KETONE ESTERS: WHAT, WHY AND HOW?

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Awareness of the numerous health benefits of nutritional ketosis has significantly increased in recent years. More and more people are turning to ketogenic diets and/or exogenous ketone foods (ketones identical to those made in the body but made outside of the body) to achieve their goals. The most powerful exogenous ketone supplement on the market is the ketone ester developed by Richard Veech, MD, D Phil, at the NIH and studied by Kieran Clarke, PhD and her associates at Oxford in elite athletes. Here we will talk about what ketones are, why ketone esters have come along, and how to use ketone esters.

Precautions and caveats

The ketone ester offers substantial benefits, but there are several potential side effects that many people and their physicians may not be aware of when they first begin using it. For example, taking a very large dose (50 grams or more) or taking larger doses too close together (more often than every 4-6 hours) could put a person into ketoacidosis (different from diabetic ketoacidosis) or result in hypoglycemia (low blood sugar). The information presented here should not be construed as medical advice from me or take the place of advice from your own physician. It is simply offered as guidance to help the patient and doctor decide whether to try the ketone ester, and, if they decide to go forward, how to avoid some of the known pitfalls. My husband Steve, who had early onset Alzheimer's disease, took the Veech ketone ester in a pilot study of one person, and we now know that he may have been taking much higher doses than necessary, but he did experience reversal of many symptoms that was sustained for about twenty months, and without any apparent side effects. He ultimately lost his battle with Alzheimer's disease and passed away in early 2016 about 2 ½ years after having a prolonged seizure with a head injury. Seizures are common in the later stages of Alzheimer's, and his seizure was not related to taking the ketone ester.

Safety Testing

A 28-day study published in 2019 reported safety and tolerability for healthy adults of all ages with very few minor side effects, only six reported events in over 2000 doses. Reference: "Safety and Tolerability of sustained exogenous ketosis using ketone monoester drinks for 28 days in healthy people." Soto-Mota, Clarke, et al. *Regulatory Toxicology and Pharmacology* (October 2019).

I recommend consulting a physician for approval and monitoring before using ketone ester for any medical condition or health benefit. Its use is not advised for pregnant or lactating women and children, except in rare cases where children with specific conditions may benefit, but only under medical supervision.

What are ketones and how do they work?

Ketones are an alternative fuel for the brain and other organs, except the liver where they are made. Ketones are produced naturally from stored body fat during periods of fasting and starvation. Glucose stores in the body (as glycogen) are relatively low and are used up in a matter of one or two days of fasting. At that point, beginning after as little as 10 to 14 hours without food, we begin to break down fat into fatty acids which can be used by most organs of the body. These fatty acids are relatively large molecules and do not easily cross into the brain. The brain is an active, energy-hungry organ, representing about 2-3% of our body

weight but using 20 to 25% of the calories we consume. Without another source of fuel, the brain would become damaged and eventually die. Fortunately, some of the fatty acids from the breakdown of fat are converted in the liver to ketones, which are much smaller molecules and easily cross the blood brain barrier where they enter the same metabolic pathway as glucose to generate ATP (adenosine triphosphate), the energy molecule that allows our cells to carry out their many functions.

Our natural ketones, mainly betahydroxybutyrate (BHB) and acetoacetate (acetone is mostly exhaled), also enter other metabolic pathways to reduce inflammation, reduce damage from harmful substances, and help repair DNA. Ketones also tend to suppress appetite and can promote fat burning if used as an exogenous food and especially when this is combined with an appropriate reduced calorie, higher-fat, lower-carb weight loss diet. When we burn more calories than we consume, ketones can help preserve muscle during weight loss when we use fat as the primary fuel rather than glucose which can be derived from breaking down muscle proteins.

The strictest form of the ketogenic diet, which is about 80-90% fat, adequate protein to preserve muscle, and minimal carbohydrates (sugars), has been used successfully for nearly 100 years to control epilepsy that does not respond to medications. Modifications of the diet, such as using half or more of the fat as MCT (medium-chain triglyceride) oil and using low glycemic index foods to control fluctuations in blood sugar, have made it possible to eat more carbohydrates while maintaining elevated ketone levels.

A number of small to medium-size studies completed over the past ten to fifteen years have shown that increasing ketone levels through consistently eating a high-fat, very low carbohydrate diet and/or by taking medium-chain triglycerides, which are partly converted to ketones, appear to be helpful in reducing symptoms of neurodegenerative diseases such as Alzheimer's, Parkinson's, and ALS and in certain rare enzyme deficiencies. The belief is that improvements occur by providing ketones as alternative fuel to the brain but may also work by reducing ongoing damage from reactive oxygen species and from inflammation.

Increasing ketone levels by using exogenous ketone foods in combination with a higher fat, lower carbohydrate diet can also help control type 2 diabetes, allowing reduction or even elimination of oral medications and insulin. Other conditions that are characterized by inflammation and damage from reactive oxygen species could benefit from mild to moderate nutritional ketosis as well. Healthy people using the ketogenic diet or ketogenic foods, such as MCT oil and exogenous ketone foods often report increased mental clarity and focus, improved memory, better sleep, better mood, less anxiety, and more energy.

What are ketone esters and why were they developed?

Taking the ketones betahydroxybutyrate or acetoacetate alone as acids without adequate buffers could be damaging to the stomach, so attaching the ketones to an alcohol to form an ester makes it feasible for ketones to be taken orally. Several different types of ketone esters have been in development and tested in animal research labs for many years. The first of these ketone esters became available to the public at the beginning of 2018 and in 2025 is available from **KetoneAid** (https://ketoneaid.com/MTN) and **TDeltaS** https://www.tdeltas.global). This is the Dr. Veech ester, developed at the NIH and tested at Oxford by Dr. Clarke. This is a combination of the non-racemic D-betahydroxybutyrate and D-1,3 butanediol. D-betahydroxybutyrate as an ester molecule and is the natural circulating form of the ketone betahydroxybutyrate and is more bioavailable than the L-form which is found mainly in mitochondria. Butanediol is broken down after digestion to produce more betahydroxybutyrate, thus providing a relatively sustained ketone level. This ketone ester results in "instant ketosis" with the level peaking at about 30-40 minutes after taking the ester and gradually coming back down to the baseline level over several hours.

Tecton Ketones (https://TectonKetones.com) is another ketone ester on the market that has no 1,3-butanediol but rather combines betahydroxybutyrate with glycerol, which is also the backbone of fatty acid

triglycerides. The compound is lipolyzed (microencapsulated) which helps with the taste and improves absorption of the product. There are several options for flavor (berry, pina colada, peach, etc.) and several contain additional supplement for metabolic health. It is moderately priced compared to the Veech ketone esters.

Qitone (https://www.awin1.com/cread.php?awinmid=117673&awinaffid=2330827) is a ketone ester made from the medium-chain fatty acid called C8 (caprylic acid) and butanediol. The product comes as a flavorless powder that can be added to water or any cold or hot liquid, such as coffee or tea to make a creamy drink. The product also costs considerably less than the ketone ester.

What other ketone supplements are available? What are the advantages and disadvantages? What problems can occur and how can these problems be avoided

Other types of ketone supplements are now available that can also increase ketones to moderate levels with the recommended amount of 10 to 12 grams of BHB. **Kenetik** (https://drinkkenetik.com/discount/MTN15) is a mixture of betahydroxybutyrate and butanediol rather than a compound of these two substances. The product tastes better than the ester form (citrus flavors) and, due to the lower cost of making the product it is less expensive.

There are more than 90 studies currently in progress of the ketone ester for cognition and for a variety of medical conditions such as diabetes, metabolic syndrome, neurological and psychiatric disorders, and cancers. To date, most of the completed studies of the ketone ester have been in athletes, so caution should be exercised by anyone who plans to use ketone esters for any purpose other than athletic performance. Athletes should also be aware that stacking two or more doses within a few hours at the volume recommended on the package (25 grams per dose or higher) could result in significant ketoacidosis or other side effects, such as serious hypoglycemia. The ketone level tends to come down so the effects of **ketoacidosis** would likely be temporary. This type of ketoacidosis is not the same as diabetic ketoacidosis, which usually occurs in individuals with type 1 and sometimes type 2 diabetes who cannot produce insulin and have very elevated blood glucose levels. Ketoacidosis is unlikely with **ketone salts**, another type of ketone supplement which are much more limited in how high the ketone level can go and did not produce metabolic acidosis in a study of elite athletes comparing ketone ester to ketone salts at equivalent high doses.

The main advantage to taking a ketone ester versus a ketone salt (a ketone attached to a mineral to form a salt) is that the same amount of BHB will produce a ketone level about 20 to 30% higher with the ester and without the high sodium and sometimes high potassium content of the ketone salts. Excessive minerals such as sodium and potassium may be a problem for some people, such as those with high blood pressure, or people taking diuretics (water pills) or potassium supplements. Even though the ketone ester does not contain these minerals, studies by Dr. Clarke have shown temporary shifts in the levels of sodium and potassium after taking roughly 20 grams of the ester in athletes. An advantage of ketone salts over ketone esters is that they may help to avoid **an electrolyte imbalance** of minerals (sodium, potassium, calcium, and magnesium) that are potentially lost in the urine with release of fluids from the body in the early days to weeks of starting a ketogenic diet or adding ketone supplements. **Dehydration** can occur especially in the early days and weeks of taking the ketone ester or salts but also with a ketogenic diet alone due to loss of fluids from muscles, so it is very important to drink plenty of fluids.

Theoretically, blood pressure could increase or decrease from taking a ketone ester. People with **high blood pressure** should monitor their blood pressure closely.

Both the ketone salts and ketone ester tend to **lower blood glucose and insulin levels** significantly, but this appears to be more prominent with the ester. This could be a problem for people who are prone to

hypoglycemia or are diabetic and taking oral medications or insulin. The blood sugar should be monitored closely, and the patient and physician should work together to reduce these medications if indicated.

The **effect on gout** is a paradox with increasing ketones—at the beginning of a ketogenic diet or ketone supplement a gout flare-up could occur in people who are prone to gout, however, increasing ketone levels has anti-inflammatory results and studies show that it can reduce inflammation from gout as well. People with epilepsy who are on a strict ketogenic diet are often given a supplement of potassium citrate daily to prevent gout and kidney stones, another potential problem. The amount depends greatly on age, weight and what other medications and supplements a person may be taking, so it is advised to consult with your physician on this.

What kind of ketone levels can I expect?

The peak level obtained through taking ketone salts with 10 to 12 grams betahydroxybutyrate per serving is limited to an increase of about 0.5 to 1 mM/L and does not go much higher by adding a second serving later in the day; the peak level from taking a ketone ester increases with the amount of the dose and can easily increase by 4 or 5 mM/L or even higher with a dose of 25 grams, which is why ketoacidosis is possible (levels of $\geq$7 mM/L) if a very large dose (50 grams) is taken or two or more large doses (20 to 30 grams) are stacked too close together. Ketoacidosis could also occur in someone eating a strict ketogenic diet who already has high ketones levels (such as 4 to 6 mM/L) and takes a dose of the ketone ester. When we were trying to figure out how much ketone ester to give Steve, his betahydroxybutyrate levels reached 6 to 7 mM/L with doses of 35 and 50 grams, so we reduced his dose thereafter. Unlike untreated diabetic ketoacidosis, in most cases, the acidosis should be resolved within a few hours without any special treatment and increasing fluid intake could help speed it up. **If someone has significant symptoms related to high ketone levels, such as vomiting, confusion, shortness of breath, chest or abdominal pain, a trip to the emergency room is warranted.**

The studies performed by Clarke and her associates have shown that a dose equivalent to about 20 grams for a 154-pound person increases the ketone levels to an average of 2.4 mM/L but also results in mild metabolic acidosis that is not fully corrected within two hours. The dose of 30 grams of ketone ester, as sometimes recommended on the packaging for athletes, could easily increase the betahydroxybutyrate level to 4 or 5 mM/L or even higher, which may be desirable for improving athletic performance, but is likely much higher than the level that would be needed to see some improvement in people with a medical condition such as Alzheimer's or Parkinson's; studies with medium-chain triglyceride (MCT) oil show improvement in many people with much lower levels of 0.5 mM/L.

Should I monitor my ketone levels?

I recommend monitoring with a ketone meter and ketone strips (**Keto-mojo.com** has the least expensive strips at present) for anyone taking moderate to high doses (20 grams or more) of a ketone ester and for people taking lower doses who may want to experiment with dosing or adding ketone ester or ketone salts to a ketogenic diet.

What are some of the advantages and disadvantages of taking a ketone ester versus coconut/MCT oil?

The main advantage of taking the ketone ester over MCT or coconut oil, is that few people have reported diarrhea or other intestinal upset, which affects 20 to 25% of people taking MCT oil. However, certain fatty acids in MCT oil and coconut oil have special properties that may not be characteristic of ketone esters or salts. For example, lauric acid (C12:0), which is half the fat in coconut oil, has antimicrobial effects, killing many viruses, bacteria, yeasts, and other organisms—microbes have been implicated in numerous studies as possible causes of neurological conditions such as Alzheimer's. Lauric acid has also been shown to stimulate ketone production directly in cultures of astrocytes (brain cells that nourish other

brain cells), though this needs to be proven in living creatures. Capric acid (C10:0) has anticonvulsant effects and increases the numbers of mitochondria in cells (the mitochondria generate ATP). A recent study shows that MCTs act directly as fuel in the mitochondria of brain cells and are, therefore, also an alternative fuel for the brain.

Use of the ketone esters, ketone salts, coconut oil, and MCT oil do not need to be mutually exclusive. The supplements can be at different times, such as combining coconut or MCT oil with foods and taking the ketone ester or ketone salts in between, such as first thing in the morning an hour or so before eating or midway between meals. I have also noticed from testing myself that taking MCT/coconut oil at about the same time as ketone salts or ketone esters tends to keep the higher ketone level sustained for a couple hours longer, even if the MCT/coconut is eaten with food. There are no hard and fast rules on this yet. I suggest experimentation to see what works best for you.

How much ketone ester?

A serving of ketone ester with 2.5 to 5 grams one to three times per day could provide a peak betahydroxybutyrate level of 0.5 to 1.5 mM/L or a little higher; the dilution of the product differs between the two companies that sell the ketone ester, so check the label carefully to figure out the proper dose. This could be a good starting place for someone looking for health benefits or symptomatic improvement and should be taken only with their doctor's approval and close monitoring for those with medical conditions, people who are elderly and for children. If well-tolerated, possibly doubling this amount could be more effective, again with doctor's approval. I do not recommend even small doses of the ketone ester (or ketone salts) for women who are pregnant or breastfeeding.

At this time there are no human clinical trials reported of the ketone ester (or ketone salts) for people with Alzheimer's except for the **pilot study of my husband Steve** which was published as a case report in *Alzheimer's and Dementia (2015)*. It is unknown if the ketone ester will bring about improvement in such diseases, but there is sound scientific evidence that this may be possible. Anecdotal reports detail improvements in people with certain conditions taking just 5 grams once a day in the morning, but these do not carry the weight of a clinical trial as evidence. Many people report improved sleep after a low dose of ketone esters, but studies are not published yet.

A study in healthy adults demonstrated that the ketone ester provides greater stability in brain energy after an overnight fast compared to glucose (Mujica-Parodi, et al. in PNAS March 2020). The dose used in this study was equivalent to about 20-25 grams for an average adult.

There is considerably more about the ketogenic diet and using ketone esters and ketone salts alone and in combination in my book The Complete Book of Ketones: A Practical Guide to Ketogenic Diets and Ketone Supplements. My website is also a great source on everything keto: https://coconutketones.com.

Recap

• Ketones naturally occur in the body from breakdown of fat and serve as alternative fuels for the brain and most other organs during fasting and starvation.

• Ketone esters can rapidly increase ketones to levels that could benefit people with a variety of medical and neurological conditions—studies need to be done to prove benefit.

• There are several common effects from taking ketone esters to be aware of—low blood sugar, low insulin levels, changes in electrolyte levels such as sodium and potassium, and dehydration.

• Ketone esters are recognized as safe for use in endurance athletes. All others should consult with their physician before using so that the person can be monitored for side effects. Diabetics in particular should

monitor blood sugar levels closely and should work with their doctor to adjust insulin and other medications that lower blood sugar as needed. People with high blood pressure should monitor blood pressure closely.

• People prone to gout or kidney stones should consider taking a potassium citrate supplement in consultation with their doctor.

• Current ketone ester products suggest servings of 30 grams, but this may be much higher that needed to bring about improvement in someone with a condition such as Alzheimer's or Parkinson's. There are reports that doses as small as 5 grams of betahydroxybutyrate (10 ml of product) once or twice a day may show benefit.

• This should not be construed as medical advice from me (Dr. Mary Newport). My first concern is safety, recognizing that people will be tempted to use ketone esters despite lack of study results and without being aware of side effects that could be significant and even serious, especially at larger doses. I suggest people take this information to discuss with their physician.

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

By Mary T. Newport, MD –Available on Amazon: https://amzn.to/2AxBcLp

More info on everything keto and links to my other books and supplements at https://coconutketones.com