Nutrition Research Virtual 2020 Webinar







ketone ester
appleadonester
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betappleadonest





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

Seizures that result from breathing O₂ at hyperbaric pressures (>2.4 atmospheres O₂)

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.



main chamber 5 ATA Air



animal chamber

Telemetry module

5 ATA O₂

EEG ECG

dEMG

receiver

Seizure onset in rats: tonic/clonic movements of forelimbs and head at rest during seizures



Air (surface)

5 ATA O₂ (132 ft; 40 m)

What we recorded DURING THE DIVE



Strategies to prevent CNS O₂ toxicity seizures

- ✓ Antioxidants
- ✓ Anti-epileptic drugs
- Starvation ketosis

0

Special-Ops Diving

Length of <u>ex</u>posure

(mins)

240 80

25

10

Depth

(fsw)

30 35

50

25 or less

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Do ketone esters show any anticonvulsant effects against seizures?



What level of Ketosis is optimal?



Page 91: The Art and Science of Low Carbohydrate Performance Jeff S. Volek and Stephen D. Phinney

Keto-Adaptation

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?



Hippocrates

Annu. Rev. Nutr. 2006. 26:1–22 doi: 10.1146/annurev.nutr.26.061505.111258 Copyright © 2006 by Annual Reviews. All rights reserved First published online as a Review in Advance on May 9, 2006

FUEL METABOLISM IN STARVATION

George F. Cahill, Jr.* Department of Medicine, Harvard Medical School. Boston. Massachusetts 02115: email: gcahill1@cheshire.net

Key Words starvation, ketosis, β-h

Abstract This article, which is particular to the second secon rizes a life in academic medicine. It 1 and then to academic and research : ing of human biology to college under 1953) treating a youngster in diabet the controls in human fuel metabolis known, insulin could not be measured which was difficult to measure, was central role of insulin and the metabo tate, and pyruvate, combined with inc near-steady state, namely prolonged s ter. Due to its use by brain, D-β-hyc to survive prolonged starvation, but al greater efficiency in providing cellula ocardial insufficiency, neonatal stress, fatigue.



In little

Seizure Protection

Ketones preserve brain metabolism extreme metabolic demands

10

Time (min)

20

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. Dean¹

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

Submitted 8 November 2012; accepted in final form 20 March 2013

100



70

574 % increase in latency to seizure in "rat divers"



University of Salerno

Insum

Director: Professor Giangennaro Coppola

M

Rat model of epilepsy

N-N





BD-AcAc₂

water

Neuroprotective effect of ketones

Ketogenic diet mimics starvation

Thursday 1st December 2011

Reported p diet:

 Weig Quickly Find... Home | Front Page Lotterv Alzhe Big Brother NEW Reader Offers iPad App Puzzle App Parkir MyEXPRESS Have Your Say News / Showbiz Sunday Express Lou G Scottish Sport Pictures Features Traun Day & Night - Express Yourself Fashion & Beauty Gliob Gardening - Food & Recipes Horoscope Our Comment The Crusader

👝 Site HOME > FEATURES > HEALTH > The bizarre diet that helps ease epilepsy

your**health**

EXPRESS.co.uk

THE BIZARRE DIET THAT HELPS EASE **EPILEPSY**



EPILEPSY: Mike Dancer Raffaele Pilla and 12 others Recommend recommend this.

Tuesday June 15,2010

SEARCH

Google

Have your say(0)

After drugs failed to control Mike Dancer's epilepsy he turned to an Atkins-style regime for help. He tells ROZ LEWIS how the unusual eating plan has improved his quality of life

Our Paper

Front and

twitter Follow Us

Back Pages, E-Edition and Back Issues...

WHEN epilepsy sufferer Mike Dancer sits down to breakfast he tucks into a can of tuna, two avocados and a rocket salad.

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





Editorial

Open Access

The Ketogenic Diet Approach as Metabolic Treatment for a Variety of Diseases

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Journal of Translational Science

Review Article

ISSN: 2059-268X

Ketosis as a treatment for multiple metabolic and neurodegenerative pathologies

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Special Medical Purposes Food



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Keto Plus grissino Rapporto 2:1

Keto Plus

Rapporto 2:1

panino



Keto Plus biscotto naturale Rapporto 2:1

Keto Plus

cornetto

Rapporto 2:1





Keto Plus crostino all'olio Rapporto 2:1



Keto Plus pancarrè Rapporto 3:1







Keto Plus focaccina all'olio Rapporto 2:1



Keto Plus riso





- 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

CASE REPORT

- Conventional therapy → Leuprorelin acetate (hormone therapy)
- 1^{st} month on a strict **3:1 KD** \rightarrow 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 \rightarrow 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^{st} month on a strict **4:1 KD** \rightarrow 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 \rightarrow 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
- 1st treatment→ Selective Internal Radiation Therapy (S.I.R.T.) on liver and surgery for metastases removal
- 2^{nd} treatment \rightarrow cyberknife intervention on lung lesions
- 1 year and 3 months on a strict **4:1 KD**
 - Ketosis was stable (~4 mM)
- KD implemented with *Le Gamberi* products → increase of compliance
- Computerized Axial Tomography (CAT) scan after 10 months on a KD → 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 ${\sim}500$ to ${\sim}250U/L$
- 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.

- Case Report
- Diagnosis: Glioblastoma Multiforme
- 1st 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



1st European Conference

on **GLUT1** Deficiency



Milan, Italy 7th- 8th October 2016



Prof. Anna Tagliabue



^{3rd} University Course on Ketogenic Dietary Therapies University of Pavia - June 14 – 16, 2017

« 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 »

Literature: KD Vs. Parkinson's disease



NIH Public Access

2006

Behav Pharmacol. Author manuscript; available in PMC 2008 May 5.

Published in final edited form as: Behav Pharmacol. 2006 September ; 17(5-6): 431–439.

Neuroprotective and disease-modifying effects of the ketogenic diet

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

aEpilepsy Research Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda

bThe 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 个 mitochondrial ATP synthesis

Literature: KD Vs. Parkinson's disease

frontiers in **PHARMACOLOGY**

REVIEW ARTICLE published: 09 April 2012 doi: 10.3389/fphar.2012.00059



2012

The ketogenic diet as a treatment paradigm for diverse neurological disorders

Carl E. Stafstrom^{1,2} and Jong M. Rho^{3,4}*

- 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. VanItallie¹

Department of Medicine, St. Luke's-Roosevelt Hospital and Columbia University College of Physicians and Surgeons, New York, NY 10025

2014

- 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



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



Movement analysis





time up & go (with torsion)

10-meter walking test


Neurocognitive tests



OBJECTIVE (3 months) **Evaluation of KD impact on:**

- cognitive performances
- cognitive decline
- motor conditions
 - autonomy
 - self-confidence
- non-motor conditions





RESEARCH ARTICLE

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, FRACP^{1,3} 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

Parkinson Sannio Association







Next step...



Italian Glut1 Deficit Association

President: Massimiliano Barone



RareConnect.org



Connecting rare disease patients globally

Connecting Rare Disease Patients Globally



ANIEL, FROM RUSSIA, LIVING WITH WILLIAMS SYNDROME. PHOTO COURTESY OF EURORDIS PHOTO CONTEST.

Collaboration with Dr. Cosimina Cusano, MD, RD



- ALS

- Mitochondrial Encephalopathy
- Pancreatic cancer
- Epilepsy
- Refractory Epilepsy
- Refractory Epilectic Encephalopathy
- Autism
- Glioblastoma
- Overweight

SOMETHING HAPPENED 30 YEARS AGO...





ATLAS FILMS HERE ALCOLONI AN ARTEMIS RISING / DIAMOND DOCS JOHN STEPHANIC SOECHTIS 'FED UP' "Smichael Brook ""Jernan Lazarte tina nguyen dan Swettlik Jac Communy's scott Sinkler opporter Kristin Lazare Sarah Gibson "Beeskatie Couric Lairie David Heather Reisman Regna K. Scouly Michelle Walrath Michael Walrath Atlas Joos "Mark Monroe" Marson Sarah Olson "Kriephyrstephane Slechtig



Congress says pizza is a vegetable.



FEDUP

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IN THEATERS MAY 9

THAT SUGAR FILM – February 2015



THE MAGIC PILL – September 2017





Official Trailer

BUTTER MAKES MY PANTS FALL OFF August 2014



Special thanks to:









Madison Stoddard



Glenna Steele



Dr. Andrea Dr. Giangennaro Viggiano Coppola

Exogenous Ketone Administration as a Therapy Supplement?





the USF TAMPA TEAM

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-

Teryn Gerhed



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Dr. J.B. Dean

Hyperbaric Biomedical Research Laboratory supported in part by:

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Thank you for your attention!