

KETONE ESTERS: WHAT, WHY, AND HOW?

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There has been growing awareness of the many health benefits of ketosis over the last few 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. One of the newest exogenous ketone foods 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.

There are several potential side effects, and I am concerned that many people will begin taking a ketone ester product without being aware of these side effects and may take too much, which could easily put a person into ketoacidosis (different from diabetic ketoacidosis) or result in hypoglycemia (low blood sugar). I offer this, not to take the place of advice from your own physician, but to provide information so that the person and their doctor will be aware of these potential side effects and how to monitor and possibly overcome side effects if the patient and doctor decide to go forward with trying this. None of the information in the article should be construed as medical advice from me. It is simply offered as guidance to help the patient and doctor make a decision to try the ketone ester or not, and, if they do, 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. He ultimately lost his battle with Alzheimer's disease and passed away in early 2016.

NOTE: Previously, the Veech ketone ester is recognized as a food by the FDA for use in endurance athletes for up to five days. A recent 28-day study published in 2019 reported safety and tolerability for healthy adults of all ages with very few minor side effects (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)

On that note, I recommend to everyone who wishes to use the ketone ester for a medical condition or for general health benefits to consult with their physician for approval and close monitoring. I do not recommend the ketone ester at all for pregnant or breastfeeding women or children with the exception that children with certain rare medical conditions could benefit but should only be used with their physician's approval and close monitoring.

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 come into play as fuel naturally 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% of our body weight but using 20 to 25% of the calories we consume. Without another source of fuel, the brain would suffer dire consequences in short order. 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 beta-hydroxybutyrate 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 is mostly 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 in a significant number of people 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 as a result of 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 possible 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 from two companies, but is currently only available in July 2021 from KetoneAid (<http://KetoneAid.com>) 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 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 40 to 60 minutes after taking the ester and gradually coming back down to the baseline level over several hours. A third product recently became available that gives similar good increases in ketone levels and is a mixture of betahydroxybutyrate and butanediol but not combined into one molecule as an ester. The product tastes better than the ester form and, due to the lower cost of making the product, it is less expensive—Kenetik (<https://drinkkenetik.com/discount/PURE%2520ENERGY?redirect=%2Fpages%2Fcognition>).

The ketone ester has been studied mainly in athletes, so caution should be exercised by anyone who is 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. This side effect is unlikely with ketone salts 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 large 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 betahydroxybutyrate 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 replenish the minerals (sodium, potassium, calcium, and magnesium) that are potentially lost in the urine with release of fluids from the body.

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 as a result of 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.

The peak level obtained through taking ketone salts with 5 to 8 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, which is why ketoacidosis is possible (levels of 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 also 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 resolve 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 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, where studies with medium-chain triglyceride (MCT) oil show improvement in many people with much lower levels of 0.5 mM/L.

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) and for people taking lower doses who may want to experiment with dosing or adding ketone ester or ketone salts to a ketogenic diet.

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 (half of 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 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 the brain.

Use of the ketone esters, ketone salts, coconut oil, and MCT oil do not need to be mutually exclusive. I suggest taking them 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. There are no hard and fast rules yet on this. I suggest experimentation to see what works best for each person.

How much?

A serving of ketone ester with 2.5 to 5 grams one to three times per day could provide a peak beta-hydroxybutyrate 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 medical conditions except for the one-person pilot study of my husband Steve mentioned above. 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 recent 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 size adult.

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 than 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 and 2 or 3 grams would be a good starting dose.
- 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.

Recent Books by Mary T. Newport, MD:

Clearly Keto for Healthy Brain Aging and Alzheimer's Prevention (November 29, 2022 – available for preorder). Amazon link: <https://amzn.to/3MS9SJe>

The Complete Book of Ketones: A Practical Guide to Ketogenic Diets and Ketone Supplements (2019) Amazon link: <https://amzn.to/2AxBcLp>

More information on everything keto at <https://coconutketones.com>