORKS

Search for a rare disease community or discussion group

VISIT OUR DISCUSSION GROUPS / SEE ALL OUR COMMUNITIES
Collaboration with Dr. Cosimina Cusano, MD, RD

- ALS
- Mitochondrial Encephalopathy
- Pancreatic cancer
- Epilepsy
- Refractory Epilepsy
- Refractory Epileptic Encephalopathy
- Autism
- Glioblastoma
- Overweight
SOMETHING HAPPENED 30 YEARS AGO...

FROM EXECUTIVE PRODUCERS KATIE COURIC AND LAURIE DAVID

FED UP

A FILM BY STEPHANIE SOECHTIG

ATLAS FILMS PRESENTS BRICKSTONE MEDIA GROUP AND RIZZOLI 360 IN ASSOCIATION WITH ARTIEME RISING AND DIAMOND DOCS. DIRECTED BY STEPHANIE SOECHTIG. PRODUCED BY KATIE COURIC, LAURIE DAVID, JAY REISS, AND KATE COURIC. WRITTEN BY JAY REISS. PRODUCED AND DISTRUBTED BY ATLAS FILMS.
THAT SUGAR FILM – February 2015
BUTTER MAKES MY PANTS FALL OFF
August 2014
Special thanks to:

- Madison Stoddard
- Glenna Steele
- Dr. Andrea Viggiano
- Dr. Giangennaro Coppola

GLUT1 Associazione Italiana

Some1 with Glut1

Glut1 Deficiency Foundation

www.G1DFoundation.org
Exogenous Ketone Administration as a Therapy Supplement?
Thank you for your attention!