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The Pros and Cons of Ketone Supplementation

Analysis by Dr. Joseph Mercola | March 17, 2024

STORY AT-A-GLANCE

- Endogenous ketone production is an emergency response that relies on the activation of stress hormones. For this reason, I suspect chronic ketosis may be inadvisable. Taking exogenous ketones, however, does not activate stress hormones, and can be very helpful in some instances
- While ketones are generally known to be good for your brain and lower inflammation, your brain cannot function on ketones alone. It requires glucose. If you do not consume enough carbs, your body will sacrifice muscle tissue to make the glucose it needs
- There are several different types of ketone products available, including MCT-C8 oil, racemic ketone salts (beta-hydroxybutyrate), chiral ketone salts (D-beta-hydroxybutyrate), ketone esters and R 1,3-butanediol
- One of the best therapeutic applications for exogenous ketones is when you need to decrease oxidative stress, such as when getting a CT scan, x-ray or chemotherapy, or when flying
- On the rare occasion where radiation or chemo may be warranted, high doses of ketone esters may help protect healthy cells from being damaged, specifically your immune cells

In this interview, Frank Llosa, founder and CEO of KetoneAid Inc., and I discuss the pros and cons of exogenous ketones (supplemental ketones). Your body makes ketones under certain conditions (so-called endogenous ketones), but you can also take them orally.

I used to take ketones, but over the past year or so have changed my position on this. I now believe that it's relatively unhealthy for your body to create ketones on a chronic basis. Not that you should never do it, but it's an emergency mechanism that requires the activation of stress hormones.

There's great value to that, and it can keep you alive. But it's an emergency response. You're going to have to activate cortisol, adrenaline and glucagon, and that choice will worsen, not improve, your biology over time. That doesn't mean ketones are dangerous. They're a powerful tool that, when used selectively, can indeed improve your health. We're discuss that in this interview.

But if you choose to allow your body to produce high levels of ketones, be aware that there's another side to it that's rarely ever discussed, which is the activation of the stress hormones. If you rarely do this there is no problem, as it is a rescue mechanism designed to keep you alive in times of food scarcity. But if you do it every day, I think you're asking for trouble.

Llosa started exploring the exogenous ketones business by way of the late Dr. Richard Veech, a prominent ketone expert. Veech was his wife's godfather. Veech had been sitting on a ketone ester for 10 years and couldn't get it to market. So, that's where Llosa got involved.

Benefits and Drawbacks of Ketones

While ketones are generally known to be good for your brain and lower inflammation, your brain cannot function on ketones alone. It's biologically impossible. It requires glucose. Llosa cites research from the 1970s where they water fasted people for up to 60 days, and by the end they were able to produce energy through endogenous ketones alone.

However, once you understand how glucogenesis works, it's clear that they still had glucose in the brain. Your body absolutely requires glucose, but you don't have to eat it.

However, it requires it so much that if you fail to consume glucose, it will sacrifice your muscles to create it endogenously.

Your body will break down muscle tissue and convert it into glucose by releasing the stress hormones adrenaline, glucagon and cortisol. That's what activates the destruction of lean muscle mass and bones. Even some brain tissue may be sacrificed to create glucose. So, you must have glucose. If your blood glucose ever goes down to zero, you'll die.

Ketones are indeed a great fuel, it does a lot of good things for your body, but you still need glucose. And if you want to really optimize your biology, the ideal way is to give your body the glucose it needs, along with a smaller amount of ketones. Two ways of doing that is by fasting (which activates stress hormones) or by taking exogenous ketones.

During a personal experiment, Llosa achieved very high ketone levels, but people started commenting that he looked sickly. While he felt great, he was underweight. His wife also experimented with a ketogenic diet and got the "keto flu."

"She was in a fetal position in bed with her eyes bulging, heart racing," he says. Llosa ended up calling on a couple of experts, who recommended giving her 10 capsules of pure salt. While he was skeptical, the salt had her feeling fine within 10 minutes. "It was just a salt depletion," he says.

This tends to be a very common problem and is one of the reasons people say the keto diet didn't work for them. Ketogenic diets cause tremendous salt loss, and most simply don't add enough salt back in. All of that said, there are certainly benefits to ketones. The primary one being anti-inflammatory effects. Some also experience dramatic cognitive benefits. As explained by Llosa:

> *"For cognition, the more of an issue you have with glucose reaching the brain, the more of a benefit you have. So, some people will drink it, whether it's any of these exogenous ketones and feel nothing in the brain. But your brain is being fueled by 100% or 95% [glucose], there is no improvement to be had.*

Scientist Steve Koonin talked about the brain energy gap. So, the bigger the gap, the percentage of the brain that can be fueled by glucose, it could be 60%, 70%. When you add exogenous ketones, it uses a different pathway, reaches the brain and gets you closer to that 100%.

So, some people, for example, TBI [traumatic brain injured] people, they have brain fog, they take the ketone ester and it is instant, immediate, and predictable, within 15 minutes. So, the bigger the [energy] gap, the more you feel it."

The Different Kinds of Exogenous Ketones

At present, there are several different types of ketone products available, including the following:

- **MCT-C8 oil —** MCT oil is a dietary fat, so it counts toward your macro nutrients. However, 10% to 15% of it goes through the liver and creates ketones (D-beta-hydroxybutyrate). As noted by Llosa, theoretically, you could take some MCT oil with a piece of store-bought cake and still raise your ketones. This rise is not an indication that you're burning fat, however.

- **Racemic ketone salts (beta-hydroxybutyrate) —** These were the first exogenous ketones on the market, but they are hardly worth the investment, as they barely raise your ketone levels. "You'd have an entire serving of ketone salts and be lucky if you get a 0.3 rise in your millimolars," Llosa says.

  "If you took the capsules of racemic salts, maybe if you took half of the bottle, 15 out of the 30 capsules, you might be able to have a 0.2, 0.3 rise." One of the reasons people claimed they worked to prevent keto flu is because ketone salts are very high in salt. But you can get the same effect simply taking pink Himalayan salt and save a ton of money.

- **Chiral ketone salts (D-beta-hydroxybutyrate) —** The chiral version of the salts, which is more expensive to produce and therefore retails for a higher price.

- **Ketone ester —** This is D-beta-hydroxybutyrate, the free acid form, bound to R 1,3-butanediol (also known as D 1,3-butanediol). This allows the ester to enter your bloodstream intact. As explained by Llosa, "once in your bloodstream, enzymes will separate it, giving you a quick release of D-beta-hydroxybutyrate, the same molecule that your body makes when it burns fat.

  Then, R 1,3-butanediol goes through the liver and 80% of that converts to ketone. So, you have a fast release and a slow release."

  Within the ester group, there are several different versions, including monoester (developed by Veech); D-beta-hydroxybutyrate bound to two or three glycerol molecules (which is not nearly as effective); and esters made with C8, which works best when taken with food. Ketone monoester does not have good absorption when taken with food.

  So, if you need to take it with food to limit glucose spikes, the C8 ester may be a better choice. But for a fasted workout, the monoester is far superior. There's also a ketone ester made with C8 bonded to R 1,3-butanediol, but it's not nearly as bioavailable, while being one of the priciest.

- **R 1,3-butanediol —** This is half of the molecule of the ketone ester (D-beta-hydroxybutyrate bound to R 1,3). Technically, 1,3-butanediol is an alcohol (but not ethanol), so it can give you a buzz. Llosa started a company called Hard Ketones that focuses on R 1,3-butanediol as an alcohol alternative that works on your GABA receptors.

  This product is primarily aimed at helping people quit alcohol. As explained by Llosa, "the weird thing about this drink is, because of the ghrelin effect, it lowers your desire for itself. So normally with a beer, you desire another beer, and another beer.

  But with this, people have one or two and they just don't crave a third, fourth, fifth. The brain craves acetic acid as part of the cycle of ethanol. The R 1,3-butanediol converts to a four-carbon version of acetaldehyde that is not as bioavailable, so the

body can't use it as a toxin, and then it goes on to quickly convert to beta-hydroxybutyrate ketones."

Racemic Versus Chiral Ketone Salts

To understand the difference between racemic and chiral salts, imagine you have a pair of gloves, one for your left hand and one for your right hand. In a racemic ketone salt, you have an equal mix of these "left-handed" and "right-handed" molecules, also referred to as "D" (or R, for "right") and "L" for "left."

Just like your gloves, these molecules look similar but are mirror images of each other and cannot be superimposed onto one another. In chemistry, we say that the mixture is racemic because it has equal parts of these mirror-image forms.

Now, imagine if you had a pair of gloves but they were both for the same hand — let's say two left-hand gloves. In chiral ketone salts, instead of having a mix, you have molecules that are all "left-handed" (or all "right-handed"). The term "chiral" refers to a substance that does not have an identical mirror image — just like your pair of left-handed gloves.

In the context of ketone salts, this means the product is made up predominantly of one type of molecule, either the 'left-hand' or the 'right-hand' version, not a mix of both.

In our bodies, these differences can be important. Just like only one of your gloves will fit on each hand, only one form of a ketone molecule might be effectively used by the body. While racemic ketone salts offer a mix, which might not be fully utilized, chiral ketone salts provide a specific form that can be recognized and used by your body.

Ketone Esters Protect Against Oxidative Stress

According to Llosa, the ketone ester is better for brain sharpness and sports performance, while the hard ketones induce relaxation. In my view, one of the best therapeutic applications for exogenous ketones is when you need to decrease oxidative

stress, such as when getting a CT scan, x-ray or chemotherapy, or when flying. All of these cause oxidative stress that ketone esters can protect against. Llosa comments:

> *"There's going to be a paper coming out within a month; it's been seven years in the making, and it was briefly touched upon in a chemistry book, which is why I can mention it, where they gave mice enough radiation so that 70% of the mice died.*
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> *They took another group and gave them ketone ester either before and after, or just after. When they took it before and after, 100% of them survived and then lived just as long [as unexposed mice]. If they were taking just afterward, 90% of them survived. That is going to be, I think, a groundbreaking paper. It's going to open up so many possibilities.*
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> *As far as for cancer, what we really need … is to make sure that the radiation only protects the good cells and doesn't accidentally protect the bad cells. Travis Christofferson who wrote the book, 'Ketones Is the Fourth Fuel.' Great book to take a deep dive on this. He explained to me, but not in a way that I can re-explain, that the good cancer cells are protected and the bad cancer cells shouldn't be protected.*
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> *So, for potential cancer, you would want to make sure that it's only protecting the good cells and not accidentally protecting the bad cells. Because that mice study just shows that it protects the entire body, it doesn't show the difference that you need.*
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> *In cancer radiation, it's a fine balance between how much radiation you give to kill the cancer versus killing the host. You don't want to kill the person with too much radiation. So, if you have an opportunity to be more aggressive on the radiation, or protect from that, that has a lot of prospects."*

I firmly recommend against chemotherapy for cancer, as you're sabotaging your ability to survive. However, on the rare occasion where radiation or chemo may be warranted,

you'd be foolish not to consider high doses of ketone esters, as it will likely protect healthy cells from being damaged, specifically your immune cells.

When you knock out your immune system, your ability to fight cancer almost disappears. So, you must be careful. As a general guidance, Llosa suggests preloading before chemotherapy, taking two to four servings per day (10 to 20 millimolar) for two or three days. That said, Llosa warns that there's no scientific evidence to support specific dosages or frequency, so it's something you'd have to experiment with.

Again, to be clear, while I believe raising your endogenous ketones can do more harm than good for most people, taking an exogenous ketone product is a different story, because you're not activating stress hormones.

Why I Don't Recommend Chronic Keto

While Llosa believes the ideal diet is a low glycemic index, non-ketogenic diet with exogenous ketones, I disagree strongly with that. The reason being that glucose is the primary fuel for your mitochondria. Unfortunately, most people's microbiome is seriously dysfunctional as a result of eating too much refined sugar.

Refined sugar feeds gram negative bacteria that produce endotoxin. If your pathogenic bacterial load in your colon is high, even healthy carbs like ripe fruit can cause problems, as the fiber will feed the bad bacteria. However, if your microbiome is healthy, then you can eat fruit and even starches without problems.

I typically eat between 400 and 500 grams of carbs a day, and I know many who eat 600 grams of carbs a day, yet have totally normal blood sugars and normal glycohemoglobin, because our mitochondria can burn glucose effectively. We have a very active metabolism, so we can burn that fuel.

Many, like Llosa, focus on low glycemic because that's the way most people achieve normal blood sugar. But I believe it's far from ideal, because if you have a low-glycemic diet, you still run the risk of activating the stress hormones. If your carb intake is too low,

you're going to activate adrenaline and cortisol, and if you activate them all the time, you're going to run into trouble.

The other component of this is that you need to be insulin sensitive. Ideally, you'd want a fasting insulin level below 2 or even 1.5. If your fasting insulin is 5 or 10, then the glucose spike caused by, say, a glass of orange juice, is going to be problematic. If your mitochondrial function and metabolism are good, then your glucose level will temporarily spike and go right back down.

More Information

To learn more about Llosa's products, visit **ketoneaid.com** and **hardketones.com**. In closing, Llosa comments:

> *"I think the takeaway is that this isn't a supplement. We call it a food. People have to take supplements for 10 to 30 days to maybe feel something. This is something that you feel immediately, or in one or two days."*