

EXOGENOUS KETONES

WHEN AND HOW
TO
SUPPLEMENT
WITH KETONES



ingredientologist

Exogenous Ketones Guide

The ketogenic diet is gaining popularity amongst those who wish to boost productivity, lose weight or improve overall health. As a result, we're seeing a tremendous spike in supplements intended to complement the ketogenic lifestyle and boost results. The most popular, by far, is exogenous ketones with many companies jumping on the bandwagon and new products being released frequently. So, what's the deal with exogenous ketones, and how do they really work?

Briefly, let's recap a little bit about the ketogenic diet.

Scientists discovered that the absence of carbohydrates in the diet, even in the presence of food consumption, triggered the production of ketones in the body. This led to a surge in the research surrounding a diet that induced ketosis - a Ketogenic Diet - with which you can alter your physiology and induce a state of 'nutritional ketosis', which is defined by having ketone levels in the range of 0.5 - 5.0mmol/L in your blood. This means that your body begins producing ketones from fat to be used for energy, instead of relying on glucose.

The restriction of carbohydrates is the primary cause that creates 3 necessary conditions in the body:

1. Blood glucose levels are reduced
2. Glycogen stores are depleted
3. Insulin levels are reduced

These conditions force the body to use an alternative fuel source to glucose: **fatty acids**.

→ Lowering glucose availability: in the blood, and that stored as glycogen, leads to fat (ketones) being used as fuel (because there is no longer glucose available)

→ With lowered carbohydrate intake and thus lowered blood glucose, insulin is low. The hormone insulin promotes fat storage and inhibits fat breakdown. When insulin is low, stored fat (triglycerides) can be broken down and converted to ketones to be used as fuel.

In summary, the reliance on fat as fuel is enhanced when blood glucose, glycogen stores and insulin levels are lowered. Fats are converted to ketones which are an alternative, yet cleaner and more efficient fuel source for the body.

- **Ketones are a more EFFICIENT fuel source:**

Fuel, either ketone or glucose, is broken down in the cell to produce the energy we need to live. The redox potential generated by ketones is greater than glucose. This basically means that there is more of the energy molecule, ATP, produced per ketone molecule consumed compared to a glucose molecule. We're getting more bang for our buck!

- **Ketones are a CLEANER fuel source:**

Mitochondria are like car engines - they don't always function at 100%. The generation of by-products, or reactive oxygen species (ROS), can occur in the mitochondria when we create energy, which can damage cell membranes, proteins and DNA. However, there is far less of this ROS production in the cell when ketones are burned, compared to glucose. They also increase levels of NADPH in the cell - NADPH is the basis of all antioxidants (like glutathione) in the body! So, we're getting a 1-2 punch here: reduced oxidative stress AND a boost in the oxidation defence mechanism!

This is particularly important for brain neurons. Most cells in your body are continuously being regenerated, but neurons are extremely long-lasting. Any oxidative damage occurring in your neurons can accumulate & make their mitochondria less efficient (producing even more free radicals!).

Your neurons are with you for life - you need to look after them! Feed them ketones, not glucose!

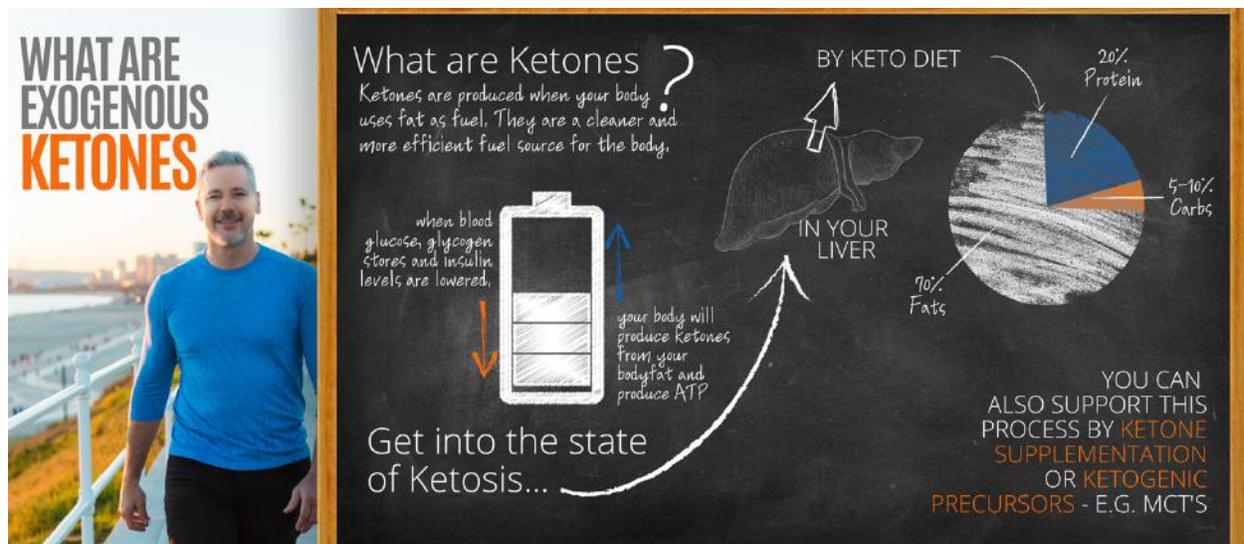
Achieving a state of ketosis (i.e. having elevated ketone levels of >0.5mM in the blood), can be achieved via 2 distinct ways, namely *endogenously* (which means "within the body") and *exogenously* (meaning "outside the body").

Endogenous ketosis: Ketones are produced by the liver naturally when on a very low carbohydrate diet (keto) or in a fasted state. This is due to a reduction in insulin, allowing free fatty acid release from fat stores, which are converted into ketone bodies.

Exogenous ketosis: Consuming ketones from an outside source, either directly via ketone supplementation, or indirectly through a ketogenic precursor, like MCT oil, that results in ketone production.

It is important to differentiate between *ketogenesis* and *ketosis*: those who elevate blood ketones exogenously are not ketogenic, but are in ketosis! Ketogenesis refers to a ketotic state that is accomplished by following a keto diet and/or fasting which causes your body to produce ketones naturally.

It is difficult to say, however, whether the state of ketosis (as induced by exogenous ketones) would have the same effects as a ketogenic state (induced by fasting and/or a ketogenic diet). Nevertheless, I am confident that when we understand exactly how ketones are working in the body, we can better decide on how to use them to support a ketogenic lifestyle.



Supporting A Ketogenic Lifestyle

The ketogenic diet can be a particularly restrictive diet for some, making it hard to adhere to for long periods of time. Fortunately, we can still benefit from ketones without prolonged fasting or being on a keto diet all the time by using exogenous ketone supplements. Generally speaking, they're marketed to help boost the effects of a ketogenic diet and/or provide many of the benefits of keto without restricting carbs.

Keep in mind, however, that it is still unknown as to whether being in a state of ketosis through consuming exogenous ketones has the same beneficial effects as being in a state of nutritional ketosis (producing ketones naturally/endogenously).

There are three types of endogenous ketone bodies:

- Beta-hydroxybutyrate (BHB)
- Acetoacetate (AcAc)
- Acetone

Most forms of exogenous ketones deliver BHB, which is the most prevalent ketone in the body when produced naturally. BHB can cross the blood brain barrier and enter the mitochondria via a specific transporter called a monocarboxylic transporter (MCT). As you become a better 'fat burner' you increase the amount of these MCTs in your cells, enabling you to be more efficient at burning ketones.

The years of ketogenic research have provided substantial evidence showing that the benefits of the diet are, in part, due to the *unique signaling properties* of the ketones themselves - in particular the ketone body beta-hydroxybutyrate. Although acetoacetate has also been shown to have more specific therapeutic benefits. This means that supplementing with ketones may be worth exploring.

Supplementing with ketones

As mentioned above, ketosis can be achieved either endogenously, or exogenously. Exogenous ketones are a quicker alternative to elevating blood ketone levels, and may be useful for athletes or people looking for a mental edge, or those looking to support their ketogenic lifestyle. The majority of products on the market are made up of BHB, likely because it is more chemically stable (than acetoacetate) and can be made into a shelf-stable product more easily.

There are two main types of exogenous ketones:

1. **Ketone Salts** are powdered exogenous ketone supplements that consist of a ketone molecule (BHB) bound to a mineral salt, such as sodium, calcium, magnesium, or potassium.

- When consumed, the salt dissociates from the ketone and causes blood ketone levels to reach between 0.5-1.0mmol/L.
- They're generally a more cost-effective way to elevate ketones.
- They can help to replenish electrolytes. For example, when they're bound to sodium and potassium, they can help boost your electrolyte levels that may be imbalanced when following a keto diet. Although caution should be taken to avoid overconsumption of certain electrolytes.
- A ketone salt is typically 75% ketones and 25% salt.
- Some ketone salt products are combined with caffeine, MCT powder, carbohydrates or amino acids. So be sure to keep an eye on the ingredient list.

2. **Ketone Esters** consist of a ketone molecule (BHB or AcAc) bound to a ketone precursor such as glycerol or butanediol and are in a liquid form.

- When ingested, the ketone ester gets broken down in the gut and the ketone precursor goes straight to the liver to be converted into another ketone.
- They cause a quicker and more sustained rise in blood glucose, compared to ketone salts - generally to between 3.0-5.0mmol/L within 30 minutes of ingestion.
- They will put you into ketosis even if you're not on the keto diet and are consuming carbohydrates.
- They're more expensive and often have an extremely bad taste!

In addition to these, **MCT oil** (medium-chain triglyceride oil) is often considered an exogenous source of ketones, but they do not contain BHB or any ketone molecule. They can however raise blood ketones to roughly 0.5-1.0mmol/L because the medium chained fat has the ability to get rapidly converted into ketones in the liver. Keep an eye out on my Instagram page as I'll be covering MCT's in more detail soon!

TOP 3 KETONE BOOSTERS

KETONE SALTS
Dose: 5-15g of the active isomer (D-BHB)

MCT OIL
They can raise blood ketones to roughly 0.5-1.0mmol/L

KETONE ESTERS
Dose: 25-30g servings. Split this dose into 2 or 3 servings.

I like to take ketones **pre-workout**, especially when fasting; they are a **great source of energy** when you reach an afternoon 'slump'.

BRANDS I LOVE:
Pruvit, Perfect Keto, Bulletproof
Brain Octane & Kiss My Keto

WHAT PRODUCTS DO YOU USE TO MAXIMIZE KETOSIS?

Choosing the right chemical form

It's also important to point out that ketones exist in two forms (called isomers): D or R -BHB and S or L - BHB. These two isomers are the same molecule, but are mirror images of one another. The D-BHB form is the most prevalent in the human body and is the form that we actually break down to use for energy. Many ketone salt supplements on the market are a 50/50 mixture of the D- and L-BHB isoforms, which in scientific terms is known as a 'racemic mixture'. It seems as though the body does not use them the same way, and L-BHB seems to be "weaker" than D-BHB.

There is also evidence to suggest that when BHB is bound to sodium, it elevates ketones 30% more effectively than calcium. Sodium is also a very important electrolyte that many keto-dieters, especially athletes need a lot more of, and calcium, when taken in excess could lead to calcification without proper levels of vitamin D₃ and K₂.

In summary, when purchasing a ketone salt supplement, it is important to look for a pure D-BHB form, and one that contains mostly BHB bound to sodium.

Dose

The ideal dose for exogenous ketones may vary depending on your lifestyle. For example, if you're a keto-adapted athlete, you may need a slightly different dose compared to someone who is sedentary and is new to keto.

Ketone Salt:

- 5-15g of the active isomer (D-BHB). Research shows that 12 grams is the minimum effective dose. But in my experience, doses of 5-10g show some benefit.

Ketone Ester:

- Usually sold in 25-30g servings. You could split this dose into 2 or 3 servings, depending on your goal. An athlete, for example, looking to use exogenous ketones for a performance boost may take the entire dose in one go.
- A 25g serving contains 120 calories, and some products have added stevia to improve the 'jet fuel' flavor they're said to have.

As mentioned, many ketone salt supplements are combined with MCT powder, which may provide a more sustained release of ketones into the bloodstream - specifically C8 MCT.

I like to take ketones pre-workout, especially if I am fasted, and they are great to give you a kick of energy when you reach an afternoon 'slump'. You could also take them in place of your morning coffee, to give you a more instant surge of ketones for mental alertness.

Side Effects

Unfortunately, side effects are very common with GI distress being the most popular. It depends on the dose and the individual. Starting with smaller doses, of both the ketone salts and esters is a good idea.

What to look out for

Some products are often "fairy dusted." Many companies are taking full advantage of the popularity of exogenous ketones by including ketone salts (in ineffective levels) in products just so they can market them as such. This is a practice known as "fairy dusting," and these products often contain other "experiential" ingredients -- namely, caffeine -- so that the user "feels" like the supplement is "working."

They are expensive. There are many options when it comes to exogenous ketones, and seemingly more pop up every day. One of the biggest downsides is that they are expensive, which may be quite surprising given the paucity of scientific support. The most popular brands of ketone salts run anywhere from \$4 - 5 a pop, and many companies recommend using 2 or

more servings daily. One commercially-available ketone ester supplement out there is priced at \$33 per serving.

They are not provided in the best form. As mentioned a few times, the research suggests that the ketone ester form of exogenous ketones outshines the ketone salt form, which has very little supporting evidence. Pretty much all of the commercially-available exogenous ketone supplements are provided in the seemingly inferior ketone salt form. Additionally, the D-BHB form is the active isomer, and many companies sell a mixture of the D and S isomers, making the product far less potent.

They may cause GI distress. As mentioned, studies investigating ketone salts suggest that negative side effects, such as nausea, diarrhea, abdominal pain, and reflux, are relatively common, and they are probably the result of the accompanying salt load and/or taste.

They don't taste great. The taste of exogenous ketone supplements has improved markedly over the last few years; however, there is still quite a bit left to be desired, as few would describe the taste any better than tolerable. Most supplement companies selling exogenous ketones don't hide this either. In fact, one popular company says in a blog post on its website, "Make no mistake, if we drink exogenous ketones for a great taste and pleasant mouthfeel, we will be disappointed. If we drink 'ketones' that taste 'great,' it is because there's little to no actual ketone bodies in the product [and/or] there's an enormous filler/garbage to ketone ratio."

Ok, what brands do I love?

For ketone salts, which I use more frequently, I like to use:

Pruvit

Perfect Keto

Bulletproof Brain Octane

Kiss My Keto

When I need an extra cognitive boost, for example for a busy day with lots of meetings or maybe a podcast, I may use a ketone ester. The brand I use is KetoneAid Pro.

Benefits of Exogenous Ketones

Quicker ketosis: Many ketone supplements can elevate blood ketones within 30 - 60min of ingestion. Thus, they can be used as a quick performance boost, just like caffeine. Although they don't increase endogenous production of ketones, they do raise ketones in the blood that are available to be used as fuel. If you're following a ketogenic diet, you're more likely to be able to use those ketones as fuel

Aid in the transition to a keto-diet: Exogenous ketones can help you get back into ketosis more quickly - perfect if you're following a carbohydrate-cycling routine or cyclical ketogenic diet. For example, if you re-introduce some carbs into your diet every weekend or once a month, you can quickly slip back into ketosis with the help of some exogenous ketones. If you're new to keto, they can help prevent the keto-flu if you haven't fully adapted yet.

What is keto-adaptation?

Keto-adaptation is the process that takes place when you start to 'teach' your body to use ketones as a primary fuel source, instead of glucose. It does not occur simultaneously to the build-up of ketones in the blood. The fundamental cellular adaptations can take anywhere from 3 or 4 weeks to several months and is dependent on factors such as previous diet, level of physical activity, age & insulin sensitivity.

Specific adaptations include: Increased fat metabolizing enzymes, greater number of mitochondria in the cell, increased ketone transporters (called MCT's), elevated ketone levels, enhanced ability of cells to metabolize ketones. These adaptations can still be occurring even after a year! Everyone is unique in how long they take to adapt to burning fat for fuel.

This adaptation phase can be lengthy, and is often accompanied by the well-known 'keto flu'; flu-like symptoms that occur as your body is switching its primary fuel source from carbs to fat. That is why it is often recommended to support this process with exogenous ketones, so that you give your body some energy supply as it adapts to making its own ketones.

There are other ways to reduce or completely avoid the keto flu. These include:

Exercise

Electrolyte replenishment

Dietary fat type

Fasting/Meal frequency adjustment

Improvement in athletic performance: This is arguably the most well-researched area of exogenous ketones (although there is still a LOT we don't know). For the most part, the scientific research has focused on ketone esters, which have been shown to improve endurance and recovery from exercise (increased muscle glycogen resynthesis and increased protein synthesis). Even with some promising performance results, many questions (and skeptics) still remain. Among the current published studies investigating the effects of ketone salts in athletes, none have demonstrated an improvement in performance. In one study, performance actually decreased by 7%. Among the participants, 60 - 78% reported GI distress (e.g., nausea, diarrhea, vomiting, lightheadedness) when the exogenous ketones were taken alongside exercise.

During exercise, we see a very evident decrease in glycolysis - the burning of carbohydrates for energy - when supplementing with ketones. Some may see this as a negative because carbohydrates are the main fuel supply during high intensity exercise. This is why I usually recommend lower intensity exercise for keto dieters, and a targeted ketogenic diet for those doing high intensity exercise often. This means that you consume more carbohydrates around more intense workouts.

On the flip side, the presence of ketones in the blood does slow down glycogen breakdown - the breakdown of stored carbohydrate. We have about 300-600 grams in our muscles, plus 80-110 grams of glycogen in our liver which can fuel an athlete for about 2-3 hours of exercise. The reason exogenous ketones are attractive to many endurance athletes is due to their 'sparing' of glycogen in our muscles and liver, enabling us to exercise for longer periods as we have this 'saved up' fuel on board.

In summary, being able to burn an alternative fuel source, ketones, during long lasting exercise may be beneficial by preserving our carbohydrate stores for later use.

Other reasons ketones support athletic performance:

- Reduced lactate
- Increased triglyceride use in the muscle

- Improved executive function

Exceptional Cognitive Focus: Many keto-dieters will be familiar with the mental clarity that comes with being in deep ketosis. You'll be surprised at how sharp your mind is after taking exogenous ketones, especially when combined with intermittent fasting. Ketones can cross the blood brain barrier and our neurons (brain cells) have the ability to burn ketones for fuel. In some cases, our neurons prefer ketones over glucose. When our brains run on this cleaner, more efficient fuel, it feels as though your mental alertness is through the roof!

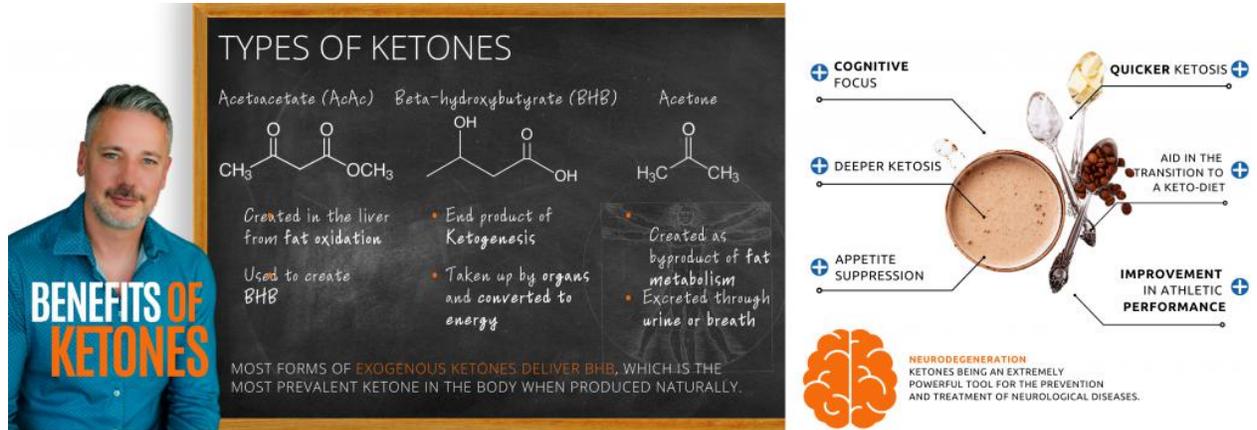
Deeper ketosis: Already in ketosis? You can achieve even higher levels of ketones than you would naturally achieve by supplementing with exogenous ketones. It is often said that there is no need to 'chase ketones', but sometimes more is better, depending on your goal.

Appetite suppression: While they may not cause weight-loss directly, exogenous ketones suppress appetite, reduce hunger and cravings. This allows you to get through fasting periods, lengthen the time between meals and ultimately reduce the amount you eat - leading to weight-loss.

Weight-Loss: Ketones are certainly not a weight-loss tool and are unlikely to directly cause fat loss - they are an energy source! However, supplementing with ketones may have indirect effects that can help fat loss, such as:

- Increased brown adipose tissue (BAT) - the type of fat we want on our bodies
- Improved insulin sensitivity, which allows us to use glucose more efficiently as opposed to just storing it
- Suppressing appetite - as discussed above, this can reduce our overall calorie consumption

The down side: Exogenous ketones suppress endogenous production of ketones. If you think about it, you're giving your body ketones, tricking it into believing that it has produced enough ketones and can now shut down the ketogenic pathways. And just because exogenous ketones increase blood ketone levels does not make you a fat burner. They can enhance the benefits mentioned above, and elicit the therapeutic effects below, but in essence, they're there to support your keto lifestyle, and not replace it.



BENEFITS OF KETONES

TYPES OF KETONES

Acetoacetate (AcAc)	Beta-hydroxybutyrate (BHB)	Acetone
<chem>CC(=O)CC(=O)OC</chem>	<chem>CC(O)CC(=O)O</chem>	<chem>CC(=O)C</chem>
<ul style="list-style-type: none"> Created in the liver from fat oxidation Used to create BHB 	<ul style="list-style-type: none"> End product of Ketogenesis Taken up by organs and converted to energy 	<ul style="list-style-type: none"> Created as byproduct of fat metabolism Excreted through urine or breath

MOST FORMS OF EXOGENOUS KETONES DELIVER BHB, WHICH IS THE MOST PREVALENT KETONE IN THE BODY WHEN PRODUCED NATURALLY.

- COGNITIVE FOCUS
- DEEPER KETOSIS
- APPETITE SUPPRESSION
- QUICKER KETOSIS
- AID IN THE TRANSITION TO A KETO-DIET
- IMPROVEMENT IN ATHLETIC PERFORMANCE

NEURODEGENERATION
KETONES BEING AN EXTREMELY POWERFUL TOOL FOR THE PREVENTION AND TREATMENT OF NEUROLOGICAL DISEASES.

Therapeutic Benefits

Neurodegeneration - As we age, our brains become less efficient at using glucose for fuel, but also, when our brains are damaged, their ability to metabolise glucose and make energy is hugely impaired.

A normal healthy brain can take up glucose from the bloodstream and make ATP to use for energy to function. The transport of glucose into the brain is impaired when trauma occurs (in the case of a TBI) or when the brain degenerates, as is the case with Alzheimer's Disease, for example. When glucose can no longer be taken up by the brain and converted into energy for the neurons, the brain begins to degenerate rapidly. Providing the brain with an alternate fuel source; ketones, can give the brain the fuel it needs to function.

Research shows that the transporters that allow ketones to pass the blood brain barrier are increased in these conditions. They are called MCT transporters and their increased number makes ketones a preferred fuel source for a damaged brain. This has led to ketones being an extremely powerful tool for the prevention and treatment of neurological diseases.

Diabetes - Several studies have looked at the effects of supplementing with ketones on blood glucose regulation and insulin sensitivity. A well known researcher in the field, Dr. Veech found that supplementing with a ketone ester which raised blood ketones to 3.5mmol/L resulted in a 40% increase in insulin sensitivity.

Dr. D'Agostino's research group examined the effect of three types of ketone supplementation: ketone salts, ketone salts with MCT oil and ketone ester on the effect of blood glucose levels in rats. All three groups showed significantly reduced blood glucose levels following supplementation, suggesting improved insulin sensitivity.

Numerous studies have confirmed that blood glucose is indeed decreased when ketones are present in the blood in a wide range of people. Improving insulin sensitivity and regulating blood glucose can have huge positive implications in those with diabetes or other metabolic diseases.

Cholesterol & Triglycerides - Two very important blood biomarkers; cholesterol and triglycerides, are indicators of heart health. The high fat nature of the keto diet has led to the misconception that the keto diet leads to high cholesterol and triglycerides in the blood - which is a known risk factor for heart disease. This leaves many people concerned. But, studies have shown that following a ketogenic diet can in fact improve cholesterol levels by lowering LDL and raising HDL and also reduce triglycerides. This is pretty powerful, but more studies are needed to determine whether the ketones themselves are responsible for some of these benefits.

Cancer - The concept of using ketones as an adjunctive therapy to cancer treatment has been around since the early 1970's. But, with the rise in chemotherapy and other radiation therapies, this has fallen by the wayside. Research is continuing, however, and we have more evidence that ketones can slow tumor growth and increase the survival time of cancer patients. There are many mechanisms by which ketones are exerting these effects on cancerous cells, which we will not go into detail with now.

Muscle Atrophy - A very serious and detrimental process that occurs with age and is often accelerated in those with diseases, like cancer, or any inflammation-related illnesses. The wasting away of muscle can cause many problems, especially in the elderly. In fact, one of the greatest ways to live a longer and healthier life is to have more muscle mass as you age. Recent studies have shown that the ketone acetoacetate can prevent muscle wasting, a very powerful finding in longevity research.

In the diseased states mentioned above, it is often the case that patients with these illnesses are not following a well-formulated ketogenic diet, and are likely heavily reliant on carbohydrates for fuel. This may not be the case for everyone, but unfortunately it probably is for the majority of these cases. Fortunately, this is exactly where exogenous ketones can be so beneficial as they provide an alternative way to achieve ketosis and raise blood ketones to a level where these therapeutic benefits are seen. Hence the ongoing research on ketones and their potential to prevent and treat these diseases.

Wow. Exogenous ketones seem like pretty powerful molecules that can really improve our health! For the most part, this is true, and is the very reason we continue to hear about many people having breakthroughs in their health all thanks to these ketone molecules.

There is one important caveat, which we have already mentioned, and that is that it is unclear whether all of these benefits occur when supplementing with exogenous ketones, as opposed to achieving a state of endogenous ketogenesis (that's accomplished via fasting and/or a ketogenic diet).

With that said, these benefits are likely to be achieved and in some cases enhanced, when adding exogenous ketones to an already well-formulated ketogenic lifestyle. That means eating a whole-foods based diet that is high in healthy fats and low in carbohydrates, specifically highly processed carbohydrates.

Exogenous ketones are a tool that can **support your ketogenic lifestyle** and enhance its many benefits, from accelerated weight loss to improved athletic performance. Just be wary about the claims that some companies make, purporting ketone supplements to be a magic bullet.

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