

## REFERENCES FOR KETOGENIC STRATEGIES FOR ALZHEIMER'S

Updated January 2023

### Coconut oil & MCT Oil: Studies & Reviews

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.

Abe S, O Ezaki, M Suzuki. "Medium-chain triglycerides in combination with leucine and vitamin D increase muscle strength and function in frail elderly adults in a randomized controlled trial." *J Nutr* Vol. 146 No. 5 (2016): 1017-26.

Castellano C-A, S Nugent, N Paquet, et al. "Lower brain <sup>18</sup>F-fluorodeoxyglucose uptake but normal <sup>11</sup>C-acetoacetate metabolism in mild Alzheimer's disease dementia." *J Alzheim Dis* Vol. 43 (2015): 1343-1353.

Chatterjee P, et al. "Potential of coconut oil and medium chain triglycerides in the prevention and treatment of Alzheimer's disease." *Mechanisms of Ageing and Development*. (2020):111209.

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* Vol. 6 No. 31 (2009): 1-25.

Courchesne-Loyer A, M Fortier, J Tremblay-Mercier, et al. Stimulation of mild, sustained ketonemia by medium-chain triacylglycerols in healthy humans: Estimated potential contribution to brain energy metabolism. *Nutrition*. (2013): 1-6.

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.

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

Cunnane S, et al. "Brain energy rescue: an emerging therapeutic concept for neurodegenerative disorders of aging." *Nature Reviews Drug Discovery* V. 19 No. 9 (2020):609-633.

Cunnane SC, A Courschesne-Loyer, V St-Pierre, et al. "Can ketones compensate for deteriorating brain glucose uptake during ageing? Implications for the risk and treatment of Alzheimer's disease." *Ann NY Acad Sci* (2016): 1-9.

De la Rubia Ortí JE, et al. "Improvement of main cognitive functions in patients with Alzheimer's disease after treatment with coconut oil enriched Mediterranean diet: A pilot study." *J Alzheimers Dis* V. 65 No. 2 (2018):577-587.

Farah BA. "Effects of caprylic triglyceride on cognitive performance and cerebral glucose metabolism in mild Alzheimer's disease: a single-case observation." *Frontiers in Ageing Neuroscience* Vol. 6 No. 133 (2014): 1-5.

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

Fortier, et al. "A ketogenic drink improves brain energy and some measures of cognition in MCI." *Alzheim and Dement* (2019): e1-10.

Kabara JJ, et al. "Fatty acids and derivatives as antimicrobial agents." *Antimicrobial Agents and Chemotherapy* (1972): 23-28.

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.

Nafar F and KM Mearow. "Coconut oil attenuates the effects of amyloid-beta on cortical neurons in vitro." *J Alzheim Dis* 39 (2014): 233–23.

Neth BJ, A Mintz, Whitlow, et al. "Modified ketogenic diet is associated with improved cerebrospinal fluid biomarker profile, cerebral perfusion, and cerebral ketone body uptake in older adults at risk for Alzheimer's disease..." *Neurobio Aging* In press 2019:00:1-10.

Newport MT, TB VanItallie, Y Kashiwaya, et al. "A new way to produce hyperketonemia: use of a ketone ester in a case of Alzheimer's." *Alzheim and Dement* Vol. 11 No. 1 (2015):99-103.

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.

Norgren J, Sindi S, Sandebring-Matton A, et al. "Ketosis after intake of coconut oil and caprylic acid-with and without glucose: A cross-over study in healthy older Adults." *Front Nutr* V. 7 (2020):40.

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

Ota M, Matsuo J, Ishida I, et al. "Effects of a medium-chain triglyceride-based ketogenic formula on cognitive function in patients with mild-to-moderate Alzheimer's disease." *Neurosci Lett* V. 690 (2019):232-236.

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.

Rahima NS, SM Li, et al. "Enhanced memory in Wistar rats by virgin coconut oil is associated with increased antioxidative, cholinergic activities and reduced oxidative stress." *Pharmac Biol* V. 55 NO. 1 (2017): 825–832.

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.

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

Roy M, Rheault F, Croteau E, et al. "Fascicle- and glucose-specific deterioration in white matter energy supply in Alzheimer's Disease." *J Alzheimers Dis* V. 76 No. 3 (2020):863-881.

Roy M, Fortier M, Rheault F, et al. "A ketogenic supplement improves white matter energy supply and processing speed in mild cognitive impairment." *Alzheimers Dement* V. 7 No. 1 (2021):e12217.

Roy M, Edde M, Fortier M, et al. "A ketogenic intervention improves dorsal attention network functional and structural connectivity in mild cognitive impairment." *Neurobiol Aging* V. 115 (2022):77-87.

Taylor M K, D K Sullivan, J D Mahnken, et al. "Feasibility and efficacy data from a ketogenic diet intervention in Alzheimer's disease." *Alzheim and Dement* (2017): 1-9.

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.

Watanabe S and Tsujino S. "Applications of medium-chain triglycerides in foods." *Frontiers in Nutrition* V. 9 June 2022

Xu Q, Y Zhang, X Zhang, et al. "Medium-chain triglycerides improved cognition and lipid metabolomics in mild to moderate Alzheimer's disease patients with APOE4-/-". *Clinical Nutrition* IN PRESS (2020).

Yang IH, et al. "Aceite de coco: tratamiento alternativo no farmacológico frente a la enfermedad de Alzheimer." *Nutr Hosp* V. 32 (2015): 2822-2827.

### **ALZHEIMER'S, MCI, KETONES, AND KETOGENIC DIET: Studies & Reviews**

Andersen JV, et al. "β-hydroxybutyrate and medium-chain fatty acids are metabolized by different cell types in mouse cerebral cortex slices." *Neurochem Res* V. 48 No. 1 (2022):54-61.

Augustin K, A Khabbush, S Williams, et al. "Mechanisms of action for the medium-chain triglyceride ketogenic diet in neurological and metabolic disorders." *Lancet Neurol* Vol. 17 (2018): 84–89.

Avgerinos KI, et al. Ketone ester effects on biomarkers of brain metabolism and cognitive performance in cognitively intact adults > 55 years old. A study protocol for a double-blinded randomized controlled clinical trial. *J Prev Alz Dis* 2022;1(9):54-66.

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

Brandt J, Buchholz A, Henry-Barron B, et al. "Preliminary Report on the Feasibility and Efficacy of the Modified Atkins Diet for Treatment of Mild Cognitive Impairment and Early Alzheimer's Disease." *J Alzheimers Dis* V. 68 No. 3 (2019):969-981.

Brownlow ML, Jung SH, Moore RJ, et al. "Nutritional Ketosis Affects Metabolism and Behavior in Sprague-Dawley Rats in Both Control and Chronic Stress Environments." *Front Mol Neurosci* V. 10 (2017):129.

Cuenoud B, M Hartweg, JP Godin, et al. "Metabolism of Exogenous D-Beta-Hydroxybutyrate, an Energy Substrate Avidly Consumed by the Heart and Kidney." *Front Nutr* V. 7 (2020):13.

Cunnane S C, C R Menard, S S Likhodil, et al. Carbon recycling into de novo lipogenesis is a major pathway in neonatal metabolism of linoleate and α-linolenate. *Prost Leukotr and Essential Fatty Acids*. Vol. 60 No. 5 & 6. (1999): 387-92.

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.

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.

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.

Feinman R D, W K Pogozelski, A Astrup, et al. "Dietary Carbohydrate restriction as the first approach in diabetes management: Critical review and evidence base." *Nutrition* Vol. 31 (2015): 1-13.

Goldberg E L, J L Asher, R D Molony, et al.  $\beta$ -hydroxybutyrate deactivates neutrophil NLRP3 inflammasome to relieve gout flares. *Cell Rep.* Vol. 18 No. 9 (2017): 2077-87.

Kashiwaya Y, K Sato, N Tsuchiya, et al. "Control of glucose utilization in working perfused rat heart." *The Journal of Biological Chemistry* Vol 269, No 41 (1994): 25502–25514.

Kashiwaya Y, T King, RL Veech. "Substrate signaling by insulin: A ketone bodies ratio mimics insulin action in heart." *American Journal of Cardiology* Vol 80, No 3A (1997): 50A–64A.

Kashiwaya Y, T Takeshima, N Mori, et al. "D-b-hydroxybutyrate protects neurons in models of Alzheimer's and Parkinson's disease." *PNAS* Vol 97, No 10 (May 2000): 5440–5444.

Kashiwaya Y, C Bergman, J-H Lee, 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." *Neurobiology of Ageing* Vol. 34 No. 6 (2013): 1530-9.

Kovács Z, B Brunner, C Ari. "Beneficial effects of exogenous ketogenic supplements on aging process and age-related neurodegenerative diseases." *Nutrients* V. 13, no. 7 (2021): 2197.

Krikorian R, Shidler MD, Summer SS, et al. "Nutritional ketosis for mild cognitive impairment in Parkinson's disease: A controlled pilot trial." *Clin Park Relat Disord* V. 1 (2019):41-47.

Morrill SJ, KJ Gibas. "Ketogenic diet rescues cognition in ApoE4 patient with mild Alzheimer's disease: A case study." *Diabetes & Metabolic Syndrome: Clinical Research & Reviews* Vol. 13 (2019): 1187-1191.

Norwitz, Mota, Norwitz, Clarke. "Multi-Loop Model of Alzheimer Disease: An Integrated Perspective on the Wnt/GSK3 $\beta$ ,  $\alpha$ -Synuclein, and Type 3 Diabetes Hypotheses." *Frontiers in Aging Neuroscience* July 31, 2019.

Nugent S, C-A Castellano, P Goffaux, et al. Glucose hypometabolism is highly localized, but lower cortical thickness and brain atrophy are widespread in cognitively normal older adults. *Am J Physiol Endocrinol Metab.* Vol. 306 (2014): e1315-21.

Nugent S, S Tremblay, K W Chen, et al. Brain glucose and acetoacetate metabolism: a comparison of young and older adults. *Neurobiol Ageing.* Vol. 35 No. 6 (2014): 1386-95.

Owen OE, AP Morgan, HG Kemp, et al. "Brain Metabolism during Fasting." *J Clin Invest* Vol. 46, No. 10 (1967): 1589-95.

Peters R. "Ageing and the Brain." *Postgrad Med J* Vol. 82 (2006):84–88.

Phillips MCL, et al. "Low-fat versus ketogenic diet in Parkinson's disease: A pilot randomized controlled trial." *Mov Disord* V. 33 No. 8 (2018):1306-1314.

Phillips MCL, et al. "Randomized crossover trial of a modified ketogenic diet in Alzheimer's disease." *Alzheimers Res Ther* V. 13 No. 1 (2021):51.

Sato K, Y Kashiwaya, RL Veech, et al. "Insulin, ketone bodies, and mitochondrial energy transduction." *FASEB Journal* Vol. 9 (1995): 651–658.

Soto-Mota A, et al. "Safety and tolerability of sustained exogenous ketosis using ketone monoester drinks for 28 days in healthy adults." *Regul Toxicol Pharmacol* V. 109 (2019):104506.

Stoykovich S, K Gibas. "APOE4, the door to insulin-resistant dyslipidemia and brain fog? A case study." *Alzheim Demen* Vol.11 (2019):264-269.

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.

Wu Y, Y Gong, Y Luan, et al. BHBA treatment improves cognitive function by targeting pleiotropic mechanisms in transgenic model of Alzheimer's disease. *FASEB* 2019:00; 1-18.

Youm YH, et al. "The ketone metabolite  $\beta$ -hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease." *Nat Med*. V. 21 No. 3 (2015):263-269.