Science and Applications of Nutritional Ketosis

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1. Co-owner of Ketone Technologies LLC
2. Presentation includes data on various technologies patented by University of South Florida and licensed to industry partners
3. Information contained in this presentation is not meant to be taken as medical advice
Research: Understanding Human Physiology to Enhance Safety, Performance and Resilience in Extreme Environments

NASA EVAs

NASA NEEMO 21

<table>
<thead>
<tr>
<th>Depth (fsw)</th>
<th>Length of exposure (mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 or less</td>
<td>240</td>
</tr>
<tr>
<td>30</td>
<td>80</td>
</tr>
<tr>
<td>35</td>
<td>25</td>
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<tr>
<td>40</td>
<td>15</td>
</tr>
<tr>
<td>50</td>
<td>10</td>
</tr>
</tbody>
</table>
CNS Oxygen Toxicity Seizures
2.8 ATA $O_2$ (~ 55 ft sea water)
Methods

- Atomic Force Microscopy (AFM)
- Fluorescence Microscopy
- Laser Scanning Confocal Microscopy
- Electrophysiology
- Radio Telemetry (EEG, EMG, EKG)

- Adapters to hyperbaric chambers
Oxygen Pressure → Free Radicals → Neuro-Inflammation → Hyper-Excitability → Seizures (Drug-Resistant)

Brain Neuron
Strategies Tested to Prevent Seizures

- Antioxidants **Fail**
- Epilepsy Drugs **Fail**
- Fasting Ketosis
  (>200% protection!)
How Does Fasting Change Brain Metabolism?
Owen OE, Morgan AP, Kemp HG, Sullivan JM, Herrera MG, Cahill GF Jr.

Diagram from: Oliver E. Owen. “Ketone Bodies as a Fuel for the Brain during Starvation, ” *Biochemistry And Molecular Biology Education* Vol. 33, No. 4, 2005:246–251
Nutritional Ketosis Mimics Fasting Ketosis

Ketogenic Diet

Body Fat

Liver

Glucose

Insulin

Ketones (energy!)
## Ketone Terminology

<table>
<thead>
<tr>
<th>Ketone Bodies</th>
<th>Energy substrates from fatty acid oxidation</th>
</tr>
</thead>
</table>
| Ketosis       | Blood $\beta$-Hydroxybutyrate (BHB) $>0.5$ mmol/L  
Urine Acetoacetate (AcAc) $>15$ mg/dL |
| Nutritional Ketosis | Dietary strategy to elevate blood ketones |
| Keto-acidosis | Pathologically high ketones ($>10$ to $25+$ mmol/L) *from Insulin Insufficiency* |
| Keto-Adaptation | Time-dependent physiological shift towards using fat and ketones for fuel |
| Exogenous Ketones | Synthetic or naturally derived substances to elevate ketone metabolites in blood |
Academic and Clinical Ketogenic Mentors and Pioneers

Jong Rho, MD
Chair Neurology
Univ. Calgary

Eric Kossoff, MD
Neurology
Johns Hopkins

Epilepsy and the Ketogenic Diet
Edited by Carl E. Stafstrom, MD, PhD
Jong M. Rho, MD

The Ketogenic Diet
A Treatment for Children and Others with Epilepsy
John M. Freeman, M.D.
Eric H. Kossoff, M.D.
Jennifer B. Freeman
Millicent T. Kelly, R.D.
2008
Mike Dancer: Diagnosed with “Terminal Epilepsy”
Applications of Nutritional Ketosis  
(Proven and Emerging)

- **Epilepsy and Seizures disorders**  

- **CNS O₂ Toxicity**  

- **Weight loss and Type-2 Diabetes**  

- **Autism**  
  *J Child Neurol.* 2013 Aug;28(8):975-82

- **Angelman’s Syndrome**  
  *Neurobiol. Disease* 2016 Dec;96:38-46

- **Alzheimer’s disease**  
  *Nutr Metabolism* 2009 Aug 10;6:31

- **Parkinson’s disease**  
  *Curr Treat Options Neurol.* 2008 Nov;10(6):410-9

- **Lou Gehrig’s disease (ALS)**  
  *BMC Neurosci.* 2006 Apr 3;7:29

- **Traumatic Brain Injury**  
  *J Neurotrauma.* 2011 Sep;28(9):1813-25

- **Exercise Performance**  
  *Cell Metabolism.* Sep 13;24(3):373-5

- **PCOS**  
  *Nutr Metab (Lond).* 2005 Dec 16;2:35

- **Acne**  
  *Skin Pharmacol Physiol.* 2012;25(3):111-7

- **Cancer**  
Exogenous Ketones Produce Rapid & Sustained Ketosis


Exogenous Ketones Prevent CNS Oxygen Toxicity Seizures

Ongoing studies in seizures

Ketone Research
(past, present, in preparation!)

- CNS O₂ Toxicity Seizures
- Neurological Disorders
- Rare Genetic Disorders
- Anxiety Behavior
- Motor Performance
- Extreme Environments
  - NASA NEEMO 22
  - Kilimanjaro Climb
- Pharmacokinetics
- Glucose Regulation
- Metastatic Cancer
- Cancer Cachexia
- Wound Healing
- Inflammation
- Longevity
- Metabolic Efficiency
Effect of Acute Ketosis (BHB salts) on Oxygen Consumption

Fixed Power Output (180 Watts)

**Test set #1**: mild nutritional ketosis

- Ketones : 0.6 mM

**Test set #2**: 15.6 gm Exogenous BHB ketone mineral salt

- Ketones : 2.0 mM (BHB salts)

<table>
<thead>
<tr>
<th>Segment</th>
<th>Test 1</th>
<th>Test 2 (BHB)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last 5 min</td>
<td>3,298 mL/min</td>
<td>3,032 mL/min</td>
<td>-8.8%</td>
</tr>
<tr>
<td>Last 10 min</td>
<td>3,255 mL/min</td>
<td>3,023 mL/min</td>
<td>-7.7%</td>
</tr>
<tr>
<td>Last 15 min</td>
<td>3,210 mL/min</td>
<td>3,012 mL/min</td>
<td>-6.6%</td>
</tr>
<tr>
<td>Full 20 min</td>
<td>3,065 mL/min</td>
<td>2,890 mL/min</td>
<td>-6.0%</td>
</tr>
</tbody>
</table>
Fueling Performance: Ketones Enter the Mix

Brendan Egan1,* and Dominic P. D’Agostino2,*
1School of Health and Human Performance, Dublin City University, Glasnevin, Dublin 9, Ireland
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*Correspondence: brendan.egan@dcu.ie (B.E.), ddagosti@health.usf.edu (D.P.D.)
http://dx.doi.org/10.1016/j.cmet.2016.08.021

Ketone body metabolites serve as alternative energy substrates during prolonged fasting, calorie restriction, or reduced carbohydrate (CHO) availability. Using a ketone ester supplement, Cox et al. (2016) demonstrate that acute nutritional ketosis alters substrate utilization patterns during exercise, reduces lactate production, and improves time-trial performance in elite cyclists.

Nutritional Ketosis Alters Fuel Preference and Thereby Endurance Performance in Athletes

Pete J. Cox,1°,2° Tom Kirk,1 Tom Ashmore,3 Kristof Willeton,1 Rhys Evans,1 Alan Smith,1 Andrew J. Murray,2 Brianna Stubbs,1 James West,1 Stewart W. McLure,1 M. Todd King,2 Michael S. Dodd,1 Cameron Holloway,1,2 Stefan Neubauer,3 Scott Drawer,1 Richard L. Weech,1 Julian L. Griffln,3, and Kieran Clarke1
1Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford OX1 3PT, UK
2Department of Cardiovascular Medicine, University of Oxford, Oxford OX3 7LJ, UK
3Department of Biochemistry & Cambridge Systems Biology, University of Cambridge & MRC Human Nutrition Research, Cambridge CB1 9YN, UK
*UK Sport, 40 Bernard Street, London WC1N 1ST, UK
°Correspondence: pete@cox.ski674mail.com
http://dx.doi.org/10.1016/j.cmet.2016.07.010

- Ketosis shifts metabolic physiology from glycolysis to fat oxidation
- Preserved muscle glycogen
- 50% reduction in lactate
- Ketone-induced reduction in perceived exertion and greater CNS motor unit recruitment
What is the Metabolic and Signaling Mechanism(s)?
Ketogenic Diet, Ketone Supplementation

FFA Oxidation + Elevated Ketones
Lowered Glucose

βHB
AcAc
Acetone
GABA/Glu Ratio

2-3x Higher TCA Cycle Intermediates

2-3x Higher Carnosine Anserine

5x Higher Adenosine

Glucose (Insulin)
ROS
Oxidative Stress
Inflammation

Neuroprotective and Anticonvulsant Effect

Modified from: Masino & Rho, 2013
Implementation of Nutritional Ketosis
Strategies for Inducing Nutritional Ketosis

Low Carb/Ketogenic Diet (variants)

Ketone Supplementation

“Ketogenic Intermittent Fasting”

Exogenous Ketones
Nutritional Ketosis for Performance and Wellness
Strategies for Assessing Nutritional Ketosis

- **Urine**: Acetoacetate (AcAc)
- **Breath**: Acetone
- **Blood**: (BHB)
- **Future Devices**: Continuous BHB/AcAc (e.g. Dexcom)
Potential Medical Applications
(Status Epilepticus, Cancer, Brain Injury, etc)

Nutrition and Metabolism (Lond). 2010 Apr 22;7:33.
Carcinogenesis. 2014, Mar;35(3):515-27
Summary Ketones as Fuel and Signaling Molecule

Starvation and Calorie Restriction (Adipose)

Ketogenic Diet

Difficult to sustain...

- Glucose
- Glycogen
- Insulin

Hepatic Ketogenesis

Liver

Ketones

Alternative Fuel

Neuroprotective Signaling Metabolites

Exogenous Ketones

Glutamate (GAD)

GABA (GABA Transaminase)

Anaplerosis (TCA Intermediates)

Longevity

- DAF-16/FOXO
- ↓ IGF-1
- ↓ mTOR

Oxidative Stress

Superoxide class 1 HDACI

Inflammation

- NLRP3
- Inflammatory Cytokines
Current Projects (seeking collaboration and volunteers)
1) NASA Extreme Environment Mission Operations (NEEMO 22) Project
2) “Informal Study” Special Operations Forces (Mountaineering)

1. Nutrition Tracking (2 wk journal prior to recruitment)
2. Body Comp (calipers, ultrasound) **
3. Ketosis Assessment (urine, blood)
4. Sleep (OURA ring) **
5. Stress (Polar V800) **
6. Gut Microbiome
7. Cognitive (NIH Toolbox, Joogle) **
8. Hormone Analysis (ZRT Labs)
9. Cardiometabolic (ZRT Labs)
10. Genetic Test + Analysis (23andMe)

Thank You!

Laboratory of Metabolic Medicine
- Dr. Angela Poff
- Dr. Csilla Ari
- Dr. Chris Rogers
- Dr. Shannon Kesl
- Nate Ward
- Andrew Koutnik

Hyperbaric Biomedical Research Lab
- Dr. Jay Dean
- Carol Landon
- Geoffrey Ciarlone
- Jacob Sherwood
- Chris Hinojo
Resources

MetabolicTherapeutics.com
Charliefoundation.org
KetoNutrition.org
Ketogenic-diet-resource.com