Coconut Oil and MCT Oil: Ketones as Alternative Fuel for the Brain in Alzheimer's and Other Disorders





Mary T. Newport MD Restorative Medicine Conference Burlington, Vermont September 27-30, 2018

Disclosures – Mary T Newport MD

- Advisor Nisshin OilliO Company LTD., Tokyo, Japan
- Advisor Keto Science, Singapore, Singapore
- Specialist, Event Speaker and Product Royalties (MCT 143) – Pruvit Ventures, Louisville, KY



Steve and Mary Newport December 2008

Accountant - Worked at home to care for our children

Physician – Neonatologist Care of sick and premature newborns

ALZHEIMER'S DISEASE

- Worldwide 46.5 million have dementia now, expected to increase to 131.5 million by 2050: *
 - 22.9 million people in Asia
 - 9.5 million in the Americas
 - 10.4 million in Europe
 - 4 million in Africa
- 60-70% of Dementia patients have Alzheimer's.
- If treatment could delay Alzheimer's onset by five years, would reduce number of people affected by half!**
- Exact cause or causes unknown
- No medication effectively treats other than slowing course of disease for 6 months in half who take them
- Lifestyle changes best hope to prevent or slow down disease lower BP systolic to <120 and Mediterranean/DASH diets, adequate sleep, and treat sleep apnea.

https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf *

Reported at Alzheimer's Association International Conference, Boston 2013 **

Plaques and Tangles



100 trillion synapses. Dozens of neurotransmitters.



Brain tour from Alzheimer's Association, alz.org. Blennow K, MJ de Leon, H Zetterberg. "Alzheimer's disease." *The Lancet*, Vol. 368 No. 9533 (2006): 387 - 403

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

Beta Amyloid PET Scan

Alzheimer's disease on the horizon? 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.

Clinical Alzheimer's

Normal



Dan Krotz. "New Clue in the Search to Predict Alzheimer's Disease." Berkley Lab News Center, December 16, 2008

FDG-PET scan in Alzheimer's brain shows decreased glucose uptake





NORMAL BRAIN

ALZHEIMER'S BRAIN

Ketones Present at Beginnings of Life

- Life on earth appeared about 3.5 billion years ago.
- Single-celled organisms called archaea, which still exist today, could use the ketone body betahydroxybutyrate (BHB) as one of three fuels may have been important when atmospheric oxygen levels were low.
- Most bacteria today (except coliforms) can use BHB as fuel, and some protozoa contain up to 90% of their dry weight as poly-BHB granules.

Alternative Fuels in Starvation

- Glucose is the predominant fuel for most cells, including brain, in the normal fed state on typical diet.
- During starvation humans easily switch over to use alternative fuels after glucose stores used up
 - Amino acids and lactate (Gluconeogenesis)
 - Fatty acids

-Ketones

Alternative Fuels in Starvation



Alternative Fuels in Starvation



Metabolic Flexibility

Glucose Normal Diet (High Carb)





Ketones Fasting MCTs



Brain cells can burn glucose or ketones for energy

Could ketones bypass fundamental problem of getting glucose into the brain by providing alternative fuel in Alzheimer's disease?

Fasting as Treatment for Epilepsy

Historical documentation of the use of fasting for seizures:

- In the 5th century B.C., Hippocrates recognized that seizures were likely a medical and not a spiritual phenomenon and reported that fasting seemed to be the only effective treatment.
- King James Version of the Bible (Mark 9:14-29). Jesus stated that the "demon" causing a boy's convulsions could only be cured with prayer and fasting.
- Fasting was documented as a treatment modality for epilepsy in early twentieth century with earliest written reports available on PubMed/gov.

Ketogenic Diet for Epilepsy - 1921

- In 1921, Rollin Woodyatt discovered and reported by that either starvation or consuming a very low-carbohydrate, high-fat diet result in production of three ketone bodies, betahydroxybutyrate, acetoacetate and acetone in people who are otherwise healthy.
- Shortly after, Russel Wilder of the Mayo Clinic began to call a diet that resulted in high levels of ketones (called ketonemia), a "ketogenic diet".
- Wilder and C.E. Baker were the first to report on the use of the ketogenic diet for epilepsy in 1921.

Woodyatt RT. Objects and method of diet adjustment in diabetics. *Arch Intern Med* Vol. 28 (1921):125–141.

Wilder RM. The effects of ketonemia on the course of epilepsy. *The Clinic Bulletin* Vol. 2 No. 307 (1921):1. Baker CE and RM Wilder. High-fat diets in epilepsy. *The Clinic Bulletin* Vol. 2 No. 308 (1921):1.

Invention of MCT Oil and Discovery of its Properties - 1959

- Dr. Sami Hashim and Vigan Babayan, an industrial chemist, decided to analyze coconut oil and learned that 8 to 10% of the fats were the medium-chain fatty acids C8 and C10.
- They used a distillation process to separate these fatty acids from the other fats in coconut oil. This process also brought along with it very small amounts of C6 and C12.
- MCTs were often considered as waste products by oil manufacturers.
- Spent more than ten years discovering the unique properties and therapeutic uses of this class of fatty acids.
- They found that MCT oil is easily absorbed, does not require pancreatic enzymes, is transported via portal vein to liver, and that it is beneficial when used in adults and children with malabsorption syndromes and following bowel surgery.

Senior, John R., Editor. *Medium-chain Triglycerides* University of Pennsylvania Press, 1968.

Invention of MCT Oil and Discovery of its Properties

- Hashim group studied the use of MCT oil in premature newborns and found that it was well tolerated and could help them gain weight more quickly—led to the use of MCT oil in the newborn intensive care units for micropremies. Later added directly to premature infant formulas.
- Also discovered the MCTs are ketogenic.

Tantibhedhyangkul P, S A Hashim. "Clinical and physiologic aspects of medium-chain triglycerides: alleviation of steatorrhea in premature infants." *Bull NY Acad Med.* Vol. 47 No. 1 (1971): 17-33. Geliebter A, N Torbay, F Bracco, et al. "Overfeeding with medium-chain triglyceride diet results in diminished deposition of fat." *Am J Clin Nutr.* Vol. 37 (1983): 1-4.

Medium chain triglycerides are converted to ketones in liver



*SS Bergen, Jr., Hashim SA, VanItallie TB "Hyperketonemia induced in man by medium-chain triglyceride," *Diabetes* Vol. 15 No. 10 (1966): 723-725

Medium Chain Fatty Acids

Abbreviation based on # carbon atoms in chain	Chemical Structure	Common Names	Special Properties
C6	CH ₃ (CH ₂) ₄ COOH	caproic acid hexanoic acid	??
C8	CH ₃ (CH ₂) ₆ COOH	caprylic acid octanoic acid	Most ketogenic
C10	CH ₃ (CH ₂) ₈ COOH	capric acid decanoic acid	Increases numbers of mitochondria in neurons
C12	CH ₃ (CH ₂) ₁₀ COOH	lauric acid dodecanoic acid	Antimicrobial; Ketogenic in astrocytes?

Ketones in Starvation: 1967 Alternative Fuel for the Brain

Obese nurse volunteer given only water, vitamins, and salt tablets for a period of forty-one days.

- Sampled blood from catheters in arteries and veins around her brain and liver – tested for many metabolites.
- Her brain survived this lengthy period of starvation by using ketones and by greatly reducing the use of glucose.
 - 2/3 of fuel used by her brain was provided by the ketone bodies beta-hydroxybutyrate and acetoacetate.
- Studies confirmed with other patients.

"Brain Metabolism during Fasting," OE Owen, AP Morgan, HG Kemp, JM Sullivan, MG Herrera, GF Cahill, Jr. *The Journal of Clinical Investigation*, Vol. 46, No. 10, 1967





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



Figure 26.2 Insulin administration to three prolonged fasted obese subjects demonstrating asymptomatic hypoglycemia, thanks to maintenance of high levels of ketoacids. 3 obese college students starved until β-OH B levels increased

Given insulin to drive blood glucose into hypoglycemic range

Developed none of usual symptoms of hypoglycemia: Brain is protected from hypoglycemia by ketone bodies.

Cahill Jr GF and TT Aoki. Alternative Fuel Utilization by Brain. *Cerebral Metabolism and Neural Function,* Chapter 26. Baltimore, Williams & Wilkins, 1980.

MCT Oil Modified Ketogenic Diet -1971

- In 1971 Dr. Huttenlocher from Yale University idea to use MCT oil in the ketogenic diet: allows for more protein and carbohydrates in the diet, and more palatable meals.
- In 1976, published positive results of study using 60% medium-chain triglycerides in the ketogenic diet for childhood epilepsy.

Huttenlocher PR, AJ Wilbourn, JM Signore. Medium-chain triglycerides as a therapy for intractable childhood epilepsy. *Neurology* Vol. 21 (1971):1097–1103.

Huttenlocher PR. Ketonemia and seizures: metabolic and anticonvulsant effects of two ketogenic

diets in childhood epilepsy. *Pediatr Res* Vol. 10 No. 5 (1976):536-40.

Glucose Hypometabolism in Dementia

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 the ratio of use of glucose to alternative fuels in cerebrum shifts with aging:
- Young normal people ratio of 100:1
- Elderly persons without Alzheimer's ratio is 29:1
- Early stages of Alzheimer's 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 in this paper).

Siegfried Hoyer. Brain metabolism and the incidence of cerebral perfusion disorders in organic psychoses. *Deutsche Zeitschrift für Nervenheilkunde* 1970, 197 (4): 285-92. Hoyer S. Abnormalities of glucose metabolism in Alzheimer's disease. *Annals New York Academy of Sciences* Vol. 640 (1991): 53-58. Hoyer S. Causes and consequences of disturbances of cerebral glucose metabolism in sporadic Alzheimer disease: Therapeutic implications. *Adv Exp Med Biol Vol. 541* (2004):135-152. Imaging techniques Show Decreased Glucose Uptake in Alzheimer's Brain – early 1980s

- Farkas T, SH Ferris, AP Wolf, et al. 18F-2-deoxy-2-fluoro-Dglucose as a tracer in the positron emission tomographic study of senile dementia." *American Journal of Psychiatry* Vol. 139 No. 3 (1982):352–353.
- De Leon MJ, SH Ferris, AE George, et al. Positron emission tomographic studies of aging and Alzheimer disease. ALNR Am J Neuroradiol Vol. 4 NO. 3 (1983):568-71.
- And many more studies to follow.

Ketone Uptake Normal in Alzheimer's Brain: Arterio-venous Difference - 1981

In 1981, Ulla Lying-Tunell and others of Karolinska Institut in Sweden used arteriovenous difference technique expressed as a cerebral metabolic rate (CMR), reported:

 Glucose uptake in the brain is decreased but ketone uptake is the same for people with mild to moderate pre-senile dementia compared to normal healthy adults.

Question: Is decreased glucose uptake in the Alzheimer's brain the result of the death of the neurons or neurons simply starved due to lack of ability to take up fuel as in insulin resistance?

• The 1981 Lying-Tunell results suggest that the neurons might be dormant, not all dead.

Lying-Tunell U, B S Lindblad, H O Malmlund, et al. "Cerebral blood flow and metabolic rate of oxygen, glucose, lactate, pyruvate, ketone bodies and amino acids." *Acta Neurol Scandinav.* Vol. 63 (1981): 337-50.

Normal Ketone Uptake in Alzheimer's Brain: Hippocampal Homogenates - 1989

BRAIN GLUCOSE AND KETONE BODY METABOLISM IN ALZHEIMER'S DISEASE

R. Swerdlow*, D.L. Marcus**, J. Landman*, M. Harooni*, and M.L. Freedman**. Dept. of Medicine, NYU Medical Center, NY, NY.

In Vitro assays of Alzheimer's brain glucose metabolism were performed using autopic temporal cortex preincubated with 2.5 Mm ATP/NAD⁺ mixture followed by an 18.5 hour incubation in the presence of 5uCi of D-[¹⁴C-[U]]-Glucose. Three unique periods of differing metabolic rates were observed: (1) An initial period of low linear glucose metabolism; (2) a period of exponential rise; (3) a final period of elevated linear glucose metabolism. During the initial period (0-4 hrs), AD brain metabolism was 24% of control levels; during the final period (14.5 – 18.5 hrs) all metabolism was essentially equal between the AD and control brains.

GLUCOSE METABOLIC RATE (p Moles CO₂/minute)

(0 – 4 hrs) (14.5 – 18.5 hrs) 11.2± 8.2 (n=7) 930± 83.0 (n=3)

CONTROL 46.1± 33.2 (n=6) 960± 81.0 (n=3)

We also examined the metabolism of D-3-hydroxy [3-¹⁴C] butyrate and found no significant difference in rate between either AD/control or ketone body/glucose

BETA-OH BUTYRATE METABOLISM (n Moles CO₂/minute)

(14.5 – 18.5 hrs)
$1 12 \pm 262 (n-2)$

AD 1.13 ± .363 (n=3) CONTROL 1.10 ± .687 (n=3)

AD

These patterns suggest that decreased metabolism in AD is related to vascular mediated glucose deprivation rather than to intrinsic cortical pathology, and that ketone bodies may serve as a potential alternate metabolic

substrate in AD. (Adapted from original abstract with permission of Russell Swerdlow, M.D.)

BAIN GLOODE AND METHER NON MELANCLISH IN ALEMETHER'S DESEASE. <u>2. Sandian</u>, D.L. Martus**, J. Landmar*, M. Narooni*, and M.L. Franklan**. Der. of Naticine. 300 Melical Organ. W. W.

In vitro samps of Altheimer's brain phones metabolism were performed using surpris temporal costss predictable of a 2.5 m $M^{-1/4}_{\rm C}$ with probability followed by an 16.5 how inclusion in the presence of Soci of D-1^{1/4}_{\rm C} with a 1.5 m metabolic metabolism that periods of differing phones metabolism that were descended (1) As initial period of low linear phones metabolism. Auring the initial period of advected linear glucose metabolism. Auring the initial period (0.4.5-23.5 km) all metabolism was essentially equal between the 10 and control brains.

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user priority suggers can secrete entrancian in AD is follow to vacular melleted glucose deprivation rather than to intrinsic cartical pathology, and that Native bolies may serve as a potential alternate metabolic substrate in AD.

Swerdlow R, Marcus DM, Landman J, Harooni M, Freedman ML. Brain glucose and ketone body metabolism in patients with Alzheimer's disease. *Clin Res.* Vol. 37 No. 461A (1989)

Ketones are Neuroprotective in Alzheimer's and Parkinson's - 2000

- Neurons were grown separately in cultures, from the hippocampus to study Alzheimer's and from the mesencephalon to study Parkinson's.
- Cells subjected to a toxin known to cause these diseases, $A\beta_{1-42}$ for Alzheimer's and 1-methyl-4-phenylpyridinium for Parkinson's.
- Ketone beta-hydroxybutyrate (BHB) added at starvation levels to some of the cell cultures and remaining cultures served as controls.
- Findings: Addition of the ketones:
 - Significantly increased the survival of the neurons compared to the controls.
 - Size of the neurons was larger and there was a greater outgrowth of neurites, suggesting that ketones can act as growth factors to neurons in culture.
- Began developing BHB monoester for therapeutic benefit.

Kashiwaya Y, T Takeshima, N Mori, K Nakashima, K Clarke, and RL Veech. D-b-Hydroxybutyrate protects neurons in models of Alzheimer's and Parkinson's disease," *PNAS* May 9, 2000, 97(10): 5440-5444.

Ketones are Neuroprotective in Alzheimer's and Parkinson's 2001-2004

Hypothesis papers

- Veech RL, B Chance, Y Kashiwaya, et al. "Hypothesis paper: ketone bodies, potential therapeutic uses." *IUBMB Life* Vol. 51 (2001): 241– 247.
- Cahill GF Jr., RL Veech. "Ketoacids? Good medicine?" *Transactions* of the American Clinical and Climatological Association Vol 114 (2003): 149–163.
- Veech RL. "The therapeutic implications of ketone bodies: the effects of ketone bodies in pathological conditions: ketosis, ketogenic diet, redox states, insulin resistance, and mitochondrial metabolism." *Prostaglandins, Leukot Essent Fatty Acids* Vol. 70 (2004): 309–319.
- VanItallie TB, TH Nufert. "Ketones: metabolism's ugly duckling." Nutr Rev Vol. 61, No 10 (2003): 327–341.

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

De la Monte SM, JR Wands. "Review of insulin and insulin-like growth factor expression, signaling, and malfunction in the central nervous system: Relevance to Alzheimer's disease." *Journal of Alzheimer's Disease* Vol. 7 (2005): 45-61

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.
- Suggested that therapies for type 1 or 2 diabetes may be beneficial.
 - Intranasal Insulin
 - Metformin or other medications for type 2 diabetes (Metformin recently reported to double risk of cognitive impairment in diabetics by interfering with absorption of vitamin B12)

De la Monte SM, JR Wands. "Alzheimer's disease is type 3 diabetes – evidence reviewed." *Journal of Diabetes Science and Technology,* Vol. 2 No. 6 (November 2008): 1101-1113

Alzheimer's is "Type 3 Diabetes"

FDG-PET studies:

 Abnormal glucose uptake may be present decades before symptoms appear - in people at risk for Alzheimer's as early as their twenties.

Reiman EM, K Chena, GE Alexander, et al. Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia. *PNAS* Vol. 101 No. 1 (2004):284–289

Alzheimer's Disease – A Fundamental Metabolic Problem

Glucose





- Insulin resistance
- Insulin deficiency
- PDH Complex deficiency Ann Neurol 1983 Jan;13(1):72-8
 - **GLUT 1 & 3** Ann Neurol 1994 May;35(5):546-5

Cunnane Group Concept: The "Push-Pull" of Brain Fuel Uptake



Cunnane S C, A Courchesne-Loyer, C Vandenberghe, et al. Can ketones help rescue brain fuel supply in later life? Implications for cognitive health during aging and the treatment of Alzheimer's Disease. *Frontiers in Molecular Neuroscience*. Open Access. Vol. 9 No. 53 (2016): e1-21.



Cunnane Group Studies: Brain takes up ketones preferentially when glucose and ketones are both available.

Figure 3. Voxel-wise three-dimensional view of the medial and lateral brain surfaces and a representative coronal slice showing the cerebral metabolic rate of acetoacetate (CMRa) and glucose (CMRglc) pre- and post-ketogenic diet (KD). Scale is shown on the right (umol/100 g/min).

Courchesne-Loyer A, E Croteau, C-A Castellano, et al. Inverse relationship between brain glucose and ketone metabolism in adults during short-term moderate dietary ketosis: A dual tracer quantitative positron emission tomography study. *JCBFM*. Open Access (2016): E1-9.


Figure 2. (a) Regional increase in cerebral metabolic rate of acetoacetate (CMRa; white bars), and decrease in cerebral metabolic rate of glucose (CMRglc; blue bars). (b) Regional% contribution of ketones to brain metabolism before (pre-KD; yellow bars) and at the end (post-KD; black bars) of four days on a ketogenic diet. Means; n¼10/region. Error bars not shown; mean SD for all 35 regions were 4.2 and 2.5mmol/100g/min (CMRglc and CMRa respectively; (a)) and 1.9 and 9.0% (pre-KD and post-KD, respectively; (b)). Repeated measures two-way ANOVA were used to assess the differences between regions; significant at p<0.05. Brain regions: (1) caudate; (2) white matter; (3) hippocampus; (4) putamen; (5) thalamus; (6) rostral anterior cingulate; (7) insula; (8) caudal anterior cingulate; (9) parahippocampus; (10) posterior cingulate; (11) transverse temporal; (12) medial orbital frontal; (13) isthmus cingulate; (14) fusiform; (15) superior temporal; (16) temporal pole; (17) entorhinal; (18) grey matter; (19) precentral; (20) lateral orbital frontal; (21) superior frontal; (22) supramarginal; (23) caudal middle frontal; (24) paracentral; (25) middle temporal; (26) inferior temporal; (27) inferior parietal; (28) inferior frontal; (29) precuneus; (30) lingual; (31) rostral middle frontal; (32) superior parietal; (33) cuneus; (34) lateral occipital; (35) frontal pole.

Courchesne-Loyer A, E Croteau, C-A Castellano, et al. Inverse relationship between brain glucose and ketone metabolism in adults during short-term moderate dietary ketosis: A dual tracer quantitative positron emission tomography study. *JCBFM*. Open Access (2016): E1-9.



Cunnane Group Studies: Linear relationship between plasma ketones and AcAc brain uptake.

Figure 2. Direct, linear relation between plasma ketone concentration and brain ketone uptake in adults. Two relationships are shown, one for plasma -hydroxybutyrate (-HB) versus the rate of brain -HB uptake (solid line, R2 = 0.97; Y = 1.57X - 0.20; P < 0.0001), and the other for plasma acetoacetate (AcAc) versus the rate of brain AcAc uptake33 (dotted line, R2 = 0.83; Y=3.46X - 0.03; P < 0.0001): Alzheimer's disease(AD); healthy age-matched controls. Units are the same for both ketones and cerebral metabolic rate (CMR; I mol/100 g/min). -HB data have been combined from several sources: postprandial state, 36 -HB infusion, 68 AD; and healthy older controls, 35 40-day fast, 22 60-day fast, 23 and AD and healthy older controls. 34 All the -HB data are from arteriovenous difference studies, except for one report that used -HB-PET.36 The AcAc data were obtained using 11C–AcAc PET.33...

Cunnane SC, A Courchesne-Loyer, V St-Pierre, et al. Can ketones compensate for deteriorating brain glucose uptake during aging? Implications for the risk and treatment of Alzheimer's disease. *Ann NY Acad Sci* Issue: Nutrition in Prevention and Management of Dementia (2016) 1–9.

Ketones use normal in mild Alzheimer's brain

- Stephen Cunnane, PhD and associates reported in people with mild Alzheimer's, compared to controls:
 - Glucose uptake is 17% lower in gray matter overall and 25% lower in areas affected by Alzheimer's
 - Ketone uptake is <u>normal</u> throughout the brain, including the areas affected by Alzheimer's – supports ketones as alternative fuel

Castellano C-A, S Nugent, N Paquet, et al. Lower Brain 18F-Fluorodeoxyglucose Uptake But Normal 11C-Acetoacetate Metabolism in Mild Alzheimer's Disease Dementia. *Journal of Alzheimer's Disease* Vol. 43 (2015): 1343–1353.

Cunnane SC, A Courschesne-Loyer, V St-Pierre, et al. Can ketones compensate for deteriorating brain glucose uptake during aging? Implications for the risk and treatment of Alzheimer's disease. *Ann NY Acad Sci* (2016).

Cunnane Group Studies: Could MCT Oil Prevent Alzheimer's?

- People at risk for Alzheimer's have a 10-12% energy deficit in the brain related to inadequate glucose uptake.
- MCT oil can result in a high enough ketone level to provide the brain with 5 to 12% of its energy needs.

Cunnane SC, A Courschesne-Loyer, V St-Pierre, et al. Can ketones compensate for deteriorating brain glucose uptake during aging? Implications for the risk and treatment of Alzheimer's disease. *Ann NY Acad Sci* (2016).



Cunnane Group Studies: MCTs could close'brain energy gap' in Mild Cognitive Impairment

Croteau E, C-A Castellano, MA Richard, et al. Ketogenic medium chain triglycerides increase brain energy metabolism in Alzheimer's disease. *Journal of Alzheimer's Disease* In press May 2018.

Croteau E, C-A Castellano, M Fortier, et al. A cross-sectional comparison of brain glucose and ketone metabolism in cognitively healthy older adults, mild cognitive impairment and early Alzheimer's disease. *Experimental Gerontology* Vol. 107 (2018):18-26.



Some Effects of Ketones

- Ketones used within mitochondria to drive the chain reaction that produces ATP.
 - Could help in conditions were there is decreased glucose uptake into neurons, such as Alzheimer's, Parkinson's, Multiple Sclerosis and Amyotrophic lateral sclerosis.
- Mimic effects of insulin when blood sugar low.
- Ketones reduce generation of free radicals, are scavengers of reactive oxygen species, and activates anti-inflammatory mechanisms.
 - Could be used to treat diseases involving free radical damage such as occurs in coronary reperfusion, diabetic angiopathy, diabetic nephropathy, inflammatory bowel disease, pancreatitis.
 - Could suppress cerebral edema and reduce extent of cerebral infarction in brain injury.
- Presence of ketone in circulation, even at low levels increases cerebral blood flow by as much as 39%.

Sato K, Y Kashiwaya, RL Veech, et al. "Insulin, ketone bodies, and mitochondrial energy transduction." *FASEB Journal* Vol. 9 (1995): 651–658. Hasselbalch SG, PL Madsen, LP Hageman, et al. "Changes in cerebral blood flow and carbohydrate metabolism during acute hyperketonemia." Amer J Physiol Vol 270 (1996): E746–751.

Ketones can drive TCA cycle to produce ATP.





Metabolism GLUCOSE **KETONES** TCA Cycle ATP

Ketones Impact Many Metabolic Pathways





Steve Early Onset Alzheimer's disease First symptoms 2001 ApoE 4/3

•By May 2008 - 58 years old

•Former accountant: can't use computer, calculator, do simple math

•Unable to read due to visual disturbance for 1 ½ years

- •Problems with word finding and spelling simple words and completing sentences
- •Doesn't recognize certain relatives
- •Slow gait, unable to run
- •Jaw tremor and intention tremor
- •Distractible, takes things apart
- •Depressed/ Personality/sense of humor fading

12 DAYS BEFORE INTERVENTION

May 9, 2008

- Steve was screened for a clinical trial at Byrd Alzheimer's Institute
 - Met criteria, except scored 12 of 30 on Mini Mental Status Exam (MMSE): required score of at least 16
 - Told to come back to try again
- A second clinical trial also became available scheduled to screen for both studies May 20 & 21

Internet search for risks and benefits of two clinical trial drugs yielded unexpected result:

PRESS RELEASE

New medical food, AC-1202, significantly improved memory and cognition in nearly half of Alzheimer's patients!

Reger MA, ST Henderson, et. al. "Effects of b-Hydroxybutyrate on cognition in memory-impaired adults,", Neurobiology of Aging, 2004, Vol. 25, 311-314

Constantini, et al. "Study of the ketogenic agent AC-1202 in mild to Moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled, multicenter trial," *Nutr and Metab 2009 6(31): 1-25*

AC-1202 -- MCT Oil for AD

Samuel Henderson, Ph.D. files first patent application for use of MCT oil to treat Alzheimer's disease in 2000:

Brilliant Insight: Mild ketosis produced by conversion of medium chain fatty acids to ketones in liver may be adequate to produce cognitive improvement in insulin resistant Alzheimer's brain

Found patent application for AC-1202

- (19) United States
- (12) Patent Application Publication Henderson
- (54) COMBINATIONS OF MEDIUM CHAIN TRIGLYCERIDES AND THERAPEUTIC AGENTS FOR THE TREATMENT AND PREVENTION OF ALZHEIMERS DISEASE AND OTHER DISEASES RESULTING FROM REDUCED NEURONAL METABOLISM
- (75) Inventor: Samuel T. Henderson, Broomfield, CO (US)



SS Bergen, Jr., Hashim SA, VanItallie TB "Hyperketonemia induced in man by medium-chain triglyceride," *Diabetes* Vol. 15 No. 10 (1966): 723-725





- MCTs are 10-17% of fats in human breast milk
- Breastfed newborn is in ketosis
- MCT oil added to feedings of very premature newborns in late 1970's to early 1980's
- Added to premature and some term infant formulas



MCT OIL COMES FROM COCONUT OIL





Foods with Medium Chain Triglycerides

Food

Coconut oil

Goat butter

Cow butter

Goat milk

Infant formula

Goat cheese

Feta cheese

Heavy cream

American cheese

Cow milk (full fat)

Human breast milk

Palm kernel oil







According to USDA National Nutrient Database (www.ars.usda.gov/nutrientdata



May 20, 2008

Steve screened for clinical trial

Scored only 14 of 30 on MMSE, needed 16 to qualify for study

Clock test– consistent with moderately severe Alzheimer's

Coconut Oil is 60% MCTs





20 gm AC-1202 = 35 gm coconut oil





Steve had 35 grams (35 ml)coconut oil in oatmeal for breakfast

- Scored 18 of 30 on MMSE four hours later
- Qualified for study!!

S-1 osla 10 a 1 Day Before Starting Coconut Oil





Steve's Improvements



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

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



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.

WHAT IF THERE WAS A CURE FOR ALZHEIMER'S DISEASE AND NO ONE KNEW

A Case Study by Dr. Mary Newport

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Getting the message out – 2008 to present coconut oil, Steve Newport's results in an early onset
Alzheimer's test gradually improved says his wife, Dr.
Mary Newport. Before
treatment, Steve could
barely remember how to
draw a clock. Two weeks
after adding coconut oil to
his diet, his drawing
improved. After 37 days,
Steve's drawing gained even
more clarity. The oil seemed
to "lift the fog," his wife

says.

After two weeks of taking

By Eve Hosley-Moore, Times Correspondent In print: Wednesday, October 29, 2008

Doctor says an oil lessened Alzheimer's effects on her husband



The only thing that kept Dr. Mary Newport positive in the face of her husband's early onset Alzheimer's disease was that he didn't seem aware of how much ground he was losing.





DR MARY T. NEWPORT

MALADIE D'ALZHEIMER

ET S'IL EXISTAIT UN TRAITEMENT ?







Coming February 2019!





Reports From Other Caregivers



Improvements were generally categorized as follows according to the wording used in reports by the caregivers:				
IMPROVED MEMORY/COGNITION	IMPROVED SOCIAL INTERACTION, BEHAVIOR, MOOD	IMPROVED SPEECH,CONVERSATION	RESUMPTION OF LOST ACTIVITIES	IMPROVED PHYSICAL SYMPTOMS
Higher scores on memory or cognitive test	More interaction with others	Speaking again	Showering again without help	Less tremor
Improved clock drawing	Better sense of humor	Clearer speech	Performing self-care again	Getting out of bed without help
Better cognition	Less agitation	Less repetitiveness	Doing things around the house	Able to walk again
More alert	Improved behavior	Making sense	Doing household chores again	Walking without assistance
Brighter	Less hostile	More logical	Preparing meals again	Improved strength
Improved awareness	Less aggressive	Improved conversation	Resumed a hobby	More ambulatory
Less foggy	Нарру	More talkative	Reading again	More energy
Less hazy	Improved mood	Improved verbal skills	More functional	Less stiffness
Recognizing people or places	Less anxiety	Better word recall		Improved balance
Less distractible	Less depression			Less dizziness
				Fewer episodes of faintness, clamminess,
Better sense of direction	Feels better	Expressing thoughts		sweating
Improved reading comprehension				Improved gait
More awareness of time and place				Fewer episodes of seizure/twitching
Able to do mental math again				Pain relief
IMPROVED SLEEP	IMPROVED APPETITE	IMPROVED VISION		
Fewer nightmares	Improved appetite	Visual disturbance gone		
Sleeping better		Able to see more clearly		
No longer sleeping excessively				
No longer twitching during sleep				

From my emails

 83 year old lady with Alzheimer's. Her daughter said, "After 2 days on MCT oil we already noticed she is speaking more clearly, almost finishes sentences that make sense, her face and eyes look younger, her appetite has improved, and she is walking around the house like she used to...without a walker."

From my emails

41 years old man with Multiple Sclerosis for twelve years reports: "After 4 months... I've noticed like a thick cloud has been lifted off, as I can use my short term memorization and I can use my mind to figure tasks in my head before I can physically perform them (do them). My mathematical formulas (numbers, math) can now be performed in my mind first."

Engineer from Taiwan



Lady from Care Home in Taiwan

Before **MCTs** No. 17 After **MCTs**
Another Published Single-Case Report

- 70 year old male with probable AD
- Caprylic triglyceride (MCT C:8) increased over several days to 20 grams daily – total 109 days
- MoCA score increased from 24 to 28/30 (now normal)
- MMSE score increased from 23 to 28/30 (now normal).
- FDG-PET stable.

Farah BA. Effects of caprylic triglyceride on cognitive performance and cerebral glucose metabolism in mild Alzheimer's disease: a single-case observation. *Frontiers in Aging Neuroscience* Vol. 6 Article 133 July 2014: 1-5

Mounting Evidence

 80% of 55 people with AD taking medical food Axona (MCT oil) were stable or improved over 15 months in memory testing and activities of daily living as reported by caregivers.

Maynard SD and J Gelblum. Retrospective cohort study of the efficacy of caprylic triglyceride in patients with mild-to-moderate Alzheimer's disease. *Neuropsychiatric Disease and Treatment* Vol. 9 (2013):1619–1627.

MCT Oil Study - Assisted Living in Japan

- Study of 38 frail elderly patients.
 - 1/3 continued their regular diet
 - 1/3 received a food containing 6 grams of MCT oil, 1.2 grams of leucine and vitamin D
 - 1/3 received the same supplement but with long-chain fats instead of MCT oil.
- After three months:
 - People taking the supplement with MCT oil had significant improvements in their cognitive testing by 10.6% in the Mini-Mental Status Exam (increasing from an average of 16.8 to 18.4 points) and by 30.6% on the Nishimura geriatric rating scale for mental status (increasing from an average of 24.6 to 32.2 points).
 - The people who were on the regular diet or took the supplement with longchain fats plus leucine and vitamin D all had worse cognitive scores.
- Also looked at effects on some physical parameters:
 - The group who received the supplement with MCT had significantly better muscle strength after three months (improved hand grip by 13.1%, speed of walking by 12.5%, and a leg open and close test by 68.2%) and also had 28.2% increase in their peak expiratory flow, a test of lung function.

Abe S, E Osamu, M Suzuki. Medium-chain triglycerides in combination with leucine and vitamin D benefit Cognition in frail elderly adults: A randomized controlled trial. *J Nutr Sci Vitaminol* Vol. 63 (2017): 133-140. Ota M, J Matsuo, I Ishida, et al. Effect of a ketogenic meal on cognitive function in elderly adults: potential for cognitive enhancement. *Psychopharmacology* (Berl) Vol. 233 No. 21-22 (2016):3797-3802.

Other Reports – MCT Studies

Abe S, E Osamu, M Suzuki. Medium-chain triglycerides in combination with leucine and vitamin D benefit Cognition in frail elderly adults: A randomized controlled trial. *J Nutr Sci Vitaminol* Vol. 63 (2017): 133-140.

Ota M, J Matsuo, I Ishida, et al. Effect of a ketogenic meal on cognitive function in elderly adults: potential for cognitive enhancement. *Psychopharmacology* (Berl) Vol. 233 No. 21-22 (2016):3797-3802.

Farah BA. Effects of caprylic triglyceride on cognitive performance and cerebral glucose metabolism in mild Alzheimer's disease: a single-case observation. *Frontiers in Aging Neuroscience* Vol. 6 Article 133 July 2014: 1-5.

Maynard SD and J Gelblum. Retrospective cohort study of the efficacy of caprylic triglyceride in patients with mild-to-moderate Alzheimer's disease. *Neuropsychiatric Disease and Treatment* Vol. 9 (2013):1619–1627.

Maynard SD and J Gelblum. Retrospective case studies of the efficacy of caprylic triglyceride in mild-to-moderate Alzheimer's disease. *Neuropsychiatric Disease and Treatment* Vol. 9 (2013):1629–1635.

Page KA, A Williamson, N Yu, et al. "Medium-chain fatty acids improve cognitive function in intensively treated type 1 diabetic patients and support *in vitro* synaptic transmission during acute hypoglycemia." *Diabetes* Vol. 58, No 5 (May 2009):1237–1244.

Rebello CJ, JN Kellera, AG Liua, et al. Pilot feasibility and safety study examining the effect of medium chain triglyceride supplementation in subjects with mild cognitive impairment: A randomized controlled trial. *BBA Clinical* Vol. 3 (2015): 123–125

Bill Curtis, Parkinson's and Coconut Oil



YouTube video: Published on Aug 12, 2015

"Before I started taking coffee with Kerrygold butter, coconut oil, cream and Stevia to raise my levels of "ketone body" D-betahydroxybutyrate, I had put this guitar up for sale because I could not play. This video shows me playing before taking coffee and after taking coffee video."

Ketone Bodies and Ketosis



Dietary and other maneuvers that produce ketosis:

- Starvation or fasting
- Ketogenic diet
- Vigorous exercise
- Medium chain triglycerides (MCTs) absorbed directly into portal vein and converted in liver to ketone bodies*
- Ketone esters, ketone triglyceride and ketone salts

*SS Bergen, Jr., Hashim SA, VanItallie TB "Hyperketonemia induced in man by medium-chain triglyceride," *Diabetes* Vol. 15 No. 10 (1966): 723-725

CLASSIC KETOGENIC DIET Very High Fat (80 - 90%) – Very Low Carb - Sufficient Protein to grow or maintain lean body mass

	QUICK REFERENCE CHART FOR MACRONUTRIENTS FOR MODERATE TO HIGH FAT DIETS									
	1600 CALORIES/DAY		1800 CALORIES/DAY		2000 CALORIES/DAY		2400 CALORIES/DAY		2800 CALORIES/DAY	
	FAT (grams)	PROTEIN & CARBS (grams)	FAT (grams)	PROTEIN & CARBS (grams)	FAT (grams)	PROTEIN & CARBS (grams)	FAT (grams)	PROTEIN & CARBS (grams)	FAT (grams)	PROTEIN & CARBS (grams)
40% FAT	71	240	80	270	89	300	107	360	124	420
45% FAT	80	220	90	247	100	275	120	330	140	385
50% FAT	89	200	100	225	111	250	133	300	156	350
55% FAT	98	180	110	203	122	225	147	270	171	315
60% FAT	106	1 <u>6</u> 0	120	180	133	200	160	240	187	280
65% FAT	115	140	130	157	144	175	173	210	202	245
70% FAT	124	120	140	135	155	150	187	<u>1</u> 80	218	210
75% FAT	133	100	150	113	166	125	200	150	233	175
80% FAT	142	80	160	90	177	100	213	120	249	140
85% FAT	151	60	170	68	189	75	227	90	264	105

Table - Copyright, Mary T Newport MD, from Complete Book of Ketones, available 2019

CLASSIC KETOGENIC DIET

Reported positive effects of ketogenic diet:

- Used successfully to treat drug resistant epilepsy for more than 90 years.
- Alzheimer's disease
- Parkinson's disease
- Lou Gehrig's disease (ALS)
- Traumatic brain injury and stroke
- Oxygen toxicity
- Glioblastoma
- Other Cancers
- Weight loss



A variation/less strict

Modifications of Classic Ketogenic Diet

MCT-Oil-Modified Diet

- Developed in 1971 by Peter R. Huttenlocher, M.D. as way to maintain ketone levels while allowing more protein and carbohydrate in the diet. Allow for more variety of foods in the diet.
- Good results in eliminating or reducing seizures.
- In this diet 60% of the total calories come from MCT oil, which works out to about 6.6 grams of fat for each 10 grams of protein and carbohydrate combined, or a 2:3 ratio.
- Big drawback: Many have bloating, diarrhea or other intestinal symptoms with this much MCT oil.
- A further modification by Ruby Schwartz, M.D. at Oxford starts MCT at 30% of total calories plus 30% of fat from longer chain fats. MCT oil is very slowly increased as tolerated to 45 or 50% of calories as fat if ketone levels are not high enough and seizures are not controlled.

Huttenlocher PR, AJ Wilbourn, JM Signore. Medium-chain triglycerides as a therapy for intractable childhood epilepsy. *Neurology* Vol. 21 (1971):1097–1103.

Modifications of Classic Ketogenic Diet

Low Glycemic Index Diet (LGIT)

- Developed by David J.A. Jenkins, D.M. in 1981 initially for use in diabetics, then for other conditions, and even became a fad diet at the time (Jenkins, 1981).
- Used for treatment of drug-resistant epilepsy in children, called the low glycemic index treatment or LGIT since 2002.
- Allows forty to sixty grams per day of carbohydrates, with emphasis on portion control, as well as eating carbohydrates together with fat and protein to lower the glycemic impact (Pfeifer, 2005).
- Rising glucose levels and falling ketone levels can rapidly provoke a seizure in someone on the ketogenic diet. LGIT helps prevent dramatic fluctuations in blood glucose levels after a meal.

Pfeifer HH, A Thiele A. "Low-glycemic-index treatment: a liberalized ketogenic diet for treatment of intractable epilepsy." *Neurology* Vol. 65 No. 1810 (2005):1810–1812.

Modifications of Classic Ketogenic Diet

Modified Atkins Diet (MAD)

- Developed in the early 2000s at Johns Hopkins by pediatric neurologist Erik Kossoff, M.D., who reported in 2003 that ketones levels remain high and many children with epilepsy respond well to this diet (Kossoff, 2006).
- Does not limit protein, though averages about 1 gram per kilogram of body weight (about 0.5 grams per pound) and encourages liberal fat intake.
- Foods do not need to be weighed and measured, with the exception that carbohydrates are monitored closely and are restricted for the first month to ten grams per day then gradually increased to between fifteen and twenty grams per day.
- On average, MAD is about 65% of total calories as fat, 30% as protein and 5% as carbohydrates.

Kossoff E H, J R McGogan, R M Bluml, et al. A modified Atkins diet is effective for the treatment of intractable pediatric epilepsy. *Epilepsia*. No. 47 No. 2 (2006): 421-4

Classic Ketogenic Diet & Modifications

RATIOS OF FAT, PROTEIN AND CARBS FOR CLASSIC KETOGENIC DIET AND MODIFICATIONS OF THE DIET—FROM THE CHARLIE FOUNDATION



MODIFIED ATKINS



Limits the amount of carbohydrate, encourages fat, and does not limit protein. Carbohydrates are to be accompanied by fat when consumed. Macromotivent Ratio (2.8.3)

LOW GLYCEMIC INDEX





An individualized but fess structured dust, it uses exchange lists for planning meal and emphasizes complex carbohydrates...It is not intended to promote leatosis.



A distany exervision that shifts the body into ketosis by limiting the window of time one wats during the day, funcing the body to access energy from body fait. *Macronwover Bottle: Kell*

INTERMITTENT FASTING

Ketogenic vs. Paleo and Mediterranean Diet

- Paleo Diet: Movement founded by Loren Cordain, Ph.D.
 - Foods to eat: grass fed meats, fish and other seafood, eggs, fresh fruits and vegetables, nuts and seeds, as well as healthful oils, including olive, walnut, flaxseed, macadamia, avocado and coconut oils.
 - Foods to avoid: cereal grains, legumes, dairy, refined sugar, potatoes, processed foods, refined vegetable oil and salt.

From: https://thepaleodiet.com/what-to-eat-on-the-paleo-diet-paul-vandyken

Ketogenic vs. Paleo and Mediterranean Diet

Mediterranean Diet: Thousands of years old, several regional variations

- Basics foods: plenty of olive oil, vegetables and fruits, legumes, fish and some alcohol every day, but not so much meat or dairy.
- Example: People on Ikaria gather more than 150 different varieties of green to use in salads and that some of these greens contain more than ten times the amount of antioxidants found in red wine. Also drink "mountain tea" every day from whatever herbs and greens are in season and start their day with a spoonful of honey, which they take like a medicine.

Information from *The Blue Zones*, 2nd Edition 2012, National Geographic Society by Daniel Buettner

Ketogenic vs. Paleo and Mediterranean Diet

 Paleo and Mediterranean Diets are not "ketogenic diets" *per se*, but could easily be adapted to ketogenic diet by adding more fat/oil and controlling protein and carbs.

Spectrum of Ketogenic Diets

- "Official" forms of KD just discussed aim for moderate to high levels of ketones.
- There is a wide spectrum of "nutritional ketosis" with levels between 0.5 and 5 mmol.
- Higher end of range for serious medical conditions epilepsy, cancer.
- "Mild" to "optimal" range for general health benefits and some with medical conditions may respond.



Graphic - Copyright, Mary T Newport MD, from Complete Book of Ketones, available 2019

Other Strategies for Increasing Ketone Levels

KETOGENIC STRATEGY :	KETONE LEVELS mmol/L:
Caffeine →	0.2 to 0.3
Coconut Oil / MCT Oil →	0.3 to 0.5
Vigorous Exercise 🗲	0.3 to 0.5
MCT Oil →	0.3 to 1.0
Branched Chain Amino Acids >	0.3 to 1.0
Ketone Mineral Salts →	0.5 to 1.0
Classic Ketogenic Diet 🗲	2 to 6
Starvation +	2 to 7
Ketone Esters (Oral or IV) →	2 to 7 or higher
Diabetic Ketoacidosis →	10 to 25

Table - Copyright, Mary T Newport MD, from *Complete Book of Ketones*, available 2019

Coconut Oil and MCT Oil:

Recommendations for adding to diet:



- Begin slowly and increase slowly to avoid diarrhea or other intestinal upset
- Start with 1/2 to 1 teaspoon (2 to 5 grams) with food 2 to 3 times a day
- If no intestinal problem, increase 1/2 to 1 teaspoon per meal every few days to 2 to 4 tablespoons or more per day, depending on tolerance and what your goals are, and divide into 3 or 4 servings.
- To lose weight or avoid weight gain, substitute coconut and MCT oil for other fats in the diet and reduce carbohydrate intake.
- Include marine source of omega-3 fatty acids for DHA.

- Ketone Salts
 - Developed at University of South Florida by Dominic D'Agostino, PhD
 - Ketone betahydroxybutyrate plus sodium, potassium, calcium and magnesium
 - Powder that can be mixed in water
 - One serving with 8 to 10 gm BHB will increase ketone level by 0.5 to 1 mmol/L from baseline

Betahydroxybutyrate-butanediol - Ketone Ester

- Developed by Dr. Richard Veech at NIH and studied extensively by Dr. Kieran Clarke at Oxford
- Extremely expensive
- Tastes like jet fuel
- On market since early 2018
- Recognized by FDA only for use for athletic performance in healthy young adults
 - All clinical trials have been in performance athletes except pilot study of one/case report (my husband)
 - Toxicity studies underway for general use
- 20 to 35 gm dose can increase levels from nil to 5 mmol/L or higher in 30 to 60 minutes.

Betahydroxybutyrate Triglyceride – Ketone ester

- Developed by Dr. Sami Hashim, inventor of MCT oil in 1950s!
- Also taste bad, but food scientists helping
- Recognized as GRAS for general use
- Undergoing phase 2 clinical trials to determine pharmacokinetics and efficacy in Alzheimer's for planned medical food at higher doses (20 grams TID).

Potential Complications of Ketogenic Diet and Supplements

- Consult with medical provider and dietician qualified in KD before starting diet for infants, children, older or with any medical condition.
- For healthy people strongly recommend same if considering more than mild nutritional ketosis.
- Avoid completely if pregnant, breastfeeding
 - Naturally in ketosis and greater tendency for higher ketone levels.
 - Case reports of severe near fatal ketoacidosis in breastfeeding mothers who were on ketogenic diet
 - Avoidance of excessive sugar and starchy foods with whole grains and healthy fat are appropriate in pregnancy and breastfeeding and could help treat or prevent gestational diabetes (Lily Nichols books – Real Food for Pregnancy and Real Food for Gestational Diabetes)
- Not appropriate for someone with liver or renal failure, although lower carb diet/avoidance of excessive sugar intake could be beneficial.

Potential Complications of Ketogenic Diet - "Keto Flu"

"Keto Flu" AKA "Keto-adaptation" may last two to six weeks or longer due to a combination of:

- Water, electrolyte and mineral imbalances involving sodium, potassium, calcium and magnesium out.
- Significant hypoglycemia and lower insulin levels.
- Adjustment to upregulation of enzymes involved in ketone metabolism.
- **Symptoms:** fatigue and lethargy, dizziness or light-headedness, trouble focusing, brain fog, headaches, sugar cravings, muscle cramping, irritability, difficulty sleeping, and upset stomach with nausea and diarrhea
- **Tips:** Consult doctor first for monitoring, drink plenty of fluids, increase salt and mineral intake (best as foods bone broth, coconut water; vegetables high in calcium and magnesium), consider electrolyte supplement, take ketone salts with electrolytes and minerals, avoid excessive exercise.
- Avoidance: Lower carbs in increments starting at <50-75 grams while increasing healthy fats

Potential Complications

of Ketogenic Diet and Ketone Supplements

- Exacerbation of dehydration and/or metabolic imbalances if taking diuretics, sodium, potassium supplements.
 - Monitor closely
 - Factor electrolytes and minerals into diet.
- Severe hypoglycemia if insulin and oral diabetic medications not adjusted
 - Monitor blood sugar closely
 - Adjust insulin and medications with medical provider help
- Lipid Aspiration
 - avoid feeding oils straight to children, elderly or people with dysphagia
- Also for Ketone Salts Exacerbation of hypertension for sodium sensitive people
 - Reduce or discontinue salts and/or factor sodium into overall diet and monitor closely
- Also for Ketone Salts Excessive potentially harmful salt and mineral load possible with excessive intake
 - Look closely at ingredients for salt and mineral contents to determine appropriate maximum serving for individual.
- Also for Ketone Esters Very likely to cause hypoglycemia. Can affect sodium and potassium levels. Mild acidosis for more than two hours with 20 gm or higher doses – Dangerous ketoacidosis possible with stacking doses
 - Should only be used with medical supervision for any use in children, elderly and those with medical conditions; strongly recommend medical supervision even for healthy people and athletes taking more than 10 grams per day of betahydroxybutyrate.

Potential Complications of Ketogenic Diet and Ketone Supplements

- Mild chronic ketoacidosis, poor growth, with osteopenia, fractures, kidney stones, gout, rarely cardiac arrhythmias related to chronic excretion of calcium in urine
 - reported mainly in children on prolonged classic KD
 - Can be prevented by taking potassium citrate and low acid diet
- Non-diabetic ketoacidosis usually levels of 7 mmol/L or higher
 - Can be serious life-threatening
 - Can happen in pregnancy and breastfeeding
 - Rare enzyme defects of ketone metabolism
 - Excessive use of exogenous ketone supplements, especially ketone esters.

Sampath A, E H Kossoff, S L Furth, et al. Kidney stones and the ketogenic diet: risk factors and prevention. *J Child Neuro*. Vol. 22 No. 4 (2007): 375-8.

Yuen A W C, I A Walcutt, J W Sander. An acidosis-sparing ketogenic (ASK) diet to improve efficacy and reduce adverse effect in the treatment of refractory epilepsy. *Epilepsy & Behavior.* Vol. 74 (2017): 15-21.

Fukao T, G Mitchell, et al. Ketone body metabolism and its defects. J Inherit Metab Dis Vol. 37 (2014): 541-551.

Potential Complications - Diabetic Ketoacidosis

STRATEGY FOR

RAISING KETONES:

Coconut Oil

Exercise

Overnight Fast

MCT Oil (30-45 gm per day)

Branched Chain Amino Acids

Ketone Mineral Salts

Classic Ketogenic Diet

Starvation

Ketone Esters

Diabetic Ketoacidosis*

KETONE LEVELS:

- 0.3 0.5 mmol/l
- 0.3 0.5 mmol/l
- 0.3 0.5 mmol/l
- 0.5 1 mmol/l
- 0.5 1 mmol/l
- 0.5 1 mmol/l
- 2-6 mmol/l
- 2-7 mmol/l
- 2-7 mmol/l
- 10-25 mmol/l

*Diabetic ketoacidosis occurs when there is no insulin and extremely high blood glucose, usually in type 1 diabetic, sometimes type 2. Fat breaks down rapidly and produces ketones too fast for body to compensate.

Ketogenic Diet Meal Planning

- Determine daily protein intake at about 0.5 gm per pound of body weight per day (more for children and body builders). Divide total into desired amounts for meals and snacks.
- Determine desired level of total calorie and percent of fat intake. Use chart to estimate # Fat Grams and # Combined protein and carbs for day.

	QUICK REFERENCE CHART FOR MACRONUTRIENTS FOR MODERATE TO HIGH FAT DIETS									
	1600 CALORIES/DAY		1800 CALORIES/DAY		2000 CALORIES/DAY		2400 CALORIES/DAY		2800 CALORIES/DAY	
	FAT (grams)	PROTEIN & CARBS (grams)	FAT (grams)	PROTEIN & CARBS (grams)	FAT (grams)	PROTEIN & CARBS (grams)	FAT (grams)	PROTEIN & CARBS (grams)	FAT (grams)	PROTEIN & CARBS (grams)
40% FAT	71	240	80	270	89	300	107	360	124	420
45% FAT	80	220	90	247	100	275	120	330	140	385
50% FAT	89	200	100	225	111	250	133	300	156	350
55% FAT	98	180	110	203	122	225	147	270	171	315
60% FAT	106	160	120	180	133	200	160	240	187	280
65% FAT	115	140	130	157	144	175	173	210	202	245
70% FAT	124	120	140	135	155	150	187	180	218	210
75% FAT	133	100	150	113	166	125	200	150	233	175
80% FAT	142	80	160	90	177	100	213	120	249	140
85% FAT	151	60	170	68	189	75	227	90	264	105

Table - Copyright, Mary T Newport MD, from Complete Book of Ketones, available 2019

Ketogenic Diet Meal Planning

- Determine daily protein intake at about 0.5 gm per pound of body weight per day (more for children and body builders). Divide total into amounts for meals and snacks.
- Determine desired level of calories and percent of fat intake for meal. This will give # Fat Grams and # Combined protein and carbs.

	QUICK REFERENCE CHART FOR MACRONUTRIENTS FOR MEAL PLANNING										
	400 CALORIE MEAL		500 CALORIE MEAL		600 CALORIE MEAL		700 CALORIE MEAL		800 CALORIE MEAL		
PERCENT CALORIES AS FAT	FAT (grams)	PROTEIN & CARBS (grams)	FAT (grams)	PROTEIN & CARBS (grams)	FAT (grams)	PROTEIN & CARBS (grams)	FAT (grams)	PROTEIN & CARBS (grams)	FAT (grams)	PROTEIN & CARBS (grams)	
50% FAT	22	50	28	63	33	74	39	87	44	100	
60% FAT	27	39	33	50	40	60	47	70	53	80	
70% FAT	31	30	39	37	47	44	54	53	62	60	
80% FAT	35	21	44	26	53	30	62	35	71	40	
90% FAT	40	10	50	13	60	15	70	18	80	20	

Table - Copyright, Mary T Newport MD, from *Complete Book of Ketones*, available 2019

Ketogenic Supplementation = "Instant Ketosis"

Rapid and Sustained Ketosis (15 minutes to >2-8 hrs)



But Isn't a High Fat Diet Bad for the Heart??



Keys A. "Atherosclerosis: a problem in newer public health." J Mt Sinai Hosp Vol. 20 (1953): 118.

Keys A. "Coronary heart disease in seven countries." Circulation Vol 41, Suppl 1 (1970): 1–211.

Keys A, JT Anderson, F Grande, "Prediction of serum cholesterol responses of man to changes in fats in the diet." *Lancet* Vol 2 (1957): 959–966.

Keys A, JT Anderson, O Mickelson, et al. "Diet and serum cholesterol in man: lack of effect of dietary cholesterol." J Nutrition Vol 59 (1956): 39.

The Problem with Cherry Picking Data



Intern Med Vol. 104 (1959): 95–103.



Figure 21.4. Disputing Keys' hypothesis that a high-fat diet causes degenerative heart disease, George Mann plotted data for all twenty-two countries available from the 1949 FAO report showing that there was no correlation between percent of fat intake and heart disease; furthermore, a graph of percent of animal protein intake versus heart disease produced a similar random pattern.

Mann GV. "Diet and coronary heart disease." AMA Arch Intern Med Vol. 104 (1959): 95–103.

Deaths from Stroke versus Percent of Calories as Fat in Diet



Figure 21.5. To illustrate the folly of hand-picking data to prove a point, Yerushalmy chose data for six of the twenty-two countries available from the 1949 FAO report to show that mortality from blood vessel lesions affecting the central nervous system (stroke) decreased as the percentage of fat in the diet increased.

Yerushalmy J, HE Hilleboe. "Fat in the diet and mortality from heart disease." *New York State J Medicine* Vol 57 (1957): 2343–2354.

Trends in Coronary Mortality and number of Radio and TV licenses in the UK



Yudkin J. "Diet and coronary thrombosis: hypothesis and fact." *Lancet* (Jul 1957): 155–162.

Ancel Keys featured on Time



As a result of Ancel Keys study, in 1956 representatives of the American Heart Association appeared on television to inform people that a diet which included large amounts of butter, lard, eggs, and beef would lead to coronary heart disease. This resulted in the American government recommending that people adopt a low-fat diet in order to prevent heart disease.

Tobacco the Real Culprit in Heart Disease?

Heart disease accounts for about 1 in 3 deaths in USA



Trends in Tobacco Use

Trends in Coronary Artery Disease
Sugar, not fat or protein intake, up over past 50 years in USA

Macronutrient Intake, 1970-2006



Prepared by Stephan Guyenet

Guyenet, Stephan. <u>http://wholehealthsource.blogspot.com/2012/09/more-thoughts-on-macronutrient-trends.html#more</u> - September 14, 2012

Trends in Overweight and Obesity in USA 1960 to 2012



From CDC Surveys

PURE Study – 2017 - Lancet

135,335 participants 35 -70 y.o. from 18 countries on 5 continents studied for average 7.4 years:

- Higher carbohydrate intake was associated with a higher risk of overall, total mortality.
- Higher intake of total fat and each type of fat, including saturated fat, was associated with a *lower than average risk of dying* prematurely and was not associated with a higher risk of heart disease, heart attacks or heart related deaths.
- Higher saturated fat intake was associated with a *lower* risk of stroke as well.

Dehghan M, A Mente, X Zhang, et al. "Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study." *Lancet* Vol. 390 No. 10107 (2017):2050-2062.

Diabetes and Dementia

- More than 100 million adults in USA have diabetes or prediabetes <u>https://www.cdc.gov/media/releases/2</u> 017/p0718-diabetes-report.html
- ¾ of people over 75 have diabetes or pre-diabetes
- Diabetes is a major risk factor for dementia – about 1/3 of diabetics will develop dementia.
- Rates of diabetes increase as sugar consumption increases in a community.
- Reducing sugar intake (including added sugar) could decrease rates of diabetes and dementia.

Guyenet, S. By 2606 the US diet will be 100% sugar. *Whole Health Source: Nutrition and Health Science* www.wholehealthsource.blogspot.com February 18, 2012



Sugary Drinks and Brain Aging

Middle-aged participants (53 to 56 years old) in the Framingham Heart Study to determine if consuming sugary drinks, including sugar sweetened soft drinks, fruit drinks with added sugar and 100% fruit juice, was associated with signs of pre-clinical Alzheimer's (that point at which Alzheimer's is underway but symptoms are not yet obvious) and vascular brain injury.

Every two years the participants had an MRI (4276 people) and/or neuropsychological testing (3846 people). They also looked at intake of diet soft drinks for comparison.

Findings, compared to people who did not consume sugary beverages:

- Consumption of one or more sugary drinks per day resulted in lower total brain volume, lower hippocampal volume (hippocampus is an important area of the brain for memory and the process of Alzheimer's disease starts there)
 - One to two sugary drinks per day resulted in 1.6 years of accelerated brain shrinkage.
 - More than two sugary drinks, 2.0 years of accelerated brain shrinkage.
 - Three or more sugary drinks, 2.6 years of accelerated brain shrinkage.
- Worse scores on delayed-recall memory testing (the ability to remember something, such as a list of words after a distraction).
 - One to two sugary drinks per day resulted in equivalent of 5.8 years of brain aging.
 - More than 2 sugary drinks per day resulted in equivalent of 11.0 years of brain aging.
 - Three or more sugary drinks per day resulted in equivalent of 13.0 years of brain aging.

Pase MP, JJ Himali, PF Jacques, et al. "Sugary beverage intake and preclinical Alzheimer's disease in the community." *Alzheimers Dement* Vol. 13 No. 9 (2017):955-964.

How could Steve improve so much with low ketone levels from coconut oil?

Ketone and glucose levels after breakfast and dinner doses of coconut oil 35 grams per dose



Ketone and glucose levels after breakfast dose of C8 20 grams



Lauric Acid and Ketogenesis

Researchers at Nisshin OilliO Group and University of Tokyo considered, since blood ketone levels from coconut oil are very low, that there might be another explanation.

Journal of Oleo Science Copyright ©2016 by Japan Oil Chemists' Society doi : 10.5650/jos.ess16069 J. Oleo Sci. 65, (8) 693-699 (2016)



Lauric Acid Stimulates Ketone Body Production in the KT-5 Astrocyte Cell Line

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Lauric Acid and Ketogenesis

Experiment 1: *In vivo* - 7 week old Sprague-Dawley rats fed coconut oil <u>OR</u> high-oleic sunflower oil (no MCTs) <u>OR</u> MCT Oil (C8/C10)

• Measured total ketone bodies (KB), total triglycerides (TG) and total free fatty acids and individual fatty acids before dosing and at 2 and 4 hours after.

Experiment 2: *In vitro* – Total ketone bodies (KB) were measured 4 hours after the following were added to cultures of KT-5 Astrocytes (mouse):

- Vehicle alone
- Vehicle + oleic acid (C18:1) at 50 and 100 μL
- Vehicle + caprylic acid (C8) at 50 and 100 μL
- Vehicle + lauric acid (C12) at 50 and 100 μL

Lauric acid stimulates ketogenesis in astrocytes

Conclusions:

- Coconut oil intake markedly increases plasma FFA and lauric acid C12 content; C8 and C10 are rapidly utilized by comparison.
- Lauric acid "directly and potently" stimulates ketone production in astrocytes *in vitro*
- May provide nearby neurons with fuel.
- Need further study of whether this occurs *in vivo* in humans.

Nonaka Y, T Tagaki, M Inai, et al. Lauric acid stimulates ketone body production in the KT-5 Astrocyte Cell Line. *J Oleo Science* Vol. 65 No. 8 (2016): 693-699

Editorial

Microbes and Alzheimer's Disease

Ruth F. Itzhaki^{a,*}, Richard Lathe^{b,*}, Brian J. Balin^c, Melvyn J. Ball^d, Elaine L. Bearer^e, Heiko Braak^f, Maria J. Bullidos, Chris Carter^h, Mario Clerici¹, S. Louise Cosby¹, Kelly Del Tredici¹, Hugh Field^k, Tamas Fulop¹, Claudio Grassi^m, W. Sue T. Griffinⁿ, Jürgen Haas^b, Alan P. Hudson^o, Angela R. Kamer^e, Douglas B. Kell⁴, Federico Licastro⁷, Luc Letenneur⁴, Hugo Lövheim⁴, Roberta Mancuso", Judith Miklossy^v, Carola Otth^w, Anna Teresa Palamara^s, George Perry^y, Christopher Preston², Etheresia Pretorius²⁴, Timo Strandberg^{bb}, Naji Tabet^{cc}, Simon D. Taylor-Robinson^{dd} and Judith A. Whittum-Hudson^{ee} ^aFaculty of Life Sciences, University of Manchester, Oxford Road, Manchester, UK ^bDivision of Infection and Pathway Medicine, University of Edinburgh, Little France, Edinburgh, UK ^cCenter for Chronic Disorders of Aging, Philadelphia College of Osteopathic Medicine, Philadelphia, USA ^dDepartment of Pathology (Neuropathology), Oregon Health and Science University, Portland, OR, USA *Department of Pathology, University of New Mexico Health Sciences Center, Albuquerque, NM, USA ⁴Clinical Neuroanatomy Section, Department of Neurology, Center for Biomedical Research, University of Ulm. Ulm, Germany Centro de Biologia Molecular 'Severo Ochoa' (CSIC-UAM), Universidad Autonoma de Madrid, and Centro de Investigación en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid. Spain ^hPolvgenic Pathways, Hastings, East Sussex, UK ¹University of Milano and IRCCS SM Nascente, Don C Gnocchi Foundation, Milan, Italy Centre for Infection and Immunity, Medical Biology Centre, Queen's University, Belfast, UK ^hQueens' College, Cambridge, UK Department of Medicine, Division of Geriatrics, Université de Sherbrooke, Sherbrooke, PQ, Canada "Institute of Human Physiology, Medical School, Universitä Cattolica, Rome; San Raffaele Pisana Scientific Institute for Research, Hospitalization, and Health Care, Rome, Italy Department of Geriatrics, University of Arkansas for Medical Sciences, and Geriatric Research. Education, and Clinical Center, Little Rock, AR, USA ^oDepartment of Immunology and Microbiology, Wayne State University School of Medicine, Detroit, MI, USA PNYU College of Dentistry, Department of Periodontology and Implant Dentistry, New York, NY, USA School of Chemistry, Manchester Institute of Biotechnology, University of Manchester, Manchester, UK Department of Experimental, Diagnostic, and Specialty Medicine, School of Medicine, University of Bologna,

Bologna, Italy

Itzhaki RF, R Lathe, BJ Balin, and many others. Microbes and Alzheimer's Disease. Editorial. *J Alzheimer's Dis* Vol 51 (2016): 979-984

Microbes and Alzheimer's

Read White Paper "It's Time to Find the Alzheimer's Germ," by Leslie Norins, MD, PhD on Alzgerm.com

Microbes and Alzheimer's

"Many studies, mainly in humans, implicate specific microbes in the elderly brain... in the etiology of Alzheimer's"

- Herpes simplex 1 (more than 100 studies since 1991
- Several types of spirochetes (syphilis, Lyme's, etc.)
- Chlamydia pneumoniae
- Fungi
- Abnormal microbiota

Still regarded by leading figures as "controversial"

Itzhaki RF, R Lathe, BJ Balin, and many others. Microbes and Alzheimer's Disease. Editorial. *J Alzheimer's Dis* Vol 51 (2016): 979-984

Herpes Viruses and Alzheimer's

Researchers at Arizona State University reported results from analysis of RNA and DNA sequencing data for 622 brains (from NIH) from people with clinical assessments before death and postmortem neuropathology consistent with AD and 322 with no signs of AD. They weren't looking for viruses, but "viruses screamed out" at them:

- Found high levels of herpesvirus 6A and 7 in AD brains in six key brain regions affected by AD compared to the unaffected brains.
- Thee viruses were perturbing and participating in networks that directly underlie Alzheimer's pathology, including AD risk genes and those that regulate processing of amyloid, which engulfs viruses as one of its functions, and also forms the hallmark plaques in AD brain.
- They are not certain if these viruses are causal of AD or opportunistic. Most people are exposed to these early in life usually through nasopharyngeal route.
- Results were replicated when they studied brains from a different cohort from the Mayo Clinic brain bank.

Readhead B, J-V Haure-Mirande, CC Funk, et al. Multiscale analysis of independent Alzheimer's cohort finds disruption of molecular, genetic and clinical networks by human herpesvirus. *Neuron* Vol. 99 (2018):e1-19.

Lauric Acid is Anti-microbial

Lauric acid (C12) and to some degree capric acid (C10) have known antimicrobial effects to a plethora of bacteria, viruses, fungi and protozoa.

- Destroy cell membranes of gram positive bacteria and lipid-coated virus
- Interfere with bacterial cellular processes such as signal transduction and transcription
- Blocks or delays production of exotoxins by gram positive bacteria
- Decreases dental plaque formation

Kabara JJ, et al. Fatty acids and derivatives as antimicrobial agents. *Antimicrobial Agents And Chemotherapy*, July 1972: 23-28 Thormar H, et al. Inactivation of enveloped viruses and killing of cells by fatty acids and monoglycerides. *Antimicrob Agents Chemother* Vol. 31 No. 1(1987): 27-31. And many other reports available

Lauric Acid Kills Microbes

- 4-6% of the fat in human breast milk is lauric acid
- Many commercial uses for lauric acid and monolaurin as antimicrobial agents
 - Used to treat difficult microbial infections in animals such as dairy cows, poultry, piglets.
 - More than 100 patents worldwide for uses of monolaurin as a microbicide or microbiostatic agent for food and non-food applications such as medical procedures, disinfection and sanitizing, and animal feed supplements

Fabian M. Dayrit. The properties of lauric acid and their significance in coconut oil. *J Am Oil Chem Soc* Vol 92 (2015): 1-15

Other Possible Coconut Oil Effects

Review article, Fernando et al: In addition to discussing benefits of medium chain triglycerides and ketones as alternative fuel, they state that:

- "Phenolic compounds and hormones (cytokinins) found in coconut may assist in preventing the aggregation of amyloid-Beta peptide."
- "Coconut is a highly nutritious 'functional food'. It is rich in dietary fiber, vitamins and minerals...and evidence is mounting that [it]may be beneficial in the treatment of obesity, dyslipidemia, elevated LDL, insulin resistance and hypertension these are the risk factors for CVD and type 2 diabetes, and also for AD."

Fernando WM, IJ Martins, KG Goozee, et al. The role of dietary coconut for the prevention and treatment of Alzheimer's disease: potential mechanisms of action. *Br J Nutr* Vol. 114 No. 1 (2015):1-14

Steve's Story

Part II Ketone Monoester

SETBACK

After long stable period, crossed over to clinical trial drug semagacestat between August and October 2009

In Feb 2010 Steve began to experience apparent side effects of semagacestat:

Poor wound healing Elevated creatine phosphokinase (CPK) – muscle component Fainting episode Hair color change Viral intestinal and upper respiratory infections Fever blisters

Discontinued study participation March 1, 2010.



Alzheimer's Disease International Conference March 2010 Thessaloniki, Greece

This trial was stopped in summer 2010 after analysis of data showed there was accelerated worsening of Alzheimer's for people taking drug compared to placebo.

Deterioration – February to April 2010

- Began to wander from home looking for brothers living 700 miles away.
- Began to talk to his father in the mirror, unable to recognize himself at times.
- Difficulty finding his way around the house, doesn't always recognize bedroom and bed as his own.
- Lost interest in personal hygiene, needed prompting.
- Needed step by step instruction with showering, shaving, brushing teeth, and help with picking out clothes and dressing.
- Unable to perform household and yard chores.
- Unable to continue as hospital warehouse volunteer wandering from the area and requiring more supervision.

Ketone Ester at NIH

In triple transgenic Alzheimer mouse model:

- Reduced plaque
- Reduced tangle
- Improved memory and learning
- Reduced anxiety

My Hero – Richard Veech, MD, PHD

Kashiwaya Y, Bergman C, Lee J-H, et al. "A ketone ester diet exhibits anxiolytic and cognition-sparing properties, and lessens amyloid and tau pathologies in a mouse model of Alzheimer's disease." *Neurobiology of Aging* (Online 2012)





D-Betahydroxybutyrate



Veech Ketone Monoester

Betahydoxybutyrate exists in two distinct forms that may behave differently in metabolism



Mitochondrial enzyme BHB dehydrogenase uses D- but not L-form



L-betahydroxybutyrate (levo = left handed)

Mostly found inside mitochondria

Undergoes beta oxidation with less energy produced than D-form

- April 29, 2010, began taking 25% solution of ester of ketone L-D-beta hydroxybutyrate from NIH lab of Dr. Richard Veech, 22 grams three times a day.
- Beta-hydroxybutyrate level 2 hours before the initial dose was 0.1 mM, at one hour after dose was 1.4 mM, and at four hours after dose level was 0.1 mM.

 Within 2 hours, immediate marked improvement in mood and affect, the ability to write out the entire alphabet, which he was unable to do for several months, recalls details of early childhood never mentioned before to spouse.

• Within 24 hours, able to choose clothing and dress himself without prompting or assistance.

- Continued ketone ester at increased dose of 85 grams divided into three doses per day and well as varying amounts of coconut and MCT oil.
- Over several days resumed activities he had not been able to perform for at least two months:
 - Showering, shaving, brushing his teeth, and changing clothes without prompting or assistance.
 - Was able to choose and order food from a menu at a restaurant
 - Was able to able to put silverware away from dishwasher, matching the utensils.
- He was no longer lost inside the house.
- Abstract thinking, insight and subtleties of sense of humor returned to his conversation.
- He stated that he felt "good", had "more energy" and was "happier", and also that he was "finding it easier to do things", which concurred with my observations.

- May, June, and early July 2010, after approximately six to eight weeks of three times a day dosing with ketone ester:
- He began to exhibit improvements in memory, spontaneously discussing events that occurred up to a week earlier.
- No longer wandering
- He was once again able to perform more complex tasks, such as vacuuming, hand washing dishes and yard work, such as mowing the lawn with tractor and edging.



Steve's Case Study Published in 2015



NIH-PA Author Manusc

NIH Public Access

Author Manuscript Alzheimers Dement: Author manuscript; available in PMC 2016 January 01

Published in final edited form as: Alzheimers Dement. 2015 January ; 11(1): 99–103. doi:10.1016/j.jalz.2014.01.006.

A new way to produce hyperketonemia: use of ketone ester in a case of Alzheimer's

Mary T. Newport^a, Theodore B. VanItallie^b, Yoshihiro Kashiwaya^c, Michael Todd King^d, and Richard L. Veech^{d,*}

- Steve's dramatic improvement with medium chain triglycerides from 2008 to 2010.
- Steve's remarkable improvement in functioning while taking beta-hydroxybutyrate ketone ester over a twenty month period beginning in mid-2010.

Preface: Recent evidence indicates:

- Amyloid beta (Aβ) is absorbed into and is transported through distal axons
- Aβ accumulates in mitochondria of cell bodies
- Aβ is further transferred to nearby neurons
- Accumulation of A β 1-42 causes mitochondrial dysfunction and failure

Binds to mitochondrial proteins and increases formation of ROS

 Alzheimer's is associated with mitochondrial dysfunction and oxidative stress

In vitro experiments on primary cortical neurons of newborn rats or mouse pups showed that a ketones (mixture of BOHB and AcAc) :

- Prevented oligo Aβ42-induced membrane dysfunction, neuronal injury, mitochondrial dysfunction, and ROS formation
- Reduced intracellular levels of Aβ42 by preventing perforation of cell membrane by Aβ42
- Protected synaptic plasticity against oligo Aβ42 toxicity

APP mice show synapse loss and learning deficits at 3-4 months and increased A β plaques at 6 months.

In vivo experiments were performed on wild type and APP mice with daily subcutaneous injections of 0.9% saline or betahydroxybutyrate (600 mg/kg) and acetoacetate (150 mg/kg) for two months beginning at 3-4 months of age.

In vivo experiments on wild type and APP mice showed that ketones:

- Improved mitochondrial dysfunction by restoring complex 1 activity and reducing soluble Aβ42 level
- Ketones did not affect wild type mice but drastically improved memory performance in APP mice on Morris Water Maze and Novel Object Recognition

Recommendations for adding Virgin Coconut Oil or MCT Oil to diet

- Begin slowly and increase slowly to avoid diarrhea or other intestinal upset
- Start with 2 to 5 grams **with food** 2 to 3 times a day
- If no intestinal problem, increase by 2 to 5 grams per meal every few days to total 60 to 120 grams per day as tolerated divided into 3 or 4 servings
- To avoid weight gain, substitute coconut oil/MCT oil for other fats in the diet and/or reduce carbohydrate intake
- Include marine source of omega-3 fatty acids for DHA

Astarita G, J Kwang-Mook, NC Berchtold, et al. "Deficient Liver Biosynthesis of Docosahexaenoic Acid Correlates with Cognitive Impairment in Alzheimer's Disease." *PloS One* Vol 5 No 9 (Sept 2010): e12538

Bill Curtis, Parkinson's and BOHB Ester



Coconut Oil Availability



My local grocery store 2018.





Disclaimer: This does not constitute my endorsement of any brands of coconut oil.


The Complete Book of Ketones: A Practical Guide to Ketogenic Diets and Ketone Supplements

by Mary T. Newport, M.D

From Turner Publishing—Now available for Pre-orders from Amazon, Barnes and Noble, and Indie Bound Shipping February 19, 2019

Pre-Order from Amazon: https://amzn.to/2AxBcLp



Carrying on his legacy – My Husband and Best Friend **Steve Newport** 1950 to 2016 Alzheimer's Disease: What If There Was a Cure? The Story of Ketones

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www.coconutketones.com

Look for "Diet Guidelines", blog and information about using ketone salts

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