The Ketogenic Diet and HBOT for Cancer

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Metabolic Therapy Research

- CNS Oxygen Toxicity (seizures)
- Neurological Disorders
- Metabolic Disorders
- Wound Healing
- Cancer
**CNS Oxygen Toxicity**

- **CNS-OT** results from breathing oxygen at >2.5 ATA O$_2$

**Hyperbaric O$_2$ Therapy**

- There is no way to prevent or predict CNS-OT
- What is the mechanism for CNS-OT?

**Diving**

<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>
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**Department of the Navy**

**USF University of South Florida**
Methods to Study CNS-OT

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

- Adapted to hyperbaric chambers
Cellular Mechanism of CNS-OT

Hyperoxia → ROS/RNS → Oxidative Stress → Neuronal Excitability & Metabolic Stress → CNS-OT Seizure

- Superoxide anion \(-\text{O}_2^\cdot-\) → \(\cdot\text{NO}\) → \(\cdot\text{ONOO}^-\)
- \(\uparrow\text{O}_2\)
- SOD
- \(\downarrow\text{Fe}^{3+}\)
- \(\cdot\text{OH}\)
- \(\downarrow\text{H}_2\text{O}_2\)

Lipid Peroxidation
Protein Oxidation
Protein Nitration
Membrane Damage

\(\downarrow\text{V}_m\)
\(\uparrow\text{Firing}\)
\(\uparrow[\text{Ca}^{2+}]_i\)

\(\uparrow\text{EEG}\)

Seizure

membrane lipid peroxidation
Strategies to prevent CNS O_2_ toxicity

- Antioxidants
- Anti-Epileptic Drugs (AEDs)
- Preconditioning
- **Starvation** (>200% delay in latency to seizure)


How Does Starvation Change Brain Metabolism?
How Does Starvation Change Brain Metabolism?

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.”

FUEL METABOLISM IN STARVATION

George E. 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 prized a life in academic medicine. It and then to academic and research ing of human biology to college and 1953) treating a youngster in diabet the controls in human fuel metabolism known, insulin could not be measure which was difficult to measure, was central role of insulin and the metabc tate, and pyruvate, combined with in near-steady state, namely prolonged ter. Due to its use by brain, D-β-hyo to survive prolonged starvation, but a greater efficiency in providing cellula ocardial insufficiency, neonatal stress, fatigue.
Ketone Bodies Fuel the Brain During Starvation

**Ketones**
- β-OHB

**Glucose**

Ketogenic Diet Mimics Fasting

Diet

Body Fat

Glucose
Insulin

Difficult to sustain...

Ketones (energy!)
Ketone Supplementation?

- MCT oil
- Ketone Salts (KetoForce)
- Naturally Derived

- Ketone Esters
- BHB
- AcAc
- Synthetic

- Ketones (energy)
Ketone Supplementation (Single Dose)

Rapid Ketosis (15-30 minutes)
Sustained Ketosis (4-8 hrs)


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

Ongoing testing in 4 seizure models

575 % Seizure Resistance

Ketone Ester

Special Ops Diving

Physiological Resilience
Cognitive Performance
Physical Performance
Elevated Ketones
Lowered Glucose

Ketogenic Diet, Ketone Esters

βHB
AcAc
Acetone
GABA/Glutamate Ratio
2-3x Higher TCA Cycle Intermediates
2-5x Higher Adenosine Carnosine Anserine

Glucose
Insulin
ROS
Oxidative Stress

Metabolic Flexibility

Glucose
Normal Diet (High Carb)

Ketones
Ketogenic Diet (High Fat)

Healthy cells in the body can burn ketones for energy
Cancer lacks metabolic flexibility. Glucose from a normal diet (High Carb) fuels cancer cells, whereas ketones from a ketogenic diet are not used by cancer cells.
FDG-PET Scan
(metastatic cancer)

Otto H. Warburg
Nobel Prize (1931) Medicine

First to Describe Cancer as a Metabolic Disease
Elevated rates of glycolysis and fermentation, excessive lactate production – up to 200 X rate of normal cells

Cancer Metabolism & The Warburg Effect

- Critical to neoplastic phenotype
- Warburg effect: Fermentation in the presence of oxygen
- Most consistent cancer phenotype, present in most, if not all, cancers

**Anaerobic Fermentation**

≈2 ATP per glucose

**Aerobic Respiration**

≈38 ATP per glucose

Glucose → Lactate

Glucose + O₂ → Acetyl CoA

Mitochondrion
Cancers thrive on glucose but are vulnerable to energy stress

- High glycemic index diets increase risk of cancer
- Hyperglycemia = poor prognosis
- Blood glucose directly correlated to tumor growth
- Ketogenic diet: 4:1 fat : protein + carbohydrate
  - Induces ketosis
  - Anti-inflammatory
  - Suppresses insulin and IGF-1

\[ r^2 = 0.539 \]


Gnagnarella et al; 2008
Tumor hypoxia promotes cancer progression and the Warburg Effect

HIF-1 implicated in every aspect of cancer progression

30-60 mmHg

2-30 mmHg

Average $\text{PO}_2$

Confers chemo/radioresistance

Regulation of cancer cell metabolism by hypoxia-inducible factor 1; Semenza, G.
Can we use ketosis and HBOT to create a physiological environment that is toxic to cancer cells?
The VM-M3 Model of Metastatic Cancer

*Developed by Dr. Thomas Seyfried, Boston College*

- Cells from spontaneous brain tumor
  - Natural tumorigenesis
- Syngeneic with VM/dK mice
  - Immunocompetent
- S.C. implantation → systemic metastasis
  - Shares many molecular and behavioral characteristics of human metastatic cancers
- Transduced with firefly luciferase gene
  - *In vivo* bioluminescence imaging
Combining the Ketogenic Diet with Hyperbaric Oxygen

Methods: Treatment Groups

**VM-M3 Survival Study:**
- Control: Standard Diet *ad libitum*
- KD: Ketovolve *ad libitum*
- HBOT
  - Diet: SD *ad libitum*
  - HBOT: 2.5 ATA, 90 min, 3/week
- KD+HBOT:
  - Diet: Ketovolve *ad libitum*
  - HBOT: 2.5 ATA, 90 min, 3/week
KD+HBOT inhibits tumor growth and metastatic spread

21 days post inoculation

**Bioluminescence (Photons/sec)**

**Tumor Growth**

- Control
- KD
- HBOT
- KD+HBOT

**Brain**

**Lungs**

**Liver**
**KD+HBOT prolongs VM-M3 mouse survival**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cohort Size (N)</th>
<th>Mean Survival Time (days)</th>
<th>Increase in Survival Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (SD)</td>
<td>13</td>
<td>31.2</td>
<td>---</td>
</tr>
<tr>
<td>KD</td>
<td>8</td>
<td>48.9</td>
<td>56.7%*</td>
</tr>
<tr>
<td>HBOT</td>
<td>8</td>
<td>38.8</td>
<td>24.4% (NS)</td>
</tr>
<tr>
<td>KD+HBOT</td>
<td>11</td>
<td>55.5</td>
<td>77.9%***</td>
</tr>
</tbody>
</table>

* *p<0.05
***p<0.001
Combination Therapy: KD + Ketone Esters + HBOT

Multi-combination treatment to maximize therapeutic potential

Methods: Treatment

• Control: SD ad libitum

• KD+KE+HBOT:
  ▫ Diet: KD-USF + 10% KE ad libitum
    • 1% saccharin
  ▫ HBOT: 100% O2, 2.5 ATA, 90 min, 3/wk

Poff et al, PLOS One (Under Review)
Combination therapy inhibits tumor growth and metastatic spread

Poff et al, PLOS One (Under Review)
Combination therapy doubles survival time in VM-M3 mice

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<th>Cohort Size (N)</th>
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<tbody>
<tr>
<td>Control</td>
<td>11</td>
<td>33.7</td>
<td>-----</td>
</tr>
<tr>
<td>HBOT</td>
<td>8</td>
<td>38.8</td>
<td>24.4%</td>
</tr>
<tr>
<td>KD</td>
<td>7</td>
<td>45.1</td>
<td>44.6%*</td>
</tr>
<tr>
<td>KE</td>
<td>8</td>
<td>52.8</td>
<td>69.2%***</td>
</tr>
<tr>
<td>KD+KE+HBOT</td>
<td>17</td>
<td>63.4</td>
<td>103.0%***</td>
</tr>
</tbody>
</table>

*p<0.05
***p<0.001
Practical Guidelines for Implementing Metabolic Therapy

* Patients should be monitored by their own physician, while working closely with the Registered Dietitian
“Standard Diet” vs. “Ketogenic Diet”

- Ketogenic Diets differ from the Standard Diet in macronutrient distribution.
- Carbohydrate intake decreases to <10% of kcals.
- Ketogenic diet is NOT a HIGH PROTEIN diet
Monitoring Biomarkers

- Urine
- Blood
  - Finger stick
  - Precision Xtra®
  - Breath (Ketonix)

“Low Carb”  2:1 KD  4:1 KD
The Metabolic Zone

Diet Initiation

Plasma [Glucose] (mM)

Plasma [Ketones] (mM)

Managed Growth

Unmanaged Growth

Days of Treatment
Challenges To Initiation

- Liver cancer and/or elevated liver enzymes
- Kidney stones and/or renal disease
- Pancreatitis
- Fat malabsorption issues
- Gallbladder obstruction or removal
- Medications
- Lack of support
- High cholesterol
- Food selection
Human Studies?

A Case Report
Stage IV Glioblastoma


Figure 1 MRI contrast enhanced images of a large multi-centric mass involving the right hemisphere pole. (A) Temporal pole, (B) frontal operculum, insular lobe, posterior putamen, (C) frontal operculum, head of caudate nucleus. Note the presence of peripheral edema (arrows).

Figure 3 Levels of circulating glucose (black line) and urinary ketones (red line) in the patient during the period from January 8 to February 7, 2009. The values are within normal physiological ranges for people who maintain low calorie dieting [46].

Figure 4 Brain MRI taken a few days after ending the standard radiotherapy plus concomitant temozolomide therapy together with KD-CR protocol. No clear evidence of tumor tissue or associated edema was seen. Arrow indicates porencephaly.
Clinical Trials

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

Nutrition 28 (2012) 1028-1035

Applied nutritional investigation

Targeting insulin inhibition as a metabolic therapy in advanced cancer: A pilot safety and feasibility dietary trial in 10 patients
There has been a surge in New Clinical Trials

<table>
<thead>
<tr>
<th>Rank</th>
<th>Status</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Recruiting</td>
<td>Ketogenic Diet With Concurrent Chemoradiation for Pancreatic Cancer</td>
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<tr>
<td></td>
<td></td>
<td><strong>Condition:</strong> Pancreatic Neoplasms</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Intervention:</strong> Dietary Supplement: Ketogenic diet</td>
</tr>
<tr>
<td>2</td>
<td>Recruiting</td>
<td>Ketogenic Diet With Chemoradiation for Lung Cancer (KETOLUNG)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Condition:</strong> Carcinoma, Non-Small-Cell Lung</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Intervention:</strong> Dietary Supplement: Ketogenic diet</td>
</tr>
<tr>
<td>3</td>
<td>Unknown †</td>
<td>The Effect of Ketogenic Diet on Malignant Tumors- Recurrence and Progress</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Condition:</strong> Malignant Tumors</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Interventions:</strong> Other: Nutritional support with Standard diet; Other: Nutritional intervention with the Ketogenic diet</td>
</tr>
<tr>
<td>4</td>
<td>Recruiting</td>
<td>Pilot Study of a Metabolic Nutritional Therapy for the Management of Primary Brain Tumors</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Condition:</strong> Glioblastoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Intervention:</strong> Dietary Supplement: Energy restricted Ketogenic Diet (ERKD) (Metabolic Nutritional Therapy)</td>
</tr>
<tr>
<td>5</td>
<td>Recruiting</td>
<td>Ketogenic Diet as Adjunctive Treatment in Refractory/End-stage Glioblastoma Multiforme: a Pilot Study</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Condition:</strong> Glioblastoma Multiforme</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Intervention:</strong> Other: ketogenic diet</td>
</tr>
<tr>
<td>6</td>
<td>Recruiting</td>
<td>Ketogenic Diet in Advanced Cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Condition:</strong> Cancer</td>
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</tbody>
</table>
Implications for Cancer Therapy

- Non-toxic, cost-effective, readily implementable
- Possibly effective against aggressive, late-stage cancers
- Potential synergy with standard care
- Protection against toxic effects of standard care
Future Directions

• Determine most effective dosing protocol for KD, ketone supplements and HBOT
• Compare to “Standard American Diet”
• Evaluate therapies in other cancer models
• Investigate mechanism of action
• Combine with standard care and other metabolic therapies
• Clinical trials
Questions and Topics of Discussion

• All Cancers Responsive?
• Dose of HBOT?
• Low Carb vs Ketogenic?
• Integration with other Therapies?
Resources

- www.ketogenic-diet-resource.com
- www.dietarytherapies.com
- http://www.charliefoundation.org/
- http://www.rsg1foundation.com/
- http://www.nutritionchoices.ie/
- www.ketonutrition.org

Questions ?
Effect of High Pressure Oxygen

Healthy Cells

Cancer Cells