

Ketones: The Fourth Fuel

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✓ Fact Checked

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STORY AT-A-GLANCE

- › Your body can use four types of fuel: carbohydrates, fats, proteins and ketones. Of these, ketones burn the cleanest. They create far fewer harmful free radicals when burned and do not rely on insulin
- › When you're generating ketones and your blood ketone levels go up, the ketone enters the cell through a monocarboxylic acid transport protein. Even without a rise in insulin, the cells are efficiently fueled
- › With today's standard American diet, most people never reach a state of fat burning and ketosis. They're constantly feeding their bodies carbohydrates, and in this high-insulin state, they simply cannot burn fat. Over time, it wears out your metabolic machinery, resulting in insulin resistance and weight gain
- › Nutritional ketosis is a powerful way to improve your body's natural antioxidant capacity
- › Optimizing your metabolic health appears to be an effective way to mitigate the severity of a COVID-19 infection. The reason for this is because when you're metabolically flexible, you're not insulin resistant, and insulin resistance is a significant risk factor

This article was previously published September 6, 2020, and has been updated with new information.

Travis Christofferson has written three books on metabolic health optimization. His third one was "[Ketones, The Fourth Fuel: Warburg to Krebs to Veech, the 250 Year Journey to Find the Fountain of Youth.](#)"

Interestingly, optimizing your metabolic health appears to be an effective way to mitigate the severity of a COVID-19 infection. The reason for this is because when you're metabolically flexible, you're not insulin resistant, and insulin resistance and diabetes are significant risk factors.

The ketogenic diet was a standard of care in the 1920s for pediatric epilepsy, but once antiseizure drugs came out in the '30s, it was shelved and eventually forgotten. Fasting encountered the same fate. As noted by Christofferson, therapeutic fasting was huge in the '60s, yet the benefits of this strategy eventually fell by the wayside of medical history as the low-fat movement took hold.

"[Nutritional ketosis] made this remarkable resurgence by the year 2000, and people began to recognize that ketones were essentially a fourth fuel, and had these incredible therapeutic side effects," Christofferson says.

Today, as we face epidemic levels of insulin resistance and its associated health effects, including diabetes, heart disease and increased vulnerability to viral infections, nutritional ketosis could not be more pertinent.

The Four Fuels

The four fuels are carbohydrates, fats, proteins and ketones. Carbs and fats are the two primary ones. Proteins are primarily used as building blocks, but they can also be broken down and be burned as fuel. They just cannot be stored for anything other than emergency starvation fuel.

Protein can also be converted back into glucose through gluconeogenic pathways. When you fast, protein can be used as an alternative fuel, but the ideal fuel is ketones. Christofferson explains the metabolic difference between carbohydrates, fats and ketones as follows:

"For some reason, life chose glucose as a primary fuel. Carbohydrates all enter the same sort of glycolytic pathway and get burned or processed through 10

enzymatic steps into Acetyl-CoA, which enters the Krebs cycle. It then spins off substrates that feed into the electron transport chain to generate energy.

How we burn fat is very dependent on insulin. So, when you're eating a lot of carbohydrates, when you're releasing insulin throughout the day, you're essentially shutting down fat processing and turning on the lipogenesis, which is fat building, and it all centers on insulin.

So, when insulin is high, it shuts down the process of fat burning, which is beta-oxidation. When insulin is low during a state of fasting or a ketogenic diet, it turns on beta-oxidation. So, fats will come in and get processed. What makes fats unique, and this doesn't get talked about a lot, is that they're extraordinarily energetic. There's tons of energy imbued in that fuel source.

So, the body really has to come up with a way to process it without blowing up the mitochondria. The way it does this is, some of the fat is processed through Complex II of the electron transport chain, which tones down or dampens the energy within fat so it can be processed without exploding the mitochondria.

Then the Acetyl-CoA enters the Krebs cycle and just goes through normal metabolism. The important point is that fat burning gets turned off by too much carbohydrate. When you enter this state of ketosis, fat burning gets turned on, and when beta-oxidation occurs, when we're burning fats, it is tethered to the process of generating ketones.

So, low insulin tells adipose cells (fat cells) to release triglycerides, stored body fat, that enters the circulation that goes into the cells, and then beta-oxidation begins. Within the liver – this is the central part of ketosis – liver hepatocytes are the manufacturing line for ketone bodies.

As beta-oxidation is ramped up, oxaloacetate, the last metabolite of the Krebs cycle, is being pulled out to generate glucose, because the body has to maintain a baseline level of glucose. The Acetyl-CoA cannot combine with the last substrate of the Krebs cycle, so it builds up in hepatocytes.

And then there's an enzyme waiting for this massive buildup of Acetyl-CoA. This enzyme begins to transfer that into acetoacetate, which then gets converted to beta-hydroxybutyrate, which now enters the bloodstream as a fourth fuel, a preferred fuel, and an extraordinarily efficient fuel. So, that's the metabolic difference between these three fuel sources."

High-Carb Diets Damage Your Metabolic Machinery

The problem is that with today's standard American diet, most people never reach this state of fat burning and ketosis. They're constantly feeding their bodies carbohydrates, and in this high-insulin state, they simply cannot burn fat. Over time, it wears out your metabolic machinery, resulting in insulin resistance and weight gain.

As explained by Christofferson, glucose is a very rigid planar molecule, and when in your blood, it damages your epithelial cells, nerves and just about everything else. For this reason, your body has to get rid of it quickly. The insulin tells your cells to take up the glucose to lower the glucose level in your blood.

It then tells the cells to process it by turning on the last step of glycolysis, the pyruvate dehydrogenase complex, so that the glucose can be processed. When those two "machineries" wear out, you develop insulin resistance. What this means is your cells no longer respond well to insulin, and as a consequence your blood glucose remains elevated.

You're also burning less fuel, which diminishes all metabolic processes. This is in context to a state of insulin resistance: Less glucose is able to enter the Krebs cycle and ATP production slows. For example, the efficiency by which your body makes antioxidants and neurotransmitters decreases. The beautiful thing about ketone metabolism is it completely bypasses all this pathology. It doesn't depend on insulin pathways.

So, when you're generating ketones and your blood ketone levels go up, the ketone enters the cell through a model carboxylic acid transport protein. Even without a rise in

insulin, the cells are efficiently fueled.

Ketones also do not need pyruvate dehydrogenase complex. Instead, ketones go directly into the Krebs cycle. So, all of a sudden, diminished metabolic pathways spring back to life and you're able to generate energy, antioxidants and all the rest. Your brain also gets the fuel it needs for optimal function.

Metabolic Benefits of Ketones

Ketones have a number of specific benefits. For starters, they're thermodynamically and metabolically efficient, meaning they burn cleaner than glucose, thus creating far less free radical damage and inflammation in your body. Christofferson explains:

"Beta-hydroxybutyrate is a metabolically superior fuel. It's thermodynamically imbued with more energy per two carbon unit than glucose. So that sets the stage. When you burn it, it widens this gap in the electron transport chain between Complex I and the Coenzyme Q couple.

The electron transport chain, what it does is, when you burn fuel, the electrons are stripped through, and they go through a series of complexes in the electron transport chain. When it does this, it injects a proton into the inner mitochondrial membrane space. That gradient of protons then generates ATP.

Beta-hydroxybutyrate widens this gap ... There's more energy ... to capture. One thing that does is, it supercharges our metabolism.

When Veech and Krebs were studying these four metabolic hubs, these coenzyme couples, where ATP is one of them, that drive all metabolism, they realized that if there was a way to increase the energetic potential of all these nucleotide coenzymes, it could therapeutically have immense benefit for metabolism.

They just didn't know a way to do this. When Veech merged with Cahill and began studying this, they realized that beta-hydroxy did exactly this. It was

metabolically imbued with the ability to increase the amount of energy in ATP, NADP, NADPH and Acetyl-CoA.

Then you look at what that does ... for example, the manufacturing of internal antioxidants ... is dependent on the charge of NADPH. Under ketosis, that charge is dramatically increased. So, we're able to process free radicals much, much better."

Ketosis Dramatically Improves Antioxidant Production

The concept of NADPH is profoundly important and not widely appreciated. It's probably every bit as important as NAD⁺, especially with respect to recharging endogenous intracellular antioxidants. As explained by Christofferson, the only thing that determines the antioxidant status of a cell is the redox ratio of NADPH, and the only known way to change that redox ratio is through burning beta-hydroxybutyrate.

There's a pervasive belief that you can diminish free radicals simply by consuming antioxidants, but that has never actually been proven. As noted by Christofferson:

"Krebs wrote Linus Pauling about this, saying, 'You don't understand what you're talking about with regard to Vitamin C.' The example I try to give in the book about this is, all these antioxidants ... have to be recycled by NADPH. So, the NADPH ratio alone is dictating the way all these antioxidants work.

If you eat antioxidants, it's just like having a full grocery store. There are 10 cash registers, and there's 10 checkers. The rate limiting step in how fast people get checked out is the 10 cash registers. If you add 20 cashiers, it doesn't help. Those 10 cash registers are the thing that determine how many people in the grocery store get checked out.

It's the same thing with antioxidants. You can eat antioxidants and add to the pool of intracellular antioxidants, but they're not being recycled any faster. So that's a huge misconception about how antioxidants work. When you shift to

ketosis, there's profound therapeutic consequences with regard to antioxidants production."

Radiation and Antiaging Benefits

Christofferson cites research showing that when you give mice ketone esters after dosing them with radiation, the chromosomal damage incurred is reduced by 50%, compared to mice fed a normal carbohydrate diet. He believes taking ketone esters is therefore advisable when getting X-rays or when flying, for example. Ketone esters may also help counteract the normal ravages of aging.

"One of the theories that's stood the test of time is the Harmon free radical theory of aging, which is that we really do produce a lot of, just endogenous free radicals, just by normal metabolism. And that has always been considered the proximal cause of aging, because it's the main damaging event within the cell," he says.

"One of the ways to mitigate this constant endogenous free radical production is through ketosis, keto metabolism, beta-hydroxybutyrate. It slows the production of free radicals ...

Beta-hydroxybutyrate metabolism in ketosis will also dramatically increase the levels of NAD in our bodies ... So, exogenous NAD precursors, ketogenic diets, fasting or ketone supplements are ways to really slow this pernicious process of epigenetic aging."

Beta-hydroxybutyrate also activates FOXO3a, which is perhaps one of the most important pathways for antiaging. FOXO3a in turn changes the expression of hundreds of other genes.

Some of those genes regulate internal antioxidant production such as catalase and superoxide dismutase. These are not like traditional antioxidants that have to be recycled by NADPH. They operate by traditional ketolysis, where superoxide is changed into hydrogen peroxide and then water.

Ketone Esters Improve Athletic Performance

Christofferson also reviews how ketone esters can improve athletic performance and recovery:

"Another good real world application of this is Tour de France riders. They discovered ketone esters back about 2012 ... The reason they're so important is, by the third week of this grueling bike race, the primary reason you're not recovering is because you're generating so many free radicals by this massive intake of oxygen and exercise.

When they take this ketone ester, they say they have an unprecedented ability to recover, and it's because it's blunting this free radical generation and massively increasing their ability to cope with all these free radicals that are damaging tissues and grinding them down as this race occurs."

Other Benefits of Ketone Esters

There's also some data suggesting ketone esters can be beneficial for certain health conditions.

"In somebody that's showing the beginning signs of dementia or Alzheimer's, the [ketone] esters are able to increase levels of beta-hydroxybutyrate to druglike levels. You get these enhanced pleiotropic effects of ketone esters.

Another effect ... is it inhibits NLRP3 inflammasome, the initial complex that kicks off inflammation. So, beta-hydroxybutyrate at higher levels can suppress inflammation. [It can also] act as an epigenetic reprogrammer. It inhibits HDAC proteins, which are proteins that install the tags on histones, to change the genetic expression.

The initial data show that people in the throes of some disease process may benefit more from an ester than somebody that's healthy and just looking for

enhanced quality of life. That being said, it's a natural compound, it's a fuel source. It's really eating food, in a way.

If you are exercising a lot, or about to have an X-ray or flying, I think a ketone ester is a perfectly reasonable thing to take for that ... But nobody suggests it's a replacement for the most important strategies, which are a good diet, exercise and fasting – those kind of global intrinsic ketone-producing [strategies]."

MCT Oil Is One Alternative

Another therapeutic option is to use MCT oil, as this type of fat lends itself readily to ketone production. I consume about 6 ounces of caprylic acid a day, as I require many calories due to my daily exercise. I need at least 3,500 to 4,000 calories a day. I get more than 1,000 calories a day from MCT oils, which works out well for me as I obtain the metabolic benefits discussed here.

MCT oil is also far less expensive than ketone esters. That said, 6 ounces is far more than most people would be able to tolerate. To start, begin taking 1 teaspoon and work your way up from there. Be careful to take them with loads of other fats and don't take more than 4 tablespoons at once – otherwise you will likely get nauseous.

"MCTs are a hack to get into ketosis [as] they bypass these control pathways," Christofferson explains. "Typically, you have to have low insulin, which releases triglycerides, which then get processed in hepatocytes to beta-hydroxybutyrate.

MCT oils go directly into the cell and force this production, because they radically increase the amount of Acetyl-CoA. That then creates beta-hydroxybutyrate. They even cross the blood-brain barrier, which most fatty acids don't.

So, neurons will directly produce ketones in the brain. One of the main pathologies of Alzheimer's is insulin resistance in the brain. So, your brain is starving of energy. It can't process glucose. MCT oils will go directly into the

brain. Or they'll produce ketones in the blood, go directly in the brain, bypass all that pathology and fill that energetic gap."

Why Cyclical Ketosis Is so Important

While many believe it's best to remain in nutritional ketosis continuously and indefinitely, I strongly disagree with such advice. I believe it can be highly counterproductive to remain on a continuously low-carb diet.

“ Glucose raises insulin, and insulin is — if you're in a high-insulin state all the time — a terrible thing. But it's also an anabolic hormone that kicks off IGF-1 and all these antibiotic pathways, for repair. ”

While it's important to remain on a low-carb diet until you are metabolically flexible and insulin sensitive, which can take months or even years for some really heavy people, once you reach that state, you'll want to increase your carbohydrate level (depending on your exercise level) to 100 or 150 grams once or twice a week, especially around the times you're exercising.

Doing so will actually further improve your metabolic flexibility, as you want to have the ability to seamlessly switch between burning fat and glucose. As mentioned, glucose is the universal fuel, so we have to be able to use that. We just don't want to use it all the time. Christofferson agrees, saying:

"You need to remember; your body is in a continual state of ... breaking down [or] repair. If you're constantly breaking down, you don't give your body the chance to repair, to be anabolic.

Glucose raises insulin, and insulin is — if you're in a high-insulin state all the time — a terrible thing. But it's also an anabolic hormone that kicks off IGF-1 and all these antibiotic pathways, for repair.

So, I think ... the most optimal strategy will be one of cycling, going back and forth. I think that probably mimics what our ancestors went through. We probably had times of deprivation. In the winter, there were very few carbohydrates or none. And then, in times of abundance, when there was plenty of carbohydrates, it was a time to repair and regenerate.

I think that in the end, that strategy will be exactly the correct one. And we don't know – even an occasional fast may be enough for people that are generally healthy."

Improving Metabolic Health Is Key in Post-COVID World

Lastly, optimizing your metabolic health through nutritional ketosis, which is best done through time-restricted eating and a cyclical ketogenic diet, will help you move forward with greater confidence and less fear in this post-COVID world. As noted by Christofferson:

"Looking at the data, and what this virus is doing, it's a no-brainer. Health officials talk about these proactive measures of social distancing and mask wearing, but it just doesn't seem like the one thing that's staring us in the face is ever addressed, which is metabolic dysfunction.

We could have said, 'One way you can potentially mitigate the severity of the disease is by eating right; starting doing these things and come out strong.' But that message has not been delivered ...

[Metabolic dysfunction] was a crisis before the virus. It was there, and we failed [to address it]. The virus exposed that [failure], and we still have to really address that publicly.

It really shows the profound biases in human thinking, and the way we react to problems, without doing full cost accounting. When you do a dispassionate look at the full cost accounting of the economic dislocations of lockdowns versus

what we're getting out of that, with the virus, it's disproportionate. We've got to find a way to balance that reasonably.

This virus disproportionately kills older people. What it costs per 80-year-old is over \$1 million, using full cost accounting, and if you could take that \$1 million, you could save hundreds of lives of younger people. So, I think our response is, in a way, absurd, and just doesn't look into the problem in the right way.

The take-home point for me is, look at health care and how we parse up and spend enormous amounts of money on each disease and make almost no progress, year after year.

We have this basically free, intrinsically installed health care therapy [i.e., ketones] installed in every one of us ... It's really empowering, and that's what I want the take-home message to be: how potent this is, and how readily available. You can access it at any time you're ready."

To learn more, be sure to pick up a copy of Christofferson's book "[Ketones, The Fourth Fuel: Warburg to Krebs to Veech, the 250 Year Journey to Find the Fountain of Youth.](#)" This really is the information you need right now, so the timing of the publication of this book couldn't be more appropriate.

In the interview, Christofferson also reviews some of the history of the key doctors and scientists responsible for identifying and understanding ketone metabolism – including Otto Warburg, Hans Adolf Krebs, George Cahill and Richard Veech – so for more details, be sure to listen to the interview.