

## **Diet Doctor Podcast with Dom D'Agustino, PhD (Episode 46)**

**Dr. Bret Scher:** Welcome back to the Diet Doctor podcast, I'm your host Dr. Bret Scher. Now I don't say this often, but this is probably my least favorite interview ever. And it's with Dom D'Agostino. So, how is that possible? Because we were on a time constraint. Here we are at the Metabolic Health Summit, he had to run downstairs to give his talk, we got started a little late. And I think he's one of the most interesting people in science.

I want to have a two or a three-hour interview with him, but we had to cut it short. But we touched on some really interesting topics about the work he's doing with ketogenic diets and exogenous ketones on brain function, how his work in extreme environments can translate to regular disease processes that aren't in extreme environments, that people get and we need some better treatments for and how ketones can play a role in the specifics of the types of diet, the specific types of exogenous ketones, some of the protein sparing effects of ketones.

So we brush the surface and talk about some of these topics, but my hope is we're going to have him back for even more interviews in the future. But hopefully this will be a great introduction for you to Dr. Dom D'Agostino, all the amazing work he's doing and get a little sense of the personality, because he's really a great guy and I hope to hear more from him. Let's get started with the interview with Dr. Dom D'Agostino.

Dr. Dom, thanks so much for joining us.

**Dr. Dominic D'Agostino:** Thanks for having me, I appreciate it.

**Bret:** I really appreciate you being here and I know you've got some time constraints, because here we are at the Metabolic Health Summit and where you are one of the organizers and speakers and you are taking time out of your day to come for this Diet Doctor podcast interview, so thank you. And I want to start, if we can, with your name.

So first of all with your name you've reached the status of Prince and Madonna of being known by just one name - Dom, and every knows who you're talking about. But, D'Agostino, when I hear D'Agostino I think lots of pasta in your upbringing. And now here you are as one of the most preeminent ketogenic diet and ketone researchers. So how did you make the transition from an Italian pasta family, assuming that assumption is right, to where you are today?

**Dominic:** Yeah, my mom is traumatized when I go home and couldn't eat pasta. Well, I started my postdoctoral fellowship that was funded by the Navy and they were interested in understanding oxygen toxicity seizures, which I will be talking today about that and that is an extreme environment.

And the military Navy in particular, the major branch that we work with, they are interested in enhancing the safety and the resilience and performance of the military personnel under particular environments.

And what I have spent most of my time developing unique technologies to understand these environments, microscopy and telemetry and different things like that in hyperbaric chambers and as we developed these technologies and understood the biological process of oxygen toxicity, we realized that getting the body and in particular feeding the brain ketones or elevating your blood ketone levels would provide metabolic resilience in an extreme environment that could help the brain function and most importantly prevent a seizure under these extreme environments.

Or delay the onset to that seizure above and beyond what we could achieve with any pharmaceutical compound, which was my main focus - drug research.

**Bret:** So, you started off with the drug research and then you were able to make the transition to the nutritional and then the exogenous supplement of ketones to do better than any drug.

**Dominic:** Yeah, there was a couple of drugs that can delay oxygen toxicity seizures, like Vigabatrin and other anticonvulsant drugs, these drugs have side effects. And the military did some research on fasting rats for 24 or 36 hours and it showed a remarkable delay in the onset of oxygen toxicity seizures, so that really interested me

and I was like how-- I didn't know anything about fasting and seizures at the time or even the ketogenic diet.

Surprisingly I went through a nutrition program at Rutgers University in New Jersey and we didn't really talk about the ketogenic diet, at least its clinical applications. So in the process of trying to develop an anti-seizure neuroprotective strategy for oxygen toxicity, I went to the epilepsy research and I was also connected with people like Mike Dancer, who is a patient, an epilepsy patient, who was diagnosed with terminal epilepsy.

And at the time I got into this advice that he perhaps used a ketogenic diet and worked remarkably well for him. I connected with Johns Hopkins and other people who actually used the ketogenic diet clinically. And it became apparent that the ketogenic diet could potentially be used for these very powerful tonic-clonic seizures that limits Navy SEAL operations, because of the special rebreather unit that they use.

**Bret:** So if it help seizures in general probably would work for a seizure in that extreme environment as well.

**Dominic:** Yes, seizures can result from over I think up to 300 different-- the etiology of epilepsy is largely unknown and there are many seizure disorders that we just don't know what caused the seizure, but the ketogenic diet tends to work for many seizure types, actually the majority, independent of the etiology and that always interested me. So I had more likely to work with these kinds of seizures.

The office of Navy research, they were not very keen on a high-fat low carbohydrate diet as part of a war fighter strategy for enhancing performance. So, at the time Jeff Volek's work really wasn't popular yet and it was a hard sell for them in particular to fund a project. So they were like, why don't you come up with a ketogenic diet and a pill?

And this was 2008 and by coincidence Dr. Jong Rho who was at Barrow Neurological Institute at the time just happened to publish a review called the Ketogenic Diet And The Pill and he talked about that epilepsy world is trying to find something that could mimic the ketogenic diet, because it works better than any antiepileptic drug that we

have right now. And he talked about exogenous ketones and the potential for that. So I got steered into Dr. Richard Veach and some work being done in Oxford by Karen Clark.

And Dr. Veach was a student upon scrub and a very well respected biochemist that developed and his whole life was really studying ketones. So it was interesting to me that these very high-level scientists were studying the therapeutic applications of ketones. Maybe it wasn't in the public domain at the time, but I saw that DARPA had funded quite a bit of money, millions of dollars, to develop these ketones for war fighter performance.

So I was like, okay there's a potential ketogenic agent that I could use for seizures and, you know, DARPA was funding it for performance. So let me see if it works in our seizure model. Surprisingly it didn't and this was a beta hydroxybutyrate mono ester. But then I connected with folks, Henry Brunengraber from Case Western and other chemists who could synthesize the compounds for me and tried a number of agents.

And the one agent that elevated beta hydroxybutyrate and acetoacetate, we discovered that that was remarkably neuroprotective.

**Bret:** So, interesting, you didn't give up with the first one that didn't-- Some people probably would have said, ketones don't work, forget it. But you kept going and that brings up the point that not all ketones are the same. Levels may matter, the specific individual ketones matter. And so that can also get confusing when we talk about taking exogenous ketones for different reasons, because all the products aren't the same.

So it can make it confusing for the individual in terms of what is doing the benefit, what is the key that's actually helping from a neurological standpoint.

**Dominic:** Yeah, and the research that we've done at least in preclinical animal models suggests that there will be unique ketogenic strategies for different applications. Obviously, I think it will be different for type 2 diabetes than epilepsy than exercise performance. We in our hands and it wasn't really talked about much in

the performance session I just came from and moderated, but we find that when certain compounds are mixed together, then you get optimal effects.

You take ketone salts, mix some of the ketone esters and mixing ketogenic fats with ketone salts or ketone esters also seems to enhance the response. If you ingest a purely exogenous ketone... it's my belief and I think some data will support this... that you're turning off your own ketone production to some extent.

But if you mix a ketogenic fat like medium chain triglycerides with a ketone ester and deliver it orally, it simultaneously stimulates your own endogenous ketone production. Because you are producing hepatic ketogenesis by-- for MCTs for example. And it also delays gastric absorption and extends that pharmacokinetic profile of that ketogenic agent, so it's elevated longer in the blood.

**Bret:** So, different scenarios. You've got the exogenous and the endogenous working together as opposed to the sort of scenario that I think some people promote that may not be as helpful, as eat whatever you want and just drink these ketones and you will be in ketosis. So it's not quite that simple.

**Dominic:** Yeah, I think certain companies that have vested in a particular compound, they kind of just show, well, eat this way and take this compound. We don't study any particular compound. We study many different compounds.

**Bret:** Right.

**Dominic:** And at this point about 60. So there are different agents that have proven through our publications to be efficacious for certain things. But what we're finding now is, taking a step back and starting to formulate ketogenic strategies or ketogenic formulations for specific applications.

And a kind of think that's the future. We're really at the cusp of figuring these things out and we have a long way to go. But we have started moving things into human clinical trials, which I will be talking about today actually; some of the work we're doing at Duke, who is a collaborator of mine.

**Dominic:** Yeah, so how do we make the jump then from deep water oxygen toxicity seizures to Alzheimer's disease, traumatic brain injury, strokes, just sort of

neurological healing from these other disorders, when they all have seemingly different mechanisms behind the disease? Is a ketone, you know, a magic bullet that's going to work for all of them? Potentially?

**Dominic:** No, I believe that we have a lot to learn from the epilepsy world and I think the ketogenic diet community really should focus on that, what has been established already in the epilepsy world, because there are sort of much further along in regards to, you know, peer-reviewed publications and a consensus as to what a ketogenic diet is and how to implement it, but we know with epilepsy, the ketogenic diet, the mechanisms are largely unknown.

If I mentioned the top 4, 1 would be-- it's enhancing brain energy metabolism and contributing to brain homeostasis and balancing energy in the areas of the brain maybe deficient in glucose metabolism, glucose hypometabolism.

**Bret:** So some sort of an injury to the brain makes it so I can't metabolize the glucose as well, so then the ketone provides an alternative fuel source?

**Dominic:** We think that that could be part of it and for some people it definitely is. And there's also an imbalance of neurotransmitters with most people who have epilepsy if you're to measure, you know, glutamate levels and even the animal models show this. So the ratio of glutamate to GABA goes down. So glutamate is an excitatory amino acid neurotransmitter and it can lead to hyper excitability that can lead to seizures.

And when you're on a ketogenic diet, for reasons we don't completely understand it activates an enzyme called glutamic acid decarboxylase. And that converts glutamate, a hyper activity enzyme, stimulatory neurotransmitter to GABA, which is an inhibitory brain stabilizing neurotransmitter, that from neuroscience perspective hyperpolarizes the membrane potential of neurons and quiets the brain down.

**Bret:** So it takes the brain from a hyper excitable state to a more relaxed state.

**Dominic:** Yes, and if you have areas of the brain that are damaged for example with TBI or rather a neurological disease... most neurological diseases are pathophysiologically linked to glutamate dysregulation, so there's excess glutamate

is causing membrane potential depolarization and hyperactivity. A ketogenic strategy, and this has been shown with the diet and now with supplementation, converts more of that glutamate to GABA. And that can be not only anticonvulsant but also neuroprotective.

**Bret:** So whether it's seizures, or whether it's trauma, or even a stroke, it sounds like there is this underlying pathophysiology of the hyper excitability.

**Dominic:** Yeah, it's well-established.

**Bret:** So even though they are different disease processes, the underlying injury or a response to injury is similar, so therefore the ketogenic diet by being able to make this transition from glutamate to GABA can be beneficial for all of them.

**Dominic:** Yeah, and two other mechanisms, but there's like a dozen, would be adenosine A1 receptor signaling. The adenosine receptor when it's activated, it quiets and stabilizes neurotransmission. And I think I'll mention that briefly in my talk coming up and also inflammation. Systemic inflammation typically leads to neuroinflammation. This could be triggered by foods that cause an autoimmune reaction. It could be triggered by stress, environmental toxin.

We know that ketones are remarkably anti-inflammatory and inflammation in the brain can lead to anxiety, inflammation in the brain can lead to seizures, inflammation in the brain can lead to headaches. Ketone bodies do have a remarkable anti-inflammatory effect that we've just published a paper on that in animal models and we can use things like LPS, lipopolysaccharide, to stimulate that inflammation.

So, and then the gut microbiome, we can get into other things, but I just mention four things: brain energy metabolism, neurotransmitters, adenosine receptor signaling and inflammation. Are four things that we know, we have really good preclinical animal model work to demonstrate that being in a state of ketosis alters these things and in a way that would be neuroprotective and anti-anticonvulsant.

**Bret:** So, when we talk about using either a ketogenic diet or exogenous ketones, it does pay to sort of be more specific, because a ketogenic diet can be the traditional

4 to 1... 4 times as much protein as-- sorry, four times as much fat as protein and carbohydrates combined, which is sort of like the classical ketogenic diet for treating seizures. But kind of not what is the most popular ketogenic diet now.

That's not probably more than modified Atkins diet. So when you're talking about a ketogenic diet for neurologic protection, does it matter the specific type of diet? And does the degree of ketone elevation matter as well do you think?

**Dominic:** Yeah, it definitely matters. What we're not fully confident about is how much it matters, but Eric Kossoff from Johns Hopkins published on the modified Atkins diet, I just call it modified ketogenic diet, because Atkins kind of gets a bad-- But that diet is now used for adult epilepsy and children who are on a classical ketogenic diet, which will be like a 4 to 1 ratio, 90% fat it ends up being.

Many of the patients can transfer to a modified ketogenic approach, which is more liberal in protein and just making a diet more liberal in protein for example from 10% to 20% that's a very big change and it makes the diet much more feasible for the parents and it's quality of life thing.

And remarkably now we realize that the diet does not have to be as strict as we once thought it was and you can also incorporate into the diet fats that are ketogenic, like medium chain triglycerides and get the same level of ketosis that you would for example with a classical or more restrictive ketogenic diet.

So our minds are changing about this and new studies are starting to come out. I chaired the American Epilepsy Society special interest group on dietary therapies where it's more of a mainstream conference and evidence is starting to accumulate that a more modified ketogenic diet approach may be advantageous for compliance and maybe even efficacy too.

**Bret:** All right, very good. Well, gosh, having you here is a bit of a torture, since you're on a time constraint because I have so many other things that I want to get into with you, but I think the future certainly seems very bright for using ketogenic diets and even exogenous ketones for treating neurologic disease, but where we stand right now in terms of where the science is, in terms of animals versus humans



and how far out are we from having solid evidence to say this is something we can use?

**Dominic:** Well, the animal data-- I'm an academic scientist, so a lot of time and effort is spent doing preclinical animal model work. Unlike animal models, for example, cancer, which don't always translate, I think they're informative animal models for cancer but not always predictive. Whereas for epilepsy and seizure models historically the animal models for seizure have been informative and predictive.

So, that gives me a little bit of confidence, what we're seeing in the lab will translate into human clinical trials, which we have now for Angelman syndrome, a registered clinical trial. One will be starting up for epilepsy. We have one, I'll be talking about today, using nutritional ketosis to enhance neuroprotection in extreme environments, which would be high oxygen environment.

And we do this in a lab at Duke University. I was actually amazed that it got approved by the IRB, because it's a rather extreme protocol that I'll be presenting today. But we are, you know, diving subjects now and implementing not only ketogenic diet, but ketone supplementation. And that was really the vision I had like 10 years ago when I started seeing the animal model work and it was very compelling, the neuroprotection that we were seeing.

So it's very satisfying to me that we're able to move things into the clinical realm with registered clinical trials now, but we do have a lot of work to do. And only the things that have been done now are mostly pilot studies, where we're recruiting, you know, more subjects to do large-scale clinical trials and ultimately multicenter clinical trials. And the direction to go at least for now is for epilepsy and seizure disorders, because there are so much data already in that, but we're also pushing to get some studies, clinical trials, for brain tumor patients too.

**Bret:** All right, that's very exciting. Now, to shift gears, real quick, you mentioned about the protein. And I've heard you say before that ketones are anti-catabolic and that they can be sort of muscle sparing. Can you give us just 30 seconds on that? And what people can take away from that standpoint?

**Dominic:** Sure, so in the context of like calorie restriction or cancer cachexia, which is a condition where there's a lot of muscle wasting occurring due to a number of factors, some of them being you know catabolic enzymes or just inflammatory processes. So in the context of, let's start with fasting for example, when you're not ingesting food, your body starts to break down. And you start breaking down protein and fatty acids for fuel.

When you've depleted your glycogen stores you make proportionally more ketone bodies through the suppression of insulin. The hormone insulin stimulates hepatic fat oxidation and then you make more ketones. The ketone bodies do largely replace glucose as a primary energy source during prolonged fasting. You know, after about a week or more.

So they become uniquely anti-catabolic because they're simply supplying an energy source and that allows your body to spare amino acids, in particular gluconeogenic amino acids so your skeletal muscle will catabolize. If those ketone bodies were not there, we would waste away much faster. So that's well-established. Dr. George Cahill has written a number of nice reviews on that.

**Bret:** Sort of an effective intervention to help you maintain your lean body mass. I think that's important from a cachexia cancer treatment standpoint and also just sort of in general, especially when you're talking about formulating the ketogenic diet properly for people.

**Dominic:** Yeah, there's a lot of interest and some research now on ketones for performance, but I think that's really-- if there is one area of science where I think you're going to get just small results or minimal results, I think it would be performance. You know, when you ingest these things acutely before exercise.

I think where ketones will shine is prolonged use of ketones can help perhaps with adaptive effects of exercise training, perhaps in the context of a calorie deficit, but I think the anti-catabolic effects of ketones are pretty real and I think the science will support that over time.

From an evolutionary standpoint we know that ketones really allow us to do and maintain prolonged fasting. And there are a number-- my student Andrew Koutnik,

who has just finished the PhD with me, his whole PhD project was basically studying the anti-catabolic effects of ketone bodies. And we wrote a review published in Cell with Dr. Brendan Egan that is an overview, maybe we don't have time to get into, and it mechanistically goes through all the potential anti-catabolic effects that ketones can have.

**Bret:** It pains me, but I think I have to let you go here, because the clock says you have to be back downstairs for the conference. I know you are very active on Twitter and Instagram where you show lots of videos of alligators in your backyard which freaks me out as a California guy, but also lots of your scientific endeavors, you have a ton of information there, so where can you direct people to find you to learn more about the exciting things you are doing?

**Dominic:** We try to compile everything on [ketonutrition.org](http://ketonutrition.org) where we have a blog and we have resources there and people can learn more about us and what we do with the company. Our company is just mostly a research company. Now we don't have any products per se, but we do test products and some of those products we have on the site too, you know, people ask me about what ketone products to use.

I do enjoy testing products and also enjoy testing devices like breath acetone meters or blood ketone meters and use those devices to test the products. And that's a fun thing that I do and kind of do it on my off time. I really like to do not only bench research, but also live this lifestyle and it's become sort of a passion to do both.

**Bret:** All right, I am sorry we have to let you go. Just promise me you'll come back where we can talk more in-depth and I want to hear more about you and the way you live your life and all the exciting things you're doing, thanks for taking the time.

**Dominic:** My pleasure.