KETONES AS AN ALTERNATIVE FUEL FOR ALZHEIMER’S DISEASE AND OTHER DISORDERS

Mary T. Newport MD
Hippocrates Institute
May 2014
Plaques and Tangles

100 billion nerve cells.
100 trillion synapses. Dozens of neurotransmitters.

*Brain tour* from Alzheimer’s Association, alz.org.
Altered morphology and 3D architecture of brain vasculature in a mouse model for Alzheimer’s disease

Eric P. Meyer*, Alexandra Ulmann-Schuler*, Matthias Staufenbiel†, and Thomas Krucker‡

PNAS 2008 105 (9): 3171-3172

4 – 8 month old WT 11.9 month old APP23 12 month old APP23

18 month old WT 18 month old APP23 18 month old APP23

A

B

C

40µm

10µm

10µm

500µm

400µm

40µm
Beta Amyloid PET Scan

- PET scans revealed beta-amyloid plaque in the brains of three Alzheimer's disease patients (left) and three normal controls (right). The yellow indicates high uptake of a label that targets beta-amyloid plaque, and the red indicates medium uptake.

FDG-PET scans show decreased glucose uptake

NORMAL BRAIN

ALZHEIMER’S BRAIN
Alzheimer’s is “Type 3 Diabetes”

Explosion of research into the relationship between AD and brain glucose metabolism in 1990’s and beyond.

In 2005, De la Monte and Wands looked at brains of persons with advanced AD who did not have type 1 or 2 diabetes:

• Levels of insulin and factors related to making and using insulin are greatly reduced.
• All of the signalling pathways involved in the use of energy are abnormal.
• The functioning of mitochondria is abnormal.
• Coined term “type 3 diabetes” to describe insulin deficiency and insulin resistance in AD brain

Alzheimer’s is “Type 3 Diabetes”

In 2008, de la Monte and Wands looked at various stages of AD brains in persons without type 1 or 2 diabetes:

• Loss of insulin and neurons with insulin growth factor receptors begins early in the disease.

• This worsens with each stage of the disease until it is very severe and occurs throughout the brain in most severe cases of AD.

• Suggest that therapies for type 1 or 2 diabetes may be beneficial.
  • Intranasal Insulin
  • Metformin or other medications for type 2 diabetes

Brain metabolism and Alzheimer’s

In 1970, Dr. Siegfried Hoyer reported decreased glucose levels & lower cerebral metabolic rate in brains of some people with dementia.

In 1991, Hoyer reported that:
• There is a shift in the types of fuel used by the brain in people as they age that is even more prominent in people with AD
• Young normal people use fuel in the cerebrum in ratio of 100:1 of glucose to alternative fuels
• Elderly persons without Alzheimer’s, this ratio is 29:1
• Early stages of Alzheimer’s this ratio is 2:1
  • Suggested fuel for brain cells must come from alternative fuels, such as fatty acids and amino acids (didn’t mention ketones)


Alternative Fuels for AD

- Glucose is the primary and preferred fuel for most cells, including brain.
- Humans are programmed by evolution to switch to use of alternative fuels during starvation when glucose stores have been used up
  - Amino acids (Gluconeogenesis)
  - Fatty acids
  - Ketones – Provide 2/3 of brain energy needs during starvation
    - Medium chain triglyceride (MCT) oil partly converts to ketones in liver
  - Lactate
- Supplying an alternative fuel could bypass problem of insulin deficiency and insulin resistance in AD brain

Ketones bypass problem of insulin resistance
Ketones use normal in mild Alzheimer’s brain

- Stephen Cunnane, PhD and associates reported in people with mild Alzheimer’s compared to controls, using FDG-PET and labeled acetoacetate ketone PET scans:
  - Glucose uptake is 17% lower in gray matter overall and 25% lower in areas affected by Alzheimer’s
  - Ketone uptake is normal throughout the brain, including the areas affected by Alzheimer’s – supports ketones as alternative fuel

KETOGENIC DIET

• 80-90% of calories as fat, the remainder as carbohydrate and sufficient protein to grow or to maintain lean body mass

• Reported positive effects of ketogenic diet:
  • Epilepsy and certain seizure disorders
  • Alzheimer’s disease
  • Parkinson’s disease
  • Lou Gehrig’s disease (ALS)
  • Cancer
  • Traumatic brain injury and stroke
  • Oxygen toxicity
  • Glioblastoma
  • Weight loss
Ketones are Neuroprotective

Basic Science: Dr. Richard Veech, NIH, 2000:
• More Alzheimer’s and Parkinson’s neuron models survive in cell cultures when the ketone known as beta-hydroxybutyrate is added to the culture.
• Developing ketone ester to treat AD and other disorders.

Clinical Science: Dr. Samuel Henderson, Axona by Accera:
• 2004: AC-1202, an MCT oil improves ADAS-Cog and paragraph recall in 9 of 20 (45%) of ApoE4- people with AD after one 40 gram dose
• 2008: Ac-1202 – ApoE- people differed from placebo by 5.73 points on ADAS-Cog at day 45 and by 4.39 points at 90 days. Some ApoE4+ people improved but on average did not.


Screening for two clinical trials.

Found press release about AC-1202, pursuing FDA approval as medical food.

Learned MCT oil is extracted from coconut oil.

Calculated 35 grams coconut oil would provide 20 grams of MCTs.

MMSE score 14 day before coconut oil and 18 four hours after first dose. Said “light switch came back on.”

During first few days more alert, less confused, personality and sense of humor returned.
Steve’s Improvements

DAY BEFORE COCONUT OIL

- More animation in face
- Personality and sense of humor returned
- Recognized family members
- No longer looked “lost”
- Facial tremor resolved
- Intention tremor occasional

14 DAYS ON COCONUT OIL

- Gait normalized and could run
- Visual disturbance resolved and was able to read again
- Resumed yard and house work
- Initiated conversation and made sense

37 DAYS ON COCONUT OIL
Nearly one year after starting coconut/MCT oil:

**ADAS-Cog** improved by 6 out of 75 points

**Activities of Daily Living** score improved by 14 out of 78 points

**MRI report** In 2010: “Stable MRI brain in comparison to prior examination” performed two years earlier in 2008 at start of coconut oil intervention.
COMMENTS: The graph depicts responses of persons with dementias to oils containing medium chain triglycerides as reported by their caregivers. Reports were sent to MTN by email or letter and were spontaneous reports, not prompted with regard to specifics of response. Specifics of the responses were then categorized for purpose of this graph. Of the 184 individuals there were 84 males, 99 females, 1 unknown; 125 of 184 reported age with range of 44 to 95 years old (average 72.5.) The positive response is presumably due to metabolism of medium chain triglycerides to ketone bodies for use by neurons as an alternative fuel in cells with decreased ability to transport glucose.
Ketone Supplementation?

- MCT oil
- Ketone Salts (KetoForce)
- Ketone Esters

Naturally Derived

Synthetic

Therapeutic Ketosis (KD)

Ketones (energy)

![Diagram showing different types of ketones and their sources.](image)
Strategies to Increase Ketone Levels

KETONE LEVELS:

- Coconut Oil/MCT Oil* 0.3 - 0.5 mmol/l
- Exercise 0.3 - 0.5 mmol/l
- Ketone Mineral Salts* 0.5 to 2.0 mmol/l
- Starvation 2-5 mmol/l
- Classic Ketogenic Diet 2-5 mmol/l
- Ketone Esters* 2-5 mmol/l or higher (PO/IV)
- Diabetic Ketoacidosis 25 mmol/l

*Will increase ketone levels without restricting carbohydrate in diet and will also lower blood glucose level.
Ketone Supplementation
Acute dose: 30-60 minutes post

↓ Glucose  ↑ BHB  ↑ Acetone (Metron)

↑ AcAc
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

Total Plasma Ketones

**575 % Seizure Resistance**

Ketone Ester
Diseases With Decreased Glucose Uptake into Brain/Nerve Cells

- Alzheimer’s disease & some other dementias
- Parkinson’s disease
- Multiple sclerosis
- Huntington’s chorea
- ALS/Lou Gehrig’s disease
- Duchene muscular dystrophy
- Some forms of autism
- Down’s syndrome – develop Alzheimer’s in middle age
- Traumatic and acute hypoxic brain injury
- Type I and Type II diabetes
- Certain rare enzyme deficiencies
SUMMARY

Ketones are not drugs but are naturally occurring molecules that act as alternative fuel to glucose in the brain.

Elevating ketone levels could bypass problem of insulin resistance in the brain of people with Alzheimer’s and other neurodegenerative disorders.

Ketone products, including ketone esters, a ketone triacylglycerol, and ketone mineral salts are in various phases of safety and efficacy testing leading to FDA approval.

Clinical testing and commercialization of ketone products are urgently needed so that people with Alzheimer’s and other neurodegenerative disorders may benefit as soon as possible.

Until these products are available, the mild elevation of ketone levels by using MCT oil and/or coconut oil could serve as a stopgap measure to provide symptomatic improvement in some people.
Website

Mary Newport, MD:
www.coconutketones.com