Blind Comparison of Two Different Compositions of Exogenous Ketones and Their Impact on Anxiety, Weight, Lean Muscle Mass and Cognitive Function

by Lisa Saff Koche, MD; Joseph Dituri, PhD, DMT, CDR - US Navy (ret); Jonathan Gacio

Introduction:

The human body naturally produces endogenous ketones during ketosis (**1**) and the same has been marketed as a dietary supplement that can be taken in conjunction with a low carb diet. Ketones first came into popularity with the existence of the ketogenic diet (**2**). Following a ketogenic diet causes the body to use all of its readily available glucose. As a response to this dearth in glucose reserves, the body burns stored fats/ketones (**3**). There are purportedly myriad benefits associated with this process. Using the body's storage of fat cells is beneficial for healthy weight loss (**4**). Additionally, the high proportion of fats that are required for this diet can be utilized to promote lean muscle gain (**5**). Any fat that isn't transformed into muscle could become a convenient fuel source. Ketones have also been found to have implications associated with increased mental acuity. A human study determined that those who adhered to this diet displayed improved alertness and cognitive function compared to their non-keto counterparts (**6**). A non-human study tested the efficiency with which ketones relieve anxiety by monitoring several Sprague Dawley rats adhering to a ketogenic diet and concluded that ketones display serious benefits when it comes to maintaining brain health and relieving anxiety (**7**).

It is possible to adhere to the dietary restrictions required by the ketogenic diet; however, enthusiasts seek the rewards of ketosis without substantially changing their daily eating habits. This is the purpose of exogenous ketones (**8**). The human body naturally produces endogenous ketone variants while in ketosis, exogenous ketones are ketones that are synthesized outside of the body to be ingested at a later date. Beta-hydroxybutyrate (BHB) is the most abundant ketone in the body, representing 78% of the total ketones that reside within human blood (**9**). Due to its unparalleled stability, BHB provides the most energy compared to other ketone variants (**10**). It is for this reason that studies have focused on synthesizing this compound in a lab setting. It is apparent that consuming exogenous BHB provides our body with an efficient fuel source that stimulates acute ketosis.

Excess calories are converted into triglycerides. These triglycerides are stored in fat cells until they are needed for energy between meals (**11**). The typical U.S. diet consists of a high proportion of Long Chain Triglycerides (LCT's), Medium Chain Triglycerides (MCT's) are a healthier alternative that can be used in combination with BHB to display multiplicative ketogenic benefits (**12**). The human body absorbs and digests MCT's at a rapid rate. This rapid rate of digestion allows the MCT's to be used right away instead of being stored as fat. LCT's have a markedly slower rate of digestion. This in turn causes the LCT's to act as a delayed energy source, leading to a higher proportion of stored fats. Most importantly, MCT's are readily broken down in the liver, providing essential substrates that can be utilized for ketone production (**13**).

The purpose of this study was to establish the effectiveness of two products with differing BHB/MCT ratios in order to determine which compound had the greatest efficacy in reducing anxiety, decreasing body fat, increasing lean muscle mass and increasing mental acuity.

Methods:

Data collection was conducted under the specifications of the in-place IRB protocol #1MAY 14-48 titled “Wavi Data Analysis Protocol Clinical EEG, Symptoms and Intervention analysis.” A normally distributed age range of both male and female subjects between 20 and 70 years of age who did not have hyperlipidemia nor diabetes and with a body mass index between 20 and 40 were selected as a study group. In order to ensure that the sample population was a true representation of the total population, a power study was conducted in order to choose the appropriate sample size. There is 95% confidence that a sample mean of 60 subjects lies within 12.7% of the true population mean (**14**). Fifty-Seven actual subjects were recruited for the purposes of this study of which 9 were male and 48 were female. Subjects were required to obtain (at cost to themselves) a blood draw for hs-CRP, Lipids, Particle size, Insulin, A1C, CMP and CBC at most a month prior to the start of the study. This blood draw was completed by different local laboratories in the Tampa Bay area. Weight and body composition were tracked using the Tanita MC-780U Multi Frequency Segmental Bio impedance Body Composition Analyzer (**15**). This analyzer works by passing an imperceptible current through the subject’s hands and feet. As the current flows through the subject it is impeded based on the makeup of the body. Tissues with large amounts of fluids/electrolytes, such as blood, have high conductivity. Fat and bone cause a reduction in signal speed. For the purposes of this experiment the following outputs were tracked: weight, body mass index (BMI), body fat percentage, body fat mass, fat free mass, visceral fat rating, body water percentage, body water mass, muscle mass, and bone mass. Throughout the course of this 2-month study subjects were weighed a total of three times: Once before the experiment began, once at the halfway mark of the study (1 month) and once at the conclusion of the study.

An FDA approved WAVi P300 evoked response device was used in conjunction with both a Mini-Mental State Examination (MMSE) and a Hamilton Anxiety Rating Scale (HAM-A) in order to track cognitive scoring for each subject throughout the course of this experiment. (**16**). The MMSE is an 11 question, 30-point test that is used extensively in clinical and research settings to test for cognitive impairments such as dementia and Alzheimer’s. (**17**) (**18**) Scoring a 30 represents full cognitive awareness while scoring a 0 represents lack thereof (**19**). The HAM-A is a 14 question, 56-point test that is used to measure the severity of anxiety symptoms. If an individual scores less than a 17 on the test, this is indicative of low levels of anxiety. A score of 18-24 represents mild to moderate anxiety where a score over 25 represents moderate to severe anxiety levels. Mental acuity is further measured through use of a series of timed tests.

The P300 test is used as a way to measure subconscious auditory reaction time. Subjects are asked to respond as quickly as possible to a high-pitched tone (**20**). Subjects were also asked to undergo two separate Trail Making Tests (A and B). These tests were employed because they are widely regarded as reliable methods for assessing both psychomotor and visual skills (**21**). The “flanker test” was also administered which is used to measure the efficiency with which the brain can suppress responses that are inappropriate in a particular context (**22**). The scores associated with these tests represent the amount of time required to complete each task. Generally, the faster the response, the more mentally acute the individual. The WAVi Desktop Report is also capable of recording the functional connectivity between the cortical regions in the brain, commonly known as coherence. Using values from all of these test criteria, researchers were able to reliably assess the mental health of each of their subjects, tracking any changes from start to finish.

After acquiring all of the necessary baseline values, subjects were randomly divided into two 30-person subgroups, each group receiving a month’s supply of differing concentrations of

BHB/MCT powder. Subjects were blinded as to what mixture they would be receiving. Group 254 was given supplements with a 20:80 ratio of BHB's to MCT's. Group 255 was given supplements that had an 80:20 ratio of BHB's to MCT's. By comparing the results of both of these treatment options, researchers were able to determine which supplement garnered the most benefit with regard to both weight and mental health.

After receiving their jar of supplements, subjects were instructed to take one scoop twice daily: Once in the morning and once in the evening. Subjects were also instructed to keep a weekly food diary listing their general eating habits. This was done to ensure some form of standardization with regard to diet. If subjects ate well beyond their means, then they would be subject to invalidation from the remaining portion of the study. Additionally, subjects were provided with a ketone meter that they were to use every other day, reporting their blood ketone levels to the study coordinator at least three days a week (Monday, Wednesday and Friday).

After 4 weeks subjects were instructed to come back in to the office to have their weight and BMI tracked and were provided their second months' supply of exogenous ketone supplements. This schedule continued for another 4 weeks at which point the subjects were asked to come back in to the office in order to complete their final series of tests including the bioimpedance scale and WAVi EEG analysis. The conclusion of these tests marked the end of this study.

Results:

Initial enrollment began with 57 recruited subjects split into two blinded groups however, some participants were unable to complete the entire study. At experiment end there was a total of 43 remaining participants. Of those 14 subjects who did not complete the study, 6 reported stomach issues, 3 chose to forego the remainder of the study via omission of contact, 1 chose to forego the remaining portion of the study due to anxiety issues, 1 was out of town throughout the scheduled times of the end date appointments, 1 chose to forego the remainder of the study due to the death of an immediate relative, 1 could not make their end date appointment as they were suffering from the flu and 1 could not make their appointment as a result of car problems.

The entire study population is summarized in Table 1 below, but the following is a highlight of the significant or relevant statistics. A comparison between statistical averages for men and women suggests that this product will provide the same benefit regardless of gender. The subjects lost an average 2.41 pounds which is very statistically significant ($p= 0.0078$). The subjects also had an average reduction of 0.42 points in their BMI rating which is very statistically significant ($p= 0.0099$). Additionally, the subjects lost an average of 1.51 pounds of body fat mass which is statistically significant ($p= 0.024$). The subjects also had an average reduction of 0.27 in their visceral fat rating which is very statistically significant ($p= 0.0058$). There was an average reduction of 2.64 points on the Hamilton Anxiety Exam score which is statistically significant ($p= 0.025$). There was an average reduction in the subject's physical reaction time of 29.77milliseconds which is very statistically significant ($p= 0.00031$). Likewise, there was an average reduction in the subject's triglyceride levels of 30.63 points which is very statistically significant ($p= 0.0069$). To see the statistically insignificant measurements that were captured for the overall population, consult Table 1. Not only that, subjects were asked to report their fasting blood ketone levels to researchers 3 times weekly. Findings show that average blood ketone levels did not change appreciably from the start of the study to its conclusion.

The individual breakdown for subject pool 254 is summarized in Table 2 below but the following is a highlight of the significant or relevant statistics for this individual group. These subjects lost and average of 1.99 pounds which is statistically significant (p= 0.038). They also had and average reduction of 0.33 points in their BMI rating which is statistically significant (p= 0.049). Additionally, there was an average reduction in their P300 score by 71.56 milliseconds which is statistically significant (p= 0.048). Finally, subject pool 254 had an average increase in their LP PLA2 scores of 7 points which is very statistically significant (p= 0.0054). To see the statistically insignificant measurements that were captured for group 254, consult Table 2.

The individual breakdown for subject pool 255 is summarized in Table 3 below but the following is a highlight of the significant or relevant statistics for this individual group. These subjects lost an average of 2.53 pounds of body fat mass which is statistically significant (p= 0.023). They also had an average reduction of 0.41 points in their visceral fat rating which is very statistically significant (p= 0.014). Additionally, there was an average reduction of 3.65 points in their HAM-A scores which statistically significant (p= 0.035). There was also an average reduction in their physical reaction time of 39.09 milliseconds which is very statistically significant (p= 0.00035). Finally, subject pool 255 had an average reduction of 39.6 points in their triglyceride levels which is statistically significant (p=0.033). To see the statistically insignificant measurements that were captured for group 255, consult Table 3.

With regard to the delta between the different groups physical benefits: Subjects in group “254” averaged weight loss at 1.99 pounds compared to the “255” grouping who averaged weight loss at 2.91 pounds. Subjects in group “254” averaged a 0.33 point reduction in their BMI scores compared to the “255” grouping who averaged a 0.52 point reduction. Subjects in group “254” averaged a 0.045% drop in their body fat percentage compared to the “255” grouping who averaged a 0.95% drop. Subjects in group “254” averaged a 0.64 pound reduction in their body fat mass compared to the “255” grouping who averaged a 2.53 pound reduction. Subjects in group “254” averaged a 0.15 point reduction in their visceral fat scores compared to the “255” grouping who averaged a 0.41 point reduction. Subjects in group “254” averaged a 19.44 point reduction in their triglyceride levels compared to the “255” grouping who averaged a 39.6 point drop (See Tables 2 & 3).

Table 1: Represents the averages/paired t-test p-values for each piece of data for the entire study population.

Average Change From Start to Finish (Total)		
	Average	p-value
Weight	-2.410810811	0.0078399
BMI	-0.4117647	0.009935
Body Fat %	-0.462162	0.1608655
Body Fat Mass	-1.508108	0.023838
Fat Free Mass	-0.41764	0.568178
Visceral Fat Rating	-0.27027	0.0057814
Body Water %	0.33515	0.170006
Body Water Mass	-0.6324324	0.245119
Extracellular Water Mass	-0.2588235	0.2000613
Intracellular Water Mass	0.0117647	0.973487
Muscle Mass	-0.3588235	0.604168
Bone Mass	0.02941176	0.4920478
Basal Metabolic Rate	-9.088235	0.306414
Daily Caloric Intake	-20.35294	0.1647908
Phase Angle	-0.12352	0.11092
Mini Mental	-0.219512	0.9448008
Hamilton Anxiety	-2.642857	0.02512
Physical Reaction Time	-29.76744186	0.000131028
Trail Making Test A	-4.360465	0.1202146
Trail Making Test B	-7.53488372	0.2863044
P300 Delay	-7.0909	0.842679
P300 Voltage	-0.383783	0.6351253
CZ eyes Closed	0.6	0.233123
F3/F4 eyes Closed	0.0190476	0.8924022
LDL-C	-1.07407407	0.743997677
HDL-C	2	0.3377528515
CHOL/HDLC Ratio	-0.25	0.1817593551
Triglycerides	-30.62962963	0.006859283406
Small LDL	11.17391304	0.8709186328
Hemoglobin A1C	0.01034482759	0.8119732856
CRP	0.61	0.55241316
Insulin	1.628	0.5502879617
Lipoprotein	3.733333	0.35921394
LP PLA2	3.9285714	0.19085313

Table 2: Represents the averages/paired t-test p-values for each piece of data for subjects in "254" treatment option.

Average Change from Start to Finish (254)		
	Average	p-value
Weight	-1.99	0.0378436
BMI	-0.326315	0.0490822
Body Fat %	-0.045	0.91488
Body Fat Mass	-0.64	0.428595
Fat Free Mass	-0.8736842	0.317287
Visceral Fat Rating	-0.15	0.186411
Body Water %	0.055	0.86423
Body Water Mass	-0.97	0.1749978
Extracellular Water Mass	-0.305263	0.19932565
Intracellular Water Mass	-0.2842105	0.531259
Muscle Mass	-0.810526	0.3277825
Bone Mass	-0.0526315	0.287139
Basal Metabolic Rate	-12.63157	0.212715
Daily Caloric Intake	-20.73684	0.224258
Phase Angle	-0.0947368	0.199411
Mini Mental	-0.047619	0.925758
Hamilton Anxiety	-1.809523	0.298933
Physical Reaction Time	-20.8636	0.0618354
Trail Making Test A	-4.954545	0.274585
Trail Making Test B	4	0.64974
P300 Delay	-71.55556	0.047806
P300 Voltage	0.38333	0.659433
CZ eyes Closed	1.063636	0.17351
F3/F4 eyes Closed	0.123809	0.497107
LDL-C	4.83333	0.1143558813
HDL-C	-0.166667	0.9491671684
CHOL/HDLC Ratio	-0.0666667	0.7349927333
Triglycerides	-19.44444	0.1039721264
Small LDL	60.5	0.5242120763
Hemoglobin A1C	0.01578947368	0.7719902006
CRP	-0.2988889	0.463703269
Insulin	3.18125	0.4575337078
Lipoprotein	1.090909091	0.7767874618
LP PLA2	7	0.005352616366

Table 3: Represents the averages/paired t-test p-values for each piece of data for subjects in “255” treatment option.

Average Change from Start to Finish (255)		
	Average	p-value
Weight	-2.90588	0.08191097
BMI	-0.52	0.0883492
Body Fat %	-0.9529411	0.0702406
Body Fat Mass	-2.529411	0.0226132
Fat Free Mass	0.16	0.9007202
Visceral Fat Rating	-0.411764	0.0143626
Body Water %	0.664705	0.080896
Body Water Mass	-0.235294	0.783165
Extracellular Water Mass	-0.2	0.578189
Intracellular Water Mass	0.3866667	0.5045409
Muscle Mass	0.213333	0.860073
Bone Mass	0	1
Basal Metabolic Rate	-4.6	0.775647
Daily Caloric Intake	-19.86667	0.450323
Phase Angle	-0.16	0.298746
Mini Mental	-0.4	1
Hamilton Anxiety	-3.65	0.034606
Physical Reaction Time	-39.0952381	0.0003548244
Trail Making Test A	-4.761904	0.286671
Trail Making Test B	-19.61904	0.07871122
P300 Delay	37.53846	0.495278
P300 Voltage	-1.110526	0.41747
CZ eyes Closed	0.1142857	0.859737
F3/F4 eyes Closed	-0.085714	0.6972316
LDL-C	-12.8888889	0.07962633233
HDL-C	6.33333	0.06981897696
CHOL/HDLC Ratio	-0.61666667	0.1432006491
Triglycerides	-39.6	0.03266803076
Small LDL	-84.375	0.1332269001
Homoglobin A1C	0	1
CRP	2.246	0.4371711154
Insulin	-1.133333	0.203653919
Lipoprotein	11	0.3872666435
LP PLA2	-7.33333	0.5272914531

Discussion:

The subjects were closely monitored from start to finish. A food regimen was detailed and recommended as to encourage consistency. Subjects were required to submit a food/exercise diary to investigators at least three times a week. Subjects were also told that if it was noticed that they were eating beyond the recommended caloric intake, they would be subject to invalidation. These actions were found to encourage standardization throughout the study.

Mental Acuity was tested using several different modes of timed trials. It is important to understand the various factors that affect reaction time. Welford et al. (**23**) published a paper in the 1980's which concluded that reaction time is fastest with an intermediate level of arousal however, reaction time deteriorates when the subject is either too relaxed or too tense. While efforts were made to construct the same testing environment during pre/post testing, some patient appointments were scheduled at different times throughout the day. The authors acknowledge this timing may have minimally affected overall arousal.

Macdonald et al. (**24**) established a trend which states that the higher a subject's reaction time variability, the slower their overall reaction time. If it was found that the difference between the averaged standard deviations pre and post experimentally was negligible this would suggest that the subjects were not practiced coming into their second round of testing. Based on the collected data, pre experiment standard deviation averages for physical reaction time averaged 63.86 milliseconds compared to the post experiment average of 60.47 milliseconds. A conclusion can be drawn stating that the decreases in overall reaction time post experimentally were brought on in part by the ketone supplements that subjects were ingesting.

The data suggests that those who took both types of ketone/MCT supplements experienced both mental and dietary benefits. With regard to the dietary benefits: Shared averages between both treatment options recorded an average weight loss of 2.41 pounds for 43 subjects. Of the averaged 2.41 pounds lost 1.50 pounds was lost as fat (see table 1). A comparison of average weight/fat loss not only indicates there was statistically compelling weight loss as a result of the study, but a significant amount of this weight was lost as fat. These observations can be explained by the structure of the diet that subjects were adhering too. By rejecting carbs, the body burns stored fats as an alternative, leading to a reduction in overall fat content.

Visceral Fat can be described as the fat that is stored within the abdominal cavity, surrounding several of the important internal organs such as the liver, pancreas and intestines. Carrying a high amount of visceral fat is known to be associated with insulin resistance, translating to glucose intolerance/type 2 diabetes (**25**). Based on the scale that was used for this study, visceral fat scores can range from 1 to 59 (**25**). There was an average reduction of 0.27 points in visceral fat scores for 43 subjects. This evidence suggests that the supplied ketone/MCT supplements the subjects ingested were responsible, in part, for the average reduction in visceral fat scores seen in table 1.

Because triglycerides are the form in which most fat exists in the body, this statistic is strongly correlated with coronary artery disease (**26**). By the end of this experiment subjects recorded an average drop in their triglyceride levels that amounted to 30.63 points. The data also suggests that the dietary ketone supplements were responsible for the more than 30-point drop that is seen from the start of this study to its finish.

With regard to overall mental acuity benefits for both compounds: At the start of this study subjects reported HAM-A score of 8.31. By the end of this study subjects reported an average anxiety score of 5.67. The 2.64 point reduction between pre and post averages appear to have been stimulated by the dietary ketone supplement that subjects were ingesting. Physical reaction time is another indicator of mental acuity. At study start the subjects' in both groups had an average physical reaction time of 385.93 milliseconds and averaged 256.12 milliseconds at the end. The 29.77 millisecond reduction in physical reaction time appears to have been stimulated by the supplements alone.

Based on the collected averages and corresponding p-values, the data suggests the supplement marked "255" showed the greatest benefit with regard to both physical and mental health compared to supplement "254". With regard to the delta between each of the groups mental benefits: Subjects in group "254" averaged a 1.809523 point reduction in their HAM-A scores compared to the "255" grouping who averaged a 3.65 point drop. Subjects in group "254" averaged a 20.8636 millisecond improvement in their physical reaction time compared to the "255" grouping who averaged a 39.10 millisecond improvement.

A full blood panel was drawn and the results were not statistically different save the following results: LDL-C is a type of lipoprotein that carries cholesterol in the blood. LDL-C is considered undesirable and is often called "bad" cholesterol as it deposits excess cholesterol into blood vessel walls, contributing to the hardening of arteries and heart disease. For this reason, it is desirable that this value be kept under 100 mg/dL. Subjects in group "254" averaged a 4.83 point gain in their LDL-C scores compared to the "255 grouping who averaged a 12.89 point drop. Based on the evidence, supplement "255" is more beneficial than supplement "254" at regulating LDL-C scores within the nationally recommended range. HDL-C is a type of lipoprotein that carries cholesterol in the blood. HDL-C is considered beneficial because it removes excess cholesterol from tissues, carrying it to the liver for disposal. For this reason, it is desirable for these values to be kept up over 60 mg/dL. Subjects in group "254" averaged a 0.07 point loss in HDL-C scores compared to the "255" grouping who averaged a 6.33 point improvement. The data suggests, supplement "255" is more beneficial than supplement "254" at regulating HDL-C scores within the nationally recommended range.

Conclusion

Post experiment averages for Weight, BMI, Body Fat Mass, Visceral Fat, Hamilton Anxiety, Physical Reaction Time and Triglycerides displayed statistically significant improvement among all of the subjects that participated throughout the course of this experiment. Undergoing a transformation from high levels of glucose to a more fuel-efficient energy source like that of BHB creates an environment that promotes increased metabolism. This is the reason why there is observable average weight loss as a result of this dietary supplement. Once acclimated to this diet, the body turns to and relies on fat as a fuel source. When these fats are ingested, they help facilitate the production of lean muscle. Any excess fat that isn't immediately utilized for muscle promotion is simply repurposed as a convenient fuel source. Mental acuity is affected as such: As a person ages their mental health takes a gradual decline as their brain is rendered unable to metabolize glucose at the same rate that it once could. In fact, a 2018 study worked to compare glucose uptake in the frontal cortex of healthy seniors and healthy young adults. Findings show that healthy seniors on average had a 14% reduction in glucose uptake when compared to healthy young adults (**27**). Not only that, individuals who are stricken with alzheimer's suffer from even lower percentages of glucose uptake. Ketones are also able to cross the blood-brain barrier. The data suggests that the differences between baseline/post experiment scoring is the result of this added fuel source,

providing energy to the brain (via the introduction of BHB) that it would be unable to accrue otherwise. Based on the results of this study authors believe that the benefits that result from taking this supplement in conjunction with a low carb diet are similar, if not the same, to the benefits that result from being in full ketosis. The only difference being: During natural ketosis the human body is producing ketone variants endogenously whereas supplement derived ketosis is brought on in part by the supplements that are provided externally.

After comparing the results for both forms of supplements (254 and 255) it can be concluded that the supplement marked “255” is more effective at promoting physical/mental acuity when compared to its counterpart. By introducing a higher proportion of BHB into the body, it is more likely that this ketone derivative will successfully cross the blood-brain barrier, making up for the shortcoming in brain activity that results from reductions in overall glucose metabolism. Since MCT is a precursor that can be broken down in the liver to produce BHB derivatives, there is no guarantee that these precursor molecules will convert into BHB exclusively. It is likely this is the reason that subjects reap the most benefit when consuming BHB’s that have been synthesized from outside the body.

It should be noted that the high concentration of ketone variants within these supplements were found to be unsuitable for 10% of the population who participated in this study resulting in 6 individuals discontinuing the remainder of the study because of reported stomach pains/issues. Of the six who bowed out of the study, one was from group 254 and five were from group 255. While this is a known side effect of ketones, care should be taken to introduce these supplements slowly.

References:

1 Pinckaers PJM, Churchward-Venne TA, Bailey D, et al. Ketone bodies and exercise performance: the next magic bullet or merely hype? Sports Med. 2017;47(3): 383-391.
doi: 10.1007/s40279-016-0577-y. PubMed PMID: 27430501

2 Masood W, Uppaluri KR. Ketogenic Diet. StatPearls Publishing. 2019; Jan.
PubMed PMID: 29763005

3 LaManna JC, Salem N, Puchowicz M, et al. Ketones suppress brain glucose consumption. Adv Exp Med Biol. 2009;645: 301-306.
doi: 10.1007/978-0-387-85998-9_45. PubMed PMID: 19227486

4 Dashti HM, Matthew TC, Hussein T, et al. Long-term effects of a ketogenic diet in obese patients. Exp Clin Cardiol. 2004;9(3): 200-205. PubMed PMID: 19641727

5 Manninen AH, Very-low-carbohydrate diets and preservation of muscle mass. Nutr Metab. 2006;3: 9. doi: 10.1186/1743-7075-3-9. PubMed PMID: 16448570

6 Ota M, Matsuo J, Hattori K, et al. Effect of a ketogenic meal on cognitive function in elderly adults: potential for cognitive enhancement. Psychopharmacology. 2016; Oct;233(21-22): 3797-3802. doi: 10.1007/s00213-016-4414-7. PubMed PMID: 27568199

7 Ari C, Kovacs Z, Juhasz G, et al. Exogenous ketone supplements reduce anxiety-related behavior in sprague-dawley and wistar albino glaxo/rijswijk rats. Front Mol Neurosci. 2016;9: 137. doi: 10.3389/fnmol.2016.00137. PubMed PMID: 2799529

8 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5858534/ - The use of nutritional supplements to induce ketosis and reduce symptoms associated with keto-induction: a narrative review

9 Kesi SL, Poff AM, Ward NP, et al. Effects of exogenous ketone supplementation on blood ketone, glucose, triglyceride, and lipoprotein levels in sprague-dawley rats. Nutr Metab. 2016; Feb;13: 9. doi: [10.1186/s12986-016-0069-y. PubMed PMID: 26855664

10 Newman JC, Verdin E. B-hydroxybutyrate: Much more than a metabolite. Diabetes Res Clin Pract. 2014; Nov;106(2): 173-181. doi: 10.1016/j.diabres.2014.08.009. PubMed PMID: 25193333

11 Feingold KR, Grunfeld C. Introduction to lipids and lipoproteins. Endotext. 2018; Feb. PubMed PMID: 26247089

12 Wang Y, Liu Z, Han Y, et al. Medium chain triglycerides enhance exercise endurance through the increased mitochondrial biogenesis and metabolism. PLoS One. 2018; Feb;13(2): e0191182. doi: 10.1371/journal.pone.0191182. PubMed PMID: 29420554

13 St-Onge MP, Jones PJH. Physiological effects of medium-chain triglycerides: potential agents in the prevention of obesity. J. Nutr. 2002; Mar;132(3): 329-332.
doi: https://doi.org/10.1093/jn/132.3.329.

14 Suresh KP, Chandrashekara S. Sample size estimation and power analysis for clinical research studies. J Hum Reprod Sci. 2012; Jan-Apr;5(1): 7-13.
doi: 10.4103/0974-1208.97779. PubMed PMID: 22870008

15 Verney J, Schwartz C, Amiche S, et al. Comparisons of a multi-frequency bioelectrical impedance analysis to the dual-energy X-ray absorptiometry scan in healthy young adults depending on their physical activity level. J Hum Kinet. 2015; Sep;(47): 73-80. doi: 10.1515/hukin-2015-0063. PubMed PMID: 26557191

16 Sur S, Sinha VK. Event-related potential: An overview. Ind Psychiatry J. 2009; Jan;18(1): 70-73. doi: 10.4103/0972-6748.57865. PubMed PMID: 21234168

17 O'Bryant SE, Humphreys JD, Smith GE, et al. Detecting dementia with the mini-mental state examination in highly educated individuals. Arch Neurol. 2008;65(7): 963-967. doi: 10.1001/archneur.65.7.963.

18 Pradier C, Sakarovitch C, Le Duff F, et al. The mini mental state examination at the time of alzheimer's disease and related disorders diagnosis, according to age, education, gender and place of residence: A cross-sectional study among the french national alzheimer database. PLoS ONE 9(8): e103630.
doi: 10.1371/journal.pone.0103630

19 Tombaugh TN, Mcintyre NJ. The mini-mental state examination: a comprehensive review. J am Geriatr Soc. 1992; Sep;40(9): 922-935. PubMed PMID: 1512391

20 Medvidovic S, Titlic M, Maras-Simunic M. P300 evoked potential in patients with mild cognitive impairment. Acta Inform Med. 2013; Jun;21(2): 89-92. doi: 10.5455/aim.2013.21.89-92. PubMed PMID: 24039332

21 Salthouse TA. What cognitive abilities are involved in trail-making performance? Intelligence. 2011; Jul;39(4): 222-232. doi: 10.1016/j.intell.2011.03.001.
PubMed PMID: 21789028

22 Zhu DC, Zacks RT, Slade JM. Brain activation during interference resolution in young and older adults: an fMRI study. Neuroimage. 2010; Apr;50(20): 810-817.
doi: 10.1016/j.neuroimage.2009.12.087. PubMed PMID: 20045067

23 Brebner, J. T. and A. T. Welford. 1980. Introduction: an historical background sketch. In A. T. Welford (Ed.), Reaction Times. Academic Press, New York, pp. 1-23.

24 Hultsch, D. F., S. W. MacDonald and R. A. Dixon. 2002. Variability in reaction time performance of younger and older adults. The Journals of Gerontology, Series B 57(2): 101.

25 Klein S. The case of visceral fat: argument for the defense. J Clin Invest. 2004; Jun;113(11): 1530-1532. doi: 10.1172/JCI200422028. PubMed PMID: 15173878

26 Liu J, Zeng F, Liu Z, et al. Effects of blood triglycerides on cardiovascular and all-cause mortality: a systematic review and meta-analysis of 61 prospective studies. Lipids Health Dis. 2013; Oct;1(12): 159. doi: 10.1186/1476-511X-12-159.

27 Cunnane SC, Nugent S, Roy M, et al. Brain fuel metabolism, aging and alzheimer's disease. Nutrition. 2011; Jan;27(1): 3-20. doi: 10.1016/j.nut.2010.07.021.
PubMed PMID: 21035308

28 Paoli A, Rubini A, Volek JS, et al. Beyond weight loss: a review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. Eur J Clin Nutr. 2013; Aug;67(8): 789-796. doi: 10.1038/ejcn.2013.116. PubMed PMID: 23801097

29 Murray AJ, Knight NS, Cole MA, et al. Novel ketone diet enhances physical and cognitive performance. FASEB J. 2016; Dec;30(12): 4021-4032. doi: 10.1096/fj.201600773R. PubMed PMID: 27528626

30 Stubbs BJ, Cox PJ, Evans RD, et al. On the metabolism of exogenous ketones in humans. Front Physiol. 2017;8: 848. doi: 10.3389/fphys.2017.00848. PubMed PMID: 29163194

31 Tombaugh TN, Trail making test A and B: normative data stratified by age and education. Arch Clin Neuropsychol. 2004; Mar;19(2): 203-214.
doi: 10.1016/S0887-6177(03)00039-8. PubMed PMID: 15010086

32 Clark DB,Donovan JE. Reliability and validity of the hamilton anxiety rating scale in an adolescent sample. J Am Acad Child Adolesc Psychiatry. 1994; Apr;33(3): 354-360.
doi: 10.1097/00004583-199403000-00009. PubMed PMID: 8169180