The Tim Ferriss Show Transcripts
Episode 117: Dominic D'Agostino
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Tim Ferriss: Quick sound check: What did you have for breakfast this morning?

Dominic D'Agostino: Eggs and sardines and oysters −

Tim Ferriss: Eggs and sardines and oysters? Did you just throw that in the −

Dominic D'Agostino: − and broccoli, a little bit of broccoli.

Tim Ferriss: − you just throw it in a Vitamix?

Hello, boys and girls. This is Tim Ferriss, and welcome to another episode of the Tim Ferriss Show where it is my job to deconstruct world-class performers. That means that I interview people ranging from chess prodigies like Josh Waitzkin to celebrities and governators like Arnold Schwarzenegger to everything in between, whether those are athletes, scientists, military strategists, or otherwise.

And this episode is a very fun one. It gets into the weeds. If you've loved the episodes with Dr. Peter Attia or Pavel Tsatsouline or others, you will most likely love this one.

My guest is Dr. Dominic D'Agostino, better known as Dom. Most people refer to him as Dom. He is an assistant professor in the Department of Molecular Pharmacology and Physiology at the University of South Florida Morsani College of Medicine and a senior research scientist at the Institute for Human and Machine Cognition.

And when I have questions about ketosis, about fasting, or about the deadlift, I call Dom. Why? Well, among other things, for instance, he has fasted for seven days and then deadlifted 500 pounds for ten reps. He is a beast, both physically and intellectually. He has published or coauthored many different fascinating papers, research papers.

And no big surprise; he's a good buddy of Dr. Peter Attia, who I mentioned shortly ago. Now, Pete of course drinks so-called

jet fuel in search of optimal athletic performance, sometimes ends up dry-heaving in the kitchen trying not to wake his family, and I enjoy these types of human guinea pigs of course.

The focus of Dom's laboratory primarily is developing and testing metabolic therapies, including ketogenic diets, ketone esters and ketone supplements to induce nutritional and therapeutic ketosis.

There is a lot more to it. Some of his research has been funded by the Office of Naval Research, Department of Defense, etc. He's a fascinating guy.

If you are remote interested in, say, cancer prevention or longevity or maximal performance, then this episode will touch on many, many cutting-edge aspects, theories, and practical implementations of research that is at the forefront right now.

So please enjoy my conversation with Dom D'Agostino.

Dom, welcome to the show.

Dominic D'Agostino: Thanks for having me, Tim, appreciate it.

Tim Ferriss: Of course. I have my notebook out always when I'm on the phone with you, walking around, I'm struggling to find paper in my pockets or record notes. So I have all of my materials ready. I've spoken with our dear friend Pete Attia to sort of plot the arc of questions that I would ask you, mostly out of pure self-interest.

But for those people who are unfamiliar with you, when someone asks you, what do you do, how do you answer that question?

Dominic D'Agostino: Well, it depends on who it is, but I tell them − I try to be brief as possible. I just say I'm a scientist, and I study nutritional neuroscience, I think, is kind of how I like to phrase it as concisely as possible.

Tim Ferriss: And if you're talking to a fellow scientist, how would that answer change, if at all?

Dominic D'Agostino: I kind of go into kind of describing how I study integrative metabolic regulation and how what we eat or certain

supplements can change our metabolic physiology to treat, prevent disease, or enhance performance.

Tim Ferriss: Very cool.

Dominic D'Agostino: That kind of sums up, yeah.

Tim Ferriss: And speaking of performance, and this is a question I ask all of my guests, but what is the most you've ever deadlifted after fasting for seven days?

Dominic D'Agostino: Wow, I imagine you get a range of responses from that question. Oh, okay, so you've talked to Peter Attia. He's filled you in on that.

So I guess going back when I really got interested in fasting, I did a seven-day fast, and it just happened to conclude right before I had to give a lecture kind of on the topic.

And I went into it with my glucose in the mid-maybe-30s, low 40s and my ketones up there at about 5 millimolars or so. And then I did go to the gym. Yeah, I deadlifted 500 for ten, and I finished off with a one rep of 585, six plates. I haven't done that since. I haven't done anything that extreme since.

But I just felt like − I was inspired by George Cahill. He was a researcher at Harvard Medical School. And he did a fascinating study that really − where he fasted people for 40 days actually. And I've delved into the literature studying that.

Well, and I thought, well, I can do seven days if these study subjects were IRB-approved [inaudible]. So, yeah, I did that, and I found the first three days were a little tough, and then I just started cruising along.

But at Day 5 and 7, I was feeling − my energy level was taking a dip for sure, but I was amazingly resilient. And I felt that had a lot to do with being in a state of fasting ketosis.

And I was firmly convinced that − and this is when I just started kind of studying this field. So I was doing a lot of bloodwork on myself, too, to figure out what was happening.

Tim Ferriss: And what was the time − what was the year roughly? When was this?

Dominic D'Agostino: This was 2010 −

Tim Ferriss: Got it.

Dominic D'Agostino: − I think, going into, yeah, 2009 into 2010. So I'd been into this area of research for about a year or so. In 2009, I'd really started getting research funding to do what I'm doing now.

Tim Ferriss: It's funny to me that these subjects were able to be fasted for 40 days and everything got approved, but if you wanted to fast animals in certain circumstances, it seems like you can't go beyond one to three days.

Dominic D'Agostino: Oh, yeah, yeah, that's good. You know, I serve on the University Institute for Animal Care and Use Committee. It's called IACUC. It's like the animal IRB. And, yeah, the committee usually has a reactionary response to anything under 25 percent calorie restriction. [Inaudible] more than 20, 25 percent of their weight for a fat rodent, really that's not much. You can't do that anymore. You've got to refeed them.

So, yeah, I am amazed that some of the stuff got approved. I think the IRB was probably on vacation or something back then. Yeah, IRBs are a little different now.

Tim Ferriss: Can you explain what IRB is or define that for people who aren't familiar with that?

Dominic D'Agostino: Yeah, it's the Institutional Review Board that will review kind of the ethics and the safety of a study before signing off on it essentially and allowing − it's a committee of people that have kind of a broad range of expertise, and they review the reason why the study is going to be done, the methodology, the ethics, the purpose and all that stuff and approve whether or not the study can be conducted.

And it really depends on what institute you're at. You can use an outside IRB that's outside of the institution, and companies do that. Industry does that. But they can be a big hurdle, and I've found vastly different IRBs.

There's a small college, about ten, 15 minutes from here that ran a ketogenic diet study in advanced lifters for us.

And the IRB was approved in, like, two weeks. At University of South Florida −

Tim Ferriss: Which is fast.

Dominic D'Agostino: Very fast, yeah, like, two or three weeks. And other IRBs, I think I did one, a pharmacokinetic study for ketone esters, which I'll probably talk more about later, but that one I think has been rejected somewhere about seven or eight times.

And, I mean, it's just giving as a single dose kind of more or less a bioidentical molecule that our body makes. And the committee is just, because it's, quote, unquote, first in human, it's very difficult. And this is an outside IRB, which is less restrictive in many cases. So they can be a big hurdle to an investigator.

Tim Ferriss: Yeah, especially if the 25 percent or more loss is deemed cruel and unusual punishment.

Dominic D'Agostino: Oh, okay, for the animal study, yes. Yeah, in these human studies, there's pretty stringent criteria on the humans and stuff. But, yeah, the animal studies would be bad.

Tim Ferriss: What was the study that you did on advanced lifters as it related to ketosis, and what's kind of the abstract on that?

Dominic D'Agostino: Yeah, that's under review right now.

Tim Ferriss: Got it.

Dominic D'Agostino: And, yeah, I'll give you kind of like the synopsis of it. So we had 12 subjects, and these were advanced resistance-trained individuals, meaning that they could squat and deadlift and bench a certain percentage of their bodyweight, which kind of puts them in the range of the Top 10 percent of lifters out there.

Tim Ferriss: What was that percentage, just out of curiosity?

Dominic D'Agostino: I've got to go back. It was some funky number. It was like 185 percent or 75 percent −

Tim Ferriss: Got it.

Dominic D'Agostino: − of their bodyweight squatting for seven reps or eight reps or something like that.

Tim Ferriss: Got it.

Dominic D'Agostino: So it was pretty − it would be like me − let me see − squatting 425 or something for a set of six or something like that.

Tim Ferriss: Okay, yeah, these are very −

Dominic D'Agostino: It was pretty significant.

Tim Ferriss: − yeah, significantly advanced trainees.

Dominic D'Agostino: Yeah. So, yeah, the gist of that is that we did a parallel. The control group was on a Western diet, which is pretty similar to kind of moderate protein, higher in carbohydrates and moderate fat.

And the ketogenic diet had roughly 75 to 80 percent fat, restricted carbohydrates to about 20 to 25 grams per day, and the fat was also supplemented to some extent with MCT oil and coconut oil. And all the subjects − it was two weeks they had to be on the diet and had to confirm ketone levels by blood and urine.

And once they did, we only did a two-week adaptation, which is kind of another subject we could talk about, but they adapted for two weeks and then kind of trained the heck out of them.

And every workout was done in the lab in a human performance laboratory. And everything was recorded. The volume was controlled. All the parameters were controlled. Bloodwork was done.

And the take-home on it was that strength, you know, I would say strength and performance were maintained and increased, and muscle hypertrophy was seen with a ketogenic diet. And there were similar increases, yeah, in power, in hypertrophy.

And the big difference was kind of the overall body composition was more favorable in the ketogenic diet group, meaning they had similar increases in lean body mass, but they lost proportionately more fat.

And that's the study we completed. It's under review right now. The first journal kicked it back, so we went in for another journal and did some follow-up work with it.

Tim Ferriss: Now, what is your hypothesis − or maybe you already know − but how would you explain the maintenance or even development of hypertrophy and power in the ketogenic group when a lot of people associate, say, insulin with different growth factors and whatnot?

And I had a conversation − I want to say it was with Steven Phinney − very short conversation, and I asked him this because I'd been in a ketotic state for two or three weeks and had experienced a non-trivial amount of muscle growth, and I was really surprised by it.

And he explained in terms that I can't recall but how the ketogenic diet might have a, I guess, like a branched-chain amino acid sparing effect of some type.

But is it possible to get very big and powerful on a ketogenic diet?

And if so, what's the mechanism in the sort of absence of higher-spiking insulin levels if that is the parent anabolic hormone, and I'm not saying it is, but a lot of people view it that way?

Dominic D'Agostino: Yeah, so there's insulin and insulin signaling, right? Certain diet − like, when you calorie-restrict a rodent or even humans or any mammal, you will enhance insulin sensitivity, right? So you will be more sensitive to a given amount of insulin. And I think we're seeing some of that in the athletes. I mean, exercise itself enhances insulin sensitivity.

So, and guys that are advanced lifters who've been at it for, like, ten years may have a different response to a ketogenic diet than, say, a 15-year-old kid who's trying to bulk up for football. He would probably not be a good candidate for the ketogenic diet.

Your sensitivity to things like IGF-1 and insulin are much higher when you're younger, in your teenage years especially. So you could compromise a lot of your potential development and strength if you're younger and doing that.

But the older we get, the less carbohydrate-tolerant we get, so we lose our ability to kind of process carbs as we get older and our insulin sensitivity declines.

Now, going back to your question, as it relates to being on a ketogenic diet, we know that ketones are anti-catabolic. That's why we can fast for 40 days. And the ketones have an anti-catabolic protein sparing effect.

And if our blood is flooded with ketones, we're less likely to liberate gluconeogenic amino acids from our skeletal muscle for fuel because the ketones can more or less replace glucose as the primary energy substrate to maintain your central nervous system, which is, like, three percent of our body by weight but sucks up 20 or 25 percent of the energy.

It's a big metabolic engine. So the ketones kind of drive a lot of that substrate energy need.

So, in a situation where you're at a caloric deficit, I think that's where ketones can shine if you're trying to make weight, if you're trying to preserve or even increase your performance and strength and alter your body composition.

So I don't think the ketogenic diet is ideal if your goal is maximum − a purely ketogenic diet. I think there are different − we have to kind of figure out what ketogenic diet we're talking about, but I don't think a purely ketogenic diet as it's kind of described in the literature, right, a 90 or 85 percent fat diet is an ideal diet for growth and repair.

The diet that we use in our study is actually a little higher in protein, like 25 percent protein, which is really almost double that used by the Johns Hopkins Group that developed the classical ketogenic diet. And it's really that that protein level is important.

So growing on a classic ketogenic diet would be pretty hard. I mean, kids do it. Their growth rates are a little bit less with these kids that have drug-resistant seizures when they're put on the diet.

But if you simply just do what's called a modified Atkins, and there's a lot of literature coming out now on the modified Atkins − Eric Kossoff at Johns Hopkins, he's a colleague of mine and more in the clinical realm, and he's done a lot of work showing that a modified Atkins, which is about 70 percent fat and 20 or 30 percent protein, has the same sort of ability to metabolically manage seizures.

And I think that sort of diet can be used pretty successfully in the performance world and specifically for body builders.

I think with that amount of protein, you would be able to grow muscle for sure.

And it's calories too, right? I mean, calories are the driver, your caloric intake. If you have a surplus amount of calories, you're more likely to push insulin up and drive anabolic processes.

But a lot of times, people when they follow a ketogenic diet, because ketones have a really good appetite suppressant effect, that they will inadvertently restrict calories and may not even know it after a while and may be losing weight without even trying, and that's one of the benefits, I guess you could say, of the ketogenic diet. You can lose weight and you can alter your body composition without necessarily even trying, just through the appetite suppressing effect.

Tim Ferriss: And let's define a few terms for folks who may be outsiders to this world. You know, you're talking about ketosis. Let's define ketosis.

What is ketosis? And I guess we could talk about nutritional end sort of fasting ketosis. But what is ketosis exactly? And what are ketones?

Dominic D'Agostino: Okay. I'd kind of like to start out with fasting, right?

Tim Ferriss: Sure, perfect.

Dominic D'Agostino: So we're on a normal diet, and we stop eating all of a sudden. We will mobilize and use up our stored glycogen, mostly in the liver, right? And our central nervous system more or less demands that we have a steady fuel supply to our brain. And in the absence of glucose availability, we'll be depleting our liver glycogen. The insulin levels will be suppressed, and we'll start mobilizing fatty acids for fuel.

But fatty acids, long-chain fatty acids don't cross the blood-brain barrier very efficiently. So the liver, while you're suppressing the hormone insulin, you'll upregulate beta oxidation of fatty acids in the liver.

And an accumulation of products from fatty acid oxidation will start forming ketone bodies. And these ketone bodies are −

they're more or less like water-soluble fat molecules, and they're small molecules that can readily cross the blood-brain barrier and get inside cells, into the mitochondria.

And as we fast, within about 24 to 48 hours, we'll start registering ketones to the level that clinically is defined as being in ketosis −

Tim Ferriss: I was going to ask you about that.

Dominic D'Agostino: − which is above 0.5 millimolar.

Tim Ferriss: Oh, above 0.5.

Dominic D'Agostino: Typically, yeah. So a person a high-carb diet would probably take about 24 to 48 hours to start even getting into mild ketosis. But fasting is the fastest way to get into ketosis.

And that's why if you have a child with drug-resistant seizures, and they're administered or they're admitted into a place like Johns Hopkins, the old protocol was to fast them.

They're not exactly sure if that's absolutely necessary with things like more − with ketogenic diets, have MCTs and stuff. But you can − fasting has classically been the fastest way to get into ketosis.

So the ketogenic diet has a macronutrient ratio that's high in fat, typically 90 to 70 −

Tim Ferriss: And by macronutrients, we're referring to protein, fat, carbohydrates.

Dominic D'Agostino: Yeah, yeah. And maybe ketones could be the fourth macronutrient maybe if you talk about exogenous ketones. But a ketogenic diet has a macronutrient ratio that mimics the metabolic physiology that you have when you're fasting.

So, if you were to take the blood out of someone, do a blood sample of someone on a strict ketogenic diet, it would look like they're fasting, like they've been fasting a few days.

And that allows you to get some − that changes your physiology incredibly. Your metabolic physiology changes acutely, and then there's long-term changes that occur with that, epigenetic changes. We know that beta-hydroxybutyrate,

which is a ketone body, can have interesting effects on gene expression.

Tim Ferriss: What types of effects?

Dominic D'Agostino: Well, there was a science paper showing that beta-hydroxybutyrate is an HDAC Class I and Class II inhibitor and can activate genes that play a role in enhancing exogenous antioxidant mechanisms, specifically superoxide dismutase and catalase.

So these mechanisms, when they're upregulated, it confers protection against the environment. It sort of enhances our cellular defense mechanisms.

It enhances the robust kind of protective mechanisms that the cell has that can preserve the genome stability. So maybe being in a state of ketosis and maintaining that can protect your DNA from damage, so that's the implications.

Also, anti-inflammatory − so we published a paper − our colleagues actually did at Yale. I developed the diet for them and sent it up to them. It was exogenous ketone. But the paper demonstrated that it activated or prevented the activation of a particular inflammasome that's linked to age-related chronic diseases.

So it inhibited a specific inflammatory pathway that is really associated with all chronic age-related diseases. And it was independent of the ketones' effect on metabolism. So they teased out − they did a lot of studies to tease out the mechanism and demonstrated that the effect of it suppressing this inflammatory pathway was completely independent of its metabolic effect.

So we understand that − you know, when I got into this, I just knew that ketones were an energy metabolite. So now we know it's much more than a metabolite. It's an HDAC inhibitor. And the pharmaceutical −

Tim Ferriss: How do you spell that? I apologize, the HDAC?

Dominic D'Agostino: Yeah, histone deacetylase inhibitor, so HDAC would be H-D-A-C.

Tim Ferriss: Got it.

Dominic D'Agostino: And then there's Class I, II, III, I think IV. So Class I and II HDAC inhibitors are a big, big − are of big interest to the pharmaceutical industry.

So there are many − for example, we do a lot of cancer research. There's a lot of pharmaceutical companies focusing on histone deacetylase inhibitors as targeting specific pathways for cancer therapy.

So you have an endogenous HDAC inhibitor with beta-hydroxybutyrate −

Tim Ferriss: And just − not to interrupt, but just for people who want to keep endogenous and exogenous straight, I've always found thinking of exoskeleton as sort of outside, as an indicator of outside. So if you're taking − please correct me if I screw this up in any way, Dom − but if you're taking exogenous ketones, that means you are consuming ketones from outside of your body. And endogenous is something you're producing yourself.

Dominic D'Agostino: Yes, right.

Tim Ferriss: So, in a case for instance with cancer, I have a friend who recently went through chemotherapy, and he would fast for three days prior to his chemotherapy. And in the same group, almost everyone was − aside from him, everyone else was laid out for days after chemotherapy, really unable to function, and he was able to go for ten-mile runs, for instance.

And I've been very fascinated by looking at the implications of combining fasting with, for instance, chemotherapy and the treatment of cancer.

If you were, say, advising someone with a family history of Alzheimer's and Parkinson's, which I have, so I don't know if those fall into the age-related issues that you were talking about, but are there implications for fasting or nutritional ketosis or exogenous ketones for helping to prevent or mitigate the onset of those type of neurodegenerative diseases?

Dominic D'Agostino: Yeah, and fasting has to be done under − you have to know your body, right? And fasting should probably be done under a pretty strict medical supervision −

Tim Ferriss: Sure, agreed.

Dominic D'Agostino: − to some extent, yeah.

Tim Ferriss: Agreed.

Dominic D'Agostino: So someone would have to do a little research on it.

And it would depend on the particular person. So, if you have a cancer person that it's a woman with breast cancer, say, and she has a BMI of 28 and is going in for chemo, I think it's a good idea for them to fast before they go in. But if you have −

Tim Ferriss: BMI, body mass index.

Dominic D'Agostino: Oh, body mass index, yeah.

Tim Ferriss: And that would make her obese? I actually don't know kind of the scale of BMI.

Dominic D'Agostino: Yeah, that would make her kind of a little pudgy, I guess, and have some extra weight to lose. So we know that getting chemo in a fasted state, there's a couple reports out there showing that it sensitizes − it can sensitize the tumor to the therapeutic effects of the agents.

And also there's some evidence showing that it could prevent some of the side effects associated with chemotherapeutic agents, specifically things that cause cell damage.

So being in a state of fasting ketosis can sensitize the tumor to the damaging effects of the chemo and enhance your healthy cells' resistance against the toxic effects of the chemotherapeutic agent.

And you'd want to do it − I think the majority of patients could probably do it, but if you have someone with severe cancer cachexia, muscle wasting, you'd want to do it in a very cautious way. But I definitely think this is something that should be implemented in our oncology wards, that fasting before chemo definitely has some real benefits that we should be utilizing.

Tim Ferriss: No, it's so fascinating. So cachexia, man, you are a treasure trove of vocabulary. So is that acute muscle loss, as opposed to sarcopenia, which would be the − I'm not up to speed on my

Latin − which would be sort of the muscle loss attributed to aging, or what is cachexia?

Dominic D'Agostino: Yeah, so cachexia would be defined as − yeah, actually, investigators are trying to get a clear definition of it and understanding of it, which our lab − I have one of my students who just studies cancer cachexia.

Cachexia's defined in cancer as you're in a physiological state where your body is releasing factors, like tumor necrosis factor alpha and inflammatory cytokines, inflammatory mediators that are catabolizing your muscle tissue, your lean body mass.

Tim Ferriss: And I apologize, I just want, for people who are unfamiliar with the vocab, so anabolism would be building tissue in general, and catabolism would be breaking down tissue? Is that fair, or is it −

Dominic D'Agostino: Exactly. Like, anabolic steroids are building, and catabolic processes are the breaking down of things.

Tim Ferriss: Great. Sorry to interrupt.

Dominic D'Agostino: Oh, no, it's great. So, yeah, you're in a state where you're basically wasting lean body mass. You're wasting tissue. And a lot of cancer patients succumb to cancer cachexia, and its mortality is closely, intimately related to that.

So, as you lose lean body mass from being in a state, say, for example, if someone has advanced metastatic cancer, that their survival will be tightly correlated with that, the ability to preserve their lean body mass and maintain their function.

And in a lot of situations, you get this situation where you have an older patient that gets cancer, like 70-year-old, and you have age-related sarcopenia, right, they're already losing muscle, compounded with cancer cachexia, which increases lean body mass loss due to the pathology, on top of chemo-induced cachexia.

Tim Ferriss: Oh, Wow.

Dominic D'Agostino: So chemotherapy is a pretty powerful destructive agent to lean body mass on top of inactivity, so being immobilized. So you have age-related sarcopenia, cancer cachexia, chemo-induced cachexia.

And this typically, you know, you have a patient that's bedridden, so they're not stimulating their muscle with activity, so you have four factors coming together that cause like a perfect storm for you to just kind of waste away. And patients can go down so fast when they're put in that situation.

So I think − so we're developing protocols to nutritional ketosis. We're looking at branched-chain amino acid formulas.

And we want to do some work to define specifically what types of exercise can mitigate all these factors and maybe some drugs and stuff too, we're interested in testing.

So, yeah, I think that's not really being studied much. There's not a whole lot of investigators out there studying this. And I've been in touch with a lot of patients, and I realize that this is key. I think a lot of patients would be alive today if we had effective ways to mitigate − because once they lose their mobility, once they get weak enough where they just can't move around, I mean, their whole psychology just deteriorates.

Tim Ferriss: I would imagine.

Dominic D'Agostino: Yeah, so there's a lot of reasons that we should be looking into keeping patients as strong and preserving their muscle as much as possible.

Tim Ferriss: Are there any knowledgeable folks out there − I was going to say scientists or researchers, but we both know a lot of folks who don't operate in the more formal worlds.

Dominic D'Agostino: Yeah.

Tim Ferriss: Are there people out there who believe that there's a role of anabolic agents, whether steroids or otherwise, in those types of circumstances with, say, cancer patients?

And I'd be really interested to hear your thoughts just because there are also a lot of people who are trying to, say, minimize IGF-1 among other things for longevity purposes or even for anti-cancer purposes. But how do you think about that, or how do other people think about that?

Dominic D'Agostino: Well, I think it's a little outside of mainstream cancer kind of world that I'm linked in with, but I think it should be. And I

think we want to develop a pretty solid program here in our lab to look into this.

When it comes to anabolic agents, I think, you know, you go to the literature, and it shows that anabolic steroids do not promote, within certain dosing levels, they do not promote the growth and the spread of cancer.

I'm pretty sure the literature says that there are specific androgen-receptor modulators out there. They're called SARMs. And there's a few SARMs −

Tim Ferriss: SARMs?

Dominic D'Agostino: − yeah, SARMs that are out there, they basically have − they're designed to have the anabolic tissue-building potency of testosterone and other anabolic steroids without the androgenic or the hormone effects. And they are actually developed specifically for cancer cachexia.

Tim Ferriss: Oh, really?

Dominic D'Agostino: So there's a few out there, yeah, there's actually a few out there. And I think, you know, we're kind of interested in studying them. We're looking at branched-chain amino acids right now, which we think are pretty important too.

But if you give − so testosterone, for example, and a lot of males take testosterone to build muscle in the gym for hormone replacement therapy − if you administer testosterone, and the studies have been done, up to a certain point, once you get to about 300 milligrams per week, say, you start to increase systemic IGF-1 levels.

And if you go up to about 600 milligrams a week, which would put you at a supraphysiological level about twice or three times that of a normal male at least, that causes the liver to increase IGF-1 release. So your systemic IGF-1 will go up.

But a dosage of, say, 100 to 200 milligrams a week does not increase, to my knowledge, factors, hormones, growth factors that would cause cancer to grow and spread.

And I think at that dosage, especially with a lot of male cancer patients, that would have a pretty remarkable protein sparing effect.

And we know that anabolic agents can be life-saving drugs for HIV patients −

Tim Ferriss: Absolutely, yeah, for muscle wasting.

Dominic D'Agostino: − for patients with wasting diseases, yeah. I mean, they can − just look at the literature, and if you talk to the physicians and the doctors that treat their patients that are familiar with these agents and know how to intelligently prescribe them and administer them, they will tell you that they save lives. And I think that application may be useful in cancer.

But I think the SARMs are kind of an interesting compound that's coming out, and I think there's definitely some potential for some drugs out there.

Tim Ferriss: Now, is the advantage of a SARM over, say, a high-anabolic, low-androgenic steroid like a nandrolone or an oxandrolone, for instance, which is very popular with HIV patients who are trying to increase their T-cell count and avoid muscle wasting, is the primary advantage of the SARM that it doesn't have the stigma associated with it of anabolic steroids?

Is it primarily kind of a political advantage that it doesn't carry that baggage, or are there other metabolic reasons to use it, as opposed to just standard kind of anabolic agents that are low-androgenic?

And just so people understand, and please correct me if I'm screwing this up, but just for people to understand the context, when people talk about anabolic steroids, they're usually talking about anabolic androgenic steroids, right, and insomuch as they have anabolic, i.e., tissue-building, muscle-building effects and then they have androgenic effects, which can accelerate the development of secondary sex characteristics, whether that's like a square jaw, male characteristics, or a deeper voice and the development of the vocal chords, more hair, acne, etc., that kind of stuff.

So, in the case of someone with, say, a wasting disease, particularly if they are female instead of male, they will want to minimize the androgenic effects because they don't want to become men or become cavemen, and maximize the muscle-building effects in this particular case.

Is that a fair description? Feel free to add or edit anything that I just said, but I'd be curious to hear sort of the advantage of SARMs over preexisting low androgenic anabolic therapies.

Dominic D'Agostino: Yeah, okay. So SARMs are designed with the intention in mind to minimize the androgenic component down to nothing. That's really the goal. And I think they're pretty close to doing that.

The problem is, in the real world when you read about guys taking this for muscle building, they have very kind of minimal anabolic properties compared to their anabolic steroid counterparts or cousins.

But the advantage is that if you have a guy with prostate cancer, or all males probably get prostate cancer in time, so you can − high testosterone could drive the growth of your prostate in prostate cancer.

And anabolic steroids could obviously have major side effects for women. I mean, we see this in women's bodybuilding, right? We see the side effects are pretty real and pretty non-reversible. So a selective androgen receptor modulator can have the advantage of potentially giving the protein sparing anabolic properties of the agents without the side effects.

So there's not − there's research going on, but I don't think it's moving as fast as what we had initially anticipated, as far as them being super potent anabolic agents that would make anabolic steroids obsolete.

Tim Ferriss: Got it.

Dominic D'Agostino: So they're not at that level yet, but there's quite a few pharmaceutical companies working on it, and agents are − there's studies going on right now. And I think that data will probably come out in the next couple years.

Tim Ferriss: Yeah, I want to chat with you separately about how to marshal resources to do a lot more studies because I just − it's so frustrating to see these attractive targets or hypotheses that just, for lack of funding, particularly with technology and sort of the ability to do distributed studies potentially − anyway, you and I will have to chat more about that.

Dominic D'Agostino: Yeah.

Tim Ferriss: But coming back to the chemotherapy because I love looking at cancer in sort of extreme states because I think then you can form hypotheses and test in those circumstances and then adapt findings to test in normal populations, which would, you know, I suppose I would include myself in that, although normal's kind of pushing it.

Is it possible, or to what extent is it possible, to mimic the benefits of fasting pre-chemotherapy with exogenous ketones?

Dominic D'Agostino: Yeah. So I think we can view exogenous ketones are an energy-containing substance, right, so you could potentially take them as a source of energy. They're energy that your liver only produces under certain circumstances of what's considered kind of strange metabolic physiology, like a fasting state.

Tim Ferriss: Right, duress of some type.

Dominic D'Agostino: Yeah, so the ability, and we're interested in doing this, the ability to elevate, to produce an artificial state of ketosis is possible with exogenous ketones. And it mimics many effects of therapeutic fasting, which would be an acute and sustained reduction in blood glucose.

And we don't really know why there's a remarkable decrease in blood glucose that's a dose-dependent decrease. But it seems to be related to the liver's output of glucose. So your liver is a master regulator of your blood glucose really.

And so the drug Metformin in Type 2 diabetics will decrease hepatic gluconeogenesis, so the liver's ability to make glucose and put it into the bloodstream. We think that ketones are doing this also.

Tim Ferriss: Interesting.

Dominic D'Agostino: And I think maybe it's kind of telling the body, hey, you're in a fasted state, so why don't you conserve the glucose that you have?

And also, a big dose of ketones could potentially cause a small release of insulin, and that's kind of how we regulate our endogenous ketone production is that if our ketone levels get too high, that ketone will cause a very tiny release of insulin

from the pancreas, and that will signal the liver to kind of turn down or turn off hepatic ketogenesis.

And when we're in a state of ketosis, we lose ketones through our urine. We burn them up through peripheral tissues. And if they get really high, we stimulate a small amount of insulin release.

Tim Ferriss: What is really high on a millimolar basis as measured by, like, a Precision Xtra device from Abbott, which is what I have six feet from me, which I've been using? How high do your ketone levels need to get before that insulin level gets kicked out − of course, it depends on the person − but roughly speaking?

Dominic D'Agostino: Yeah, I think it's pretty rare to see over 5 millimolar. In kids, with kids that have a disorder called glucose transporter Type 1 deficiency syndrome, I'm in touch with their parents, and they routinely stay in the 3 to 5 millimolar range. But typically, that's rare. They have to be on a really strict ketogenic diet.

But typically, yeah, getting above 5 is kind of abnormal. And sometimes, if I'm measuring, sometimes I'll just hit a peak. It's kind of like your hormones. They're going to fluctuate throughout the day. So, if you measure and you hit 7, I wouldn't panic or anything because it's probably a little peak that you're getting. But, yeah, typically, most people −

Tim Ferriss: Yeah, or you're Pete Attia doing a cycling workout.

Dominic D'Agostino: Yeah, yeah, there's that − you have post-exercise ketosis where guys that are on a high-carb diet after four, five, six hours of intense exercise, they're going to deplete their liver glycogen and ramp up fatty acid oxidation so high, they're naturally just going to be in ketosis. So their body is used to seeing ketones because of the exercise that they do.

But generally, yeah, I mean, moderate to mild ketosis is kind of what I like to promote for health and longevity, and that's between 1 and 3 millimolar. If you're within that range, that's a range that you'll pretty much never get into if you're not on a ketogenic diet, not fasting.

And I think staying in that range has some real-world benefits, as far as health benefits, longevity benefits, performance, resilience. I think there's some real-world benefits to staying in that range.

And you'd be hard pressed to find any potential adverse effects that could be linked to having ketones in that range. But once you get into 5, 6 millimolar range, that produces a metabolic − a mild metabolic acidosis that needs to be compensated for through your kidneys. So it is putting a stress − it's a substrate load to your system, and your body's got to deal with that. So I think that needs to be taken into account.

Tim Ferriss: How do you currently − well, actually, let me ask a couple of questions just because I'm in the middle of doing some ketosis experiments myself with exogenous ketones, so I have two jugs of exogenous ketones in my fridge.

Then I have some powdered beta-hydroxybutyrate, which is, I guess, the − well, most people read it as KetoCaNa, the C A N A, which I guess is, what, calcium potassium? Am I getting that right? Screwing that up.

Dominic D'Agostino: Calcium sodium.

Tim Ferriss: Jesus, Ferriss, so bad. Anyway, I try. I try hard. I'm like Avis.

So I have the powdered beta-hydroxybutyrate. If I use that when I'm trying to induce ketosis, right − so, for instance, this past week, I ate a low-carb but still glucose-dependent diet up until Friday night, and then I fasted from Friday after dinner until Sunday evening. And now I'm squarely into ketosis. I'm probably at 1.1, 1.2 millimolars, I would say, upon waking.

Can I accelerate the induction of my own ketone production through use of exogenous ketones, or am I just temporarily spiking my readings when I'm ingesting these things, and really my body is going to get to its sort of steady state, 1.1, 1.2 in the same amount of time regardless? Does that question make sense?

Dominic D'Agostino: Yeah. I think there are significant advantages to speeding up the process, as far as how you feel. And I think that if you transition from a state of using glucose as your primary energy source to using ketones, that usually involves a gap in fuel flow to your brain, so your brain −

Tim Ferriss: Yeah, you feel grumpy and shitty.

Dominic D'Agostino: Yeah, you have glucose withdrawal. I mean, your brain goes through glucose withdrawal. And it uses glucose not only for energy but to make neurotransmitters.

Your brain homeostasis is, you know, your glucose levels are basically telling your brain that it's happy. It's in a homeostatic state. So if you feed your body, your brain, ketones, it is preserving more or less that neurophysiological homeostasis, I think, and you're not going to have maybe a stress reaction.

So, if you fast, and subjects that just kind of go cold-turkey and fast, within the first 24 hours, it's a stress response. Their cortisol level spikes. Their sympathetic nervous system is activated. Their immune system could be suppressed.

And I think that if you were to do the same thing but use exogenous ketones, you would cruise into a state of nutritional ketosis, sustained nutritional ketosis without some of the bumps along the way.

Tim Ferriss: Got it.

Dominic D'Agostino: And I think that you could probably reap some of the performance benefits, and I think it would maybe be − but then you could, you know, you might make the argument that that stress, that physiological stress that you're giving yourself is, you know, you're familiar with the hormetic effect?

Tim Ferriss: Yeah.

Dominic D'Agostino: Then that stress could be kicking on mechanisms that, when activated, can kind of be protective in and of itself.

Tim Ferriss: Yeah, or beneficial in some way, right, like, when people are taking ibuprofen after workouts or other anti-inflammatories and reducing subsequent hypertrophy, right, from −

Dominic D'Agostino: Yeah, yeah.

Tim Ferriss: − inhibiting the sort of pain that was unpleasant in the short term but beneficial in the longer term.

Dominic D'Agostino: Yeah, where, in the case of NSAIDs, if you dose them right after your workout, maybe those inflammatory mediators are linked to activating the signaling cascades that are responsible for the hypertrophy effect.

Tim Ferriss: Right, right.

Dominic D'Agostino: So you could be negating that effect. But we have not shown that to be the case. Actually, I think you could get a lot of benefit. I see it as not one or the other. I think the ketogenic diet actually goes pretty well with exogenous ketones, and one would not have to be on such a strict ketogenic diet because it is very restrictive.

Tim Ferriss: It is.

Dominic D'Agostino: And you could do a modified Atkins, which is kind of the way I think we should eat anyway, I mean, just eliminating all processed carbohydrates and just protein, fat, veggies is kind of how I eat, and I pretty much always stay in a state of ketosis just by using MCTs, like a little bit of exogenous ketones here and there.

And I think it would allow us to optimize the therapeutic effects of the ketogenic diet and probably further augment the therapeutic efficacy if we're talking about the clinical realm and maybe further augment the performance-enhancing effects of the ketogenic diet too.

And I think that's possible. But a lot of people just want something in a pill. And we have kind of − we did that study − well, we're doing those studies now. And I'm a big fan of the ketogenic diet, and I'm actually pretty impressed and even − shocked isn't the word, but we're getting results better than I expected just by giving pure ketones.

I thought that you would need a level of adaptation to being in a state of nutritional ketosis to get the benefits from exogenous ketones, and that's not the case. We showed that really in our first study.

Tim Ferriss: Now, is that true even in the presence of higher carbohydrate intake or higher protein intake?

Dominic D'Agostino: Yeah, it is in our animal models, and we think it is in humans right now. So we have some studies approved where we're going to be looking at that in humans, looking at the metabolic effects.

But kind of the first study that we did was a rat study where we did an acute feeding. Well, it's kind of a gavage, so we kind of give them a bolus dose. And these are rats that are maintained on a high-carbohydrate, standard rodent chow. And they've never been in a state of ketosis before, unless they were deprived of food or something, which they probably weren't.

So they've never really seen ketones before. And in this study that we did, we acutely gave them a ketone ester, and within about 15 minutes to 30 minutes, they achieved a level of ketosis that would take about seven days of fasting for a human. They were in the 4 to 5 millimolar range.

Tim Ferriss: And the bolus was, I mean, a high-dose single −

Dominic D'Agostino: Yeah, ketone ester, yes.

Tim Ferriss: And what was the ketone ester?

Dominic D'Agostino: It was − you want the chemical name?

Tim Ferriss: Or maybe I should take a different approach. For people listening, what is a ketone ester?

Dominic D'Agostino: Okay. So your body makes primarily two ketones that it uses for fuel. One is acetoacetate, and another is beta-hydroxybutyrate. And they're both kind of interchangeable, and they're converted to one another in the body.

Beta-hydroxybutyrate actually has to break down to acetoacetate to be used for energy. But the beta-hydroxybutyrate tends to be the primary − the highest level primary ketone in our body, just because it's more stable. But it does need to break down to acetoacetate.

So a ketone ester is taking one of these, acetoacetate or beta-hydroxybutyrate or both, and taking those molecules and attaching it to something with an ester bond that functions as like more or less a carrier to it.

So you can esterify a ketone with a wide range of things. You could use glycerol. You can use − we use something called 1,3-Butanediol. And you can attach ketone molecules to this with a transesterification reaction.

And when it's ingested in the body, there's various enzymes. We have hydrolytic enzymes that will − esterases that will break off the ketone, and you'll get − when you ingest it orally, you'll start to liberate the ketones from the molecule that it's esterified with, and these will build up in your blood.

And the idea, right, is to have a molecule that slowly releases the ketones in a very predictable fashion where you get a nice pharmacokinetic profile where you can take it orally, and within 10 to 15 minutes, you're in starvation ketosis, and then you stay in ketosis for 6, 8, 12 hours is ideal. And it depends on the molecule you're talking about.

So that's kind of what we're doing now where we're kind of screening various compounds to figure out which ones have a favorable pharmacokinetic profile in isolation. And then we start combining them together so we can get formulas where we hit the ideal formula for a particular application.

So a ketone ester, yeah, is a ketone that is orally active, so you can take it and it can increase blood ketone levels. In the rat study that I was describing, they are quickly put into ketosis. And then in that particular study, we would dive them in a hyperbaric chamber and increase the pressure and the level of oxygen within the chamber.

So it would simulate a Navy SEAL diving down to 132 feet of seawater breathing 100 percent oxygen in a rebreather that they use. It's called a Draeger rebreather.

Tim Ferriss: Yeah, and the purpose of that of course is so that they don't give away location by having bubbles come out of their system. Is that −

Dominic D'Agostino: Yeah, so there's definitely a stealth component to a closed-circuit rebreather. If you're using it and you're in the middle of a pond in the middle of the jungle and it's perfectly quiet, you would not know the person's under there.

Whereas, if you're using standard scuba, you would see a bubble trail coming across the pond at you, and you could just sit there patiently and wait till they come out and shoot them. So, with a rebreather, there's a big advantage, a stealth component.

The disadvantage is obviously if you go down to just 50 feet of seawater, you're at the risk of getting what's called oxygen toxicity seizures within, like, 10 to 15 minutes just at 50 feet.

Tim Ferriss: Wow.

Dominic D'Agostino: So you have to stay very shallow, which is not always hard to do during a mission if you have helicopters over you and they can see you in the water, or you're taking fire, or you've got to dive down to plant a mine on a bridge or a ship. It's not always easy to do. So we developed these things for providing resilience and safety and performance.

Tim Ferriss: Now, when you say developed these things, you're talking about the exogenous ketones?

Dominic D'Agostino: Yeah, they're developed originally with that application in mind, with sort of a defense application in mind, a military application, and that's how my project originally got started.

Tim Ferriss: Because you've had studies funded by the Department of Defense and so on; is that right?

Dominic D'Agostino: Yeah, the original idea for this was I got turned on to the ketogenic diet because it was used for drug-resistant seizures.

And my program officer, I ran the idea by him, and he didn't really like the idea of a diet per se. I mean, his attitude of the diet for performance has changed over the years.

But he was, like, well, why don't you kind of look into developing a ketogenic diet in a pill and see if that's even possible? So I spent − and that was, like, 2008. And then that kind of started my journey into seeing if this was possible.

And when we tested it in our rat model, I remember the first time we did it. We fed the rat and put him in there, and we typically see a seizure in about 10 to 15 minutes. And we're standing around the chamber, and we have a video camera system and a little window port. And we're standing there, and it's, like, 30 minutes has gone by, 40 minutes, and we're up to an hour. And everybody's just kind of looking at one another.

Tim Ferriss: Whoa.

Dominic D'Agostino: This is unbelievable. And I wasn't getting excited. I was, like, okay, calm down, calm down. This could be a major outlier or something.

And then every single rat we've ever done − and we've done many rats − every single rat has gone way beyond the control to where the average is that it can resist oxygen toxicity 575 percent. And that sort of blows away any anticonvulsant drug out there, so similar to the ketogenic diet, right?

If you go to the Charlie Foundation website, the Charlie Foundation was set up − working with Johns Hopkins University − is for kids with drug-resistant seizures.

And the study published − the original study by John Freeman; it's published − showed that in kids that have failed all standard of care, all even combinations of, like, six anti-seizure drugs, when they're put on the ketogenic diet, two-thirds of those kids have seizure control, like, remarkable seizure control. And a percentage of them, like, a third of them have absolutely no seizures, like, a 95 percent reduction in seizures.

So it made sense. So I was actually thinking that, well, the original study design was to feed ketone esters for a week and then dive them. But my source was only making a little bit at a time, the chemist that I got to make the product for me. So I had little tiny vials of it.

And I was, like, well, I don't know, I was just kind of impatient. And I was, like, instead of getting enough to feed it for a week, I was, like, let's just try to give it one dose and see what happens. And when it worked, we were just blown away.

So we did, like, three or four rats, and I was, like, okay, I'm convinced, but completely unscientific, right, because usually you've got to do, like, 12 and do stats and everything and do controls, but I was − because we dove, like, four rats, and they all went way beyond any other rat we've ever seen.

So I was, like, I have to move on this fast, or someone's going to kind of take this idea or something. I was, like, we've got to move on this finding as fast as possible.

Tim Ferriss: Well, it seems also, I mean − and just like my ridiculous potassium instead of sodium remark earlier, definitely verbally club me over the head if I do anything like that − but it seems

like when you're evaluating the statistical significance of a given study, the sort of civilians, like, non-scientists will say, oh, well, how big was your sample size? And it's like, oh, it was six or ten.

And they're, like, oh, well, that's so small, you know, kind of. And they'll say it should be 100 or it should be 1,000. And they really don't know about science, and I should probably put myself in that category too.

But if you have a huge magnitude of effect that is consistent across a smaller subject size, it can still be statistically significant, can it not?

Dominic D'Agostino: Yeah, it depends on your sample population, you know, what kind of statistical power you have, or the likelihood too that the study will detect an effect, you know, is the statistical power.

And you really have to sit down with a statistician and look at the probability of making a Type 2 error or concluding that there's no effect. And I know just the − you know, I took the basic stats class, but I still consult with a statistician when we're designing a study for a proposal or something like that.

And you kind of − you need to run it by − because if you don't do it beforehand, the reviewers that are reviewing your paper, there's always that statistician that's part of the review committee who will ding you on it and be, like, no, we're not passing it. You've got to go back and do two more animals for this group. And then it's, like, ah, that could set you back, like, a year and a half in a published study. So you always want to do that upfront.

Tim Ferriss: Yeah, I mean, especially − I was looking at − with some mutual friends of ours, looking at a study involving beet juice intake and endurance gains.

And they were using a small sample size of extremely high-level endurance athletes. And if you were to take the results, it was, like, a 2 percent performance increase or whatever and try to convey it, it sounds extremely unimpressive. But the entire study was underpowered in some fatal ways.

But the question for you − so I enjoy scuba, but scuba can be dangerous, right? Who knows? So you get snagged on

something, or let's say you're − let's just take a different scenario.

So, instead of using a rebreather with pure oxygen, right, so an excess of oxygen, you risk running out of oxygen, right, or excess of CO2 levels. Let's say you're a free diver and trying to break records.

Would taking a sort of single large dose, like a bolus of exogenous ketones or ketone esters before a record attempt be − would that be a rational sort of insurance policy, or would that in any way help mitigate potential damage?

Dominic D'Agostino: Yeah, that's a really good question. So our lab, in addition to looking at oxygen, we also look at what's called hypercapnia, which is high CO2 levels, because if you're in a spaceship that's headed to Mars or you're in a submarine, the level of CO2 that you're experiencing is about on an order of ten times higher. So that's something that we're looking at.

But when it comes to oxygen utilization, I guess one the studies you could refer to is Peter Attia's blog where we look at − we've kind of set the work. Peter took a ketone salt that we had, kind of a crude version of it, and I commend Peter for his bravery in downing this.

Tim Ferriss: This is the jet fuel that made him dry-heave in the kitchen?

Dominic D'Agostino: Yeah. So, yeah, if you look at his blog there, yeah, and I think the title is Jet Fuel, and you look at the oxygen consumption for a given work output − in his case, it was on a bike at 180 watts − he had roughly five to eight percent decrease in oxygen consumption for a given work output.

So showing that your oxygen utilization was lower, and so your oxygen − your metabolic efficiency, so that's kind of the take-home is that you can potentially enhance metabolic efficiency.

So I can tell you that when I fasted for one week, I do a lot of snorkeling and a lot of diving and just kind of watersports, and out of curiosity, I was swimming around in the pool at my house, and I noticed I could stay under longer.

And I told my girlfriend, now my fiancée, it's like, I want to do an experiment and measure − I knew what my breath-hold time

was, and then in a fasted state I had never checked it before. So I was able to stay down for three and a half minutes, I think, almost four minutes, which is, like, well beyond double my breath-hold time. And it was really remarkable. So being in a state of pretty intense ketosis allowed me to withstand levels of hypoxia.

Tim Ferriss: What was your millimolars at the time? Do you know?

Dominic D'Agostino: Yeah, I was running −

Tim Ferriss: Or roughly?

Dominic D'Agostino: Yeah, I was running between 4 to 5.5.

Tim Ferriss: Oh, wow, you were up there.

Dominic D'Agostino: But I'm a good ketone user too, so I would be, if I'm sitting at my desk, so that's what I would kind of be registering, but if I got up and took a brisk walk around campus or around my place or something, that would drop down to, like, 2 because I think the peripheral uptake of ketones would be higher.

Tim Ferriss: You also have a lot of mass you're walking around with.

Dominic D'Agostino: Yeah. And I think we build our transport and mechanisms of ketones with time, so the mono − it's called the monocarboxylate transporter, sort of the protein that gets the ketones across the membrane and allows cells to use it, is upregulated over time.

So the longer you're on a ketogenic diet, the more benefits you could potentially derive from it because your body is adapting to that state of ketosis by upregulating transporter mechanisms.

And a few of my colleagues study this. And at least in a rodent model, it takes about four weeks, and you could actually double the protein level.

The actual subunits of the proteins that are part of the transporter goes up about 50 percent when you transition an animal to a ketogenic diet for four weeks. So that's a pretty remarkable −

Tim Ferriss: That is.

Dominic D'Agostino: − increase in the potential of utilizing ketones as an energy source.

And I think some of the work by Jeff Volek − I just had an opportunity to visit him at Ohio State just last week, and he's done some remarkable work just showing between fat-adapted athletes and carb-adapted athletes, and they're both at elite levels.

If you look at substrate utilization between these two groups, it's like night and day. Even the best carb-adapted athletes, they're the ones that are using fat at the highest level, are using much less fat than the fat-adapted athletes, than the guys that are on the ketogenic diet. I mean, they're literally using about two to three times more fat during exercise.

And I think that's what happens. So I think resting and just kind of being in a calm state and letting your sympathetic nervous system kind of chill out and having a good − diving is − a lot of mental preparation goes into diving. But I've found that if I can just kind of calm my body down, and if I'm in the state of nutritional ketosis, fasting ketosis, I could increase my breath-hold time by, like, three times, like, 300 percent. And that blows my mind, so I need to study this.

Tim Ferriss: I've also replicated that myself in two different experiments. I mean, it's an N of 1, but, yeah, the magnitude of difference, it's kind of like you're a rat swimming around for an hour instead of 25 minutes or 15 minutes rather, double or triple breath-hold time at even low 1s, like 1.3 millimolars.

Even on a very strict, calorically restricted ketogenic diet, I very rarely get past 3 unless I'm ingesting stuff that facilitates it, meaning supplemental ketones, MCT oil, etc.

But question for you on the adaptation: I'm so interested in this. So, for instance, people talk about muscle memory, right, where people regain weight faster, muscle weight after they've gained it once before, even if they lose, say, 50, 60 pounds like Casey Viator did at one point, and then regained it, and they're, like, oh, well, that's muscle memory.

And some people, at least based on reading I've done, attribute that to satellite cell growth and so on that happened the first

time around that facilitate this kind of regrowth. So there's a persistent benefit to that one-time event.

What is the persistence of the upregulation after four weeks of being on keto? So let's say you stay on a strict keto diet for four to six weeks. You upregulate these proteins and therefore sort of the uptake or transport by 50 percent. If you stopped that and didn't follow a ketogenic diet again for another six months, is there a persistence of effect, or if you had to guess, what would you say?

Dominic D'Agostino: Yeah, anecdotally, I would say yes.

Tim Ferriss: Cool, yeah.

Dominic D'Agostino: I mean, there's just some memory going on here and, yeah, if you just − if you use ketone levels as kind of an index for this, like your body's ability to make ketones, it's definitely better. Like, if you're on a ketogenic diet and you break ketosis and go eat sushi for a couple days and come back, I can get into ketosis real quick, relative to the big learning curve I had when I started doing this.

So I would say yeah. I'm not sure we've studied it to that extent I think you're referring to, but that brings up a good question because a lot of people want to go in and out of ketosis. Like, can I just use this intermittently? Can I eat ketogenic but just throw in carbs during my workout? And people say, well, should I be on a ketogenic diet all the time? Should I always be in nutritional ketosis?

And I tend to be in that state because I just feel better generally in a moderate state of ketosis. But I think it's probably good too, to have metabolic flexibility, for your body to be able to use all sorts of food for energy. So going in and out of ketosis may be optimal to get your body in and out.

And I do that from time to time depending on − you know, I'll be traveling; I'll be in Europe the next two or three weeks actually, so trying different foods.

So I'll probably get out of ketosis. But I actually travel with ketone supplements too, so I kind of cheat along the way.

Tim Ferriss: So if you go to Italy and you're eating bread and pasta, what are the main benefits − I'm making that assumption, but that's

what I would do because I'm a glutton and love carbs when it comes down to it − but if you went to went to Italy and were consuming all of that, what is the benefit of ingesting the exogenous ketones, and how would you ingest them?

Dominic D'Agostino: Okay. Depends on kind of the person, what you wanted to − if you were working out or whatever. But just for general health and energy −

Tim Ferriss: I would say for your personal use. So, if you could describe sort of how much you're working out, just in a scenario like that, right, you're traveling with these exogenous ketones. How do you use them and why?

Dominic D'Agostino: Okay. Well, there's two that I kind of bring with me. One would be a MCT powder, and it's basically caprylic triglyceride, like a brain octane but a powdered form of it. And I'm kind of − it's not on the market yet, but I just kind of have it. And I use the KetoCaNa product that's put out by KetoSports.

It's kind of the first thing I take when I get up. Well, I drink a glass of water, and then I take some − a small amount of ketones to bump me up to about 1 millimolar, and then I eat a ketogenic diet breakfast.

Tim Ferriss: And that's the combination of the MCT powder and the KetoCaNa or KetoCaNa − God, I need to − it's like Gymkhana, like that horrible but awesome movie I saw ages ago.

Dominic D'Agostino: Yeah.

Tim Ferriss: Okay, all right, KetoCaNa, is that how you guys say it? Okay.

Dominic D'Agostino: KetoCaNa, yeah.

Tim Ferriss: So do you combine those two when you first get up and take it with water?

Dominic D'Agostino: I do sometimes, not all the time. Sometimes I'll just take the straight MCT powder.

Tim Ferriss: Got it.

Dominic D'Agostino: It just kind of depends on my mood or whatever. But I always take − MCTs are so versatile, and they're so cheap and so readily available. Traveling with MCT oil is not really that good, but so the powder is something that I've been testing, and I really love it.

And the powder, the huge advantage of an MCT powder, especially caprylic triglyceride, is that with straight MCT oil, I'm running to the bathroom, you know, when I − on an empty stomach, or if I try to get my levels up to above 1 millimolar, above whatever baseline I'm at.

Whereas, the MCT powder that I'm working − that's being formulated and tested is sort of spray-dried with a probiotic fiber that's healthy for your microbiome and has some interesting properties in and of itself. But it allows you − the powder increases tolerability, at least double or triples it.

Tim Ferriss: Wow.

Dominic D'Agostino: So it allows you to kind of cruise along at an extra 2 millimolar and stay there. And then you could take the powder and then add some KetoCaNa to it or some other ketone salt products that we're developing and basically, I mean, you're approaching the potency of a ketone ester. The ketone esters will probably always be the most potent molecules out there. It'll be hard to touch that.

But some of the more palatable ketone salt products that are being developed and tested now, and we're working really hard to make them tolerable and palatable, will be able to approach the potency of the esters that are developed for military applications, which I think is really exciting because they're going to taste − they're actually − you'll look forward to tasting them. They're that good. And they can put you into that mild ketosis range, that 1 to 3 millimolar independent of carbohydrate restriction or fasting.

So you will have the ability to derive a lot of the benefits, whether it be health, longevity, performance, of ketosis, of higher levels of ketosis than you could otherwise get with any kind of MCT oil out there or anything out there.

So I will bring that with me when I travel. And so I'll be in Budapest and Belgium and a few other places along the way. And I will probably not be eating keto. I'll be eating low-carb

but not keto. But I'll be cruising around at probably 2 to 3 millimolar, more or less off of a ketogenic diet, low-carb but not ketogenic.

Tim Ferriss: So you'll take your MCT powder in the morning with water, then you'll have a keto breakfast. What does the breakfast look like?

Dominic D'Agostino: This morning, I had eggs. I usually have four eggs and some kind of fish.

I'm a big believer − I've kind of − I eat beef, but I've been phasing out beef and chicken and probably getting about two-thirds of my protein from fish. So I had eggs and fish in the form of sardines and a half of a can of oysters. I've been on this oyster kick for a while.

Tim Ferriss: Why is that?

Dominic D'Agostino: Oysters? Well, they're like a nutrition powerhouse, right? So are sardines. So I get the sardines packed in olive oil. But they're really high in micronutrients like selenium, which are things that are maybe hard to get from other sources out there, but I just like the taste of them too.

So sardines are really good to travel with. They're in my travel food too. So whenever my bag is packed, I usually have about a dozen cans of sardines packed in extra virgin olive oil. So I tend to just − I like them so much I eat them when I'm home too.

So I have, yeah, fish and eggs and some kind of green, usually asparagus, broccoli or spinach or kale. And if I make kale, I like to cook bacon and I cook the kale in the bacon grease. But I didn't do that this morning, but I'll probably do that tomorrow. So that's what I had for breakfast.

But before I eat breakfast, I always kind of drink water first, and I take branched-chain amino acids with the ketone products that I just told you about. And that kind of gets energy to my brain immediately, and I'm kind of really good to go after that.

And usually − well, before that, I let my dog out and he just kind of goes crazy, so I kind of run around and watch him chase animals off our property, so that's always an entertaining

thing while coffee's − or I got water brewing for my coffee, and I got my breakfast cooking. So that usually goes on in the morning.

But, yeah, I always − my breakfast is always pretty much ketogenic. And if I have coffee, I do put butter in it, and I put MCT powder in it on top of the butter, so it's very ketogenic.

And the macronutrient ratio of my breakfast is always about 70 to 80 percent fat with the balance being protein and a little bit of carbs from whatever green vegetables I have.

Tim Ferriss: And the BCAAs, what brand are you using?

Dominic D'Agostino: Yeah, I use Scivation.

Tim Ferriss: How do you spell that?

Dominic D'Agostino: Yeah, it's short for science and innovation, so S-C-I-V-A-T-I-O-N, right, yeah, Scivation. So Scivation has been an incredible supporter of our cancer research program.

So, as you know, getting funding to do metabolic therapy research or research on diets and nutrition and just basically cancer metabolism in general, just people don't study it.

The CEO of Scivation is a close friend of mine, and he has been, for personal reasons and just kind of scientific reasons, he has supported our cancer research program.

And his branched-chain amino acid product is called XTEND, and it's probably the most popular one out there, and it's on probably the most popular on Bodybuilding.com. And it's actually the product that we're using in our cancer studies.

So he asked me − he contacted me and wanted me to study this, and I looked at the formula, and it had a high amount of glutamine in it. So I said, you know, I want to study this, but let's remove the glutamine and just do pure branched-chain amino acids.

And I think he replaced the glutamine and put some taurine in it or whatever, and we started with that. And we added branched −

Tim Ferriss: Now, is that because the glutamine is glucogenic, or what was the reason for removing the old glutamine?

Dominic D'Agostino: Yeah, I should describe − so cancer cells kind of default to a metabolic phenotype called the Warburg effect, right? So they basically derive most of their energy from glucose metabolism. And their biosynthetic processes, as a tumor grows, it's using glucose for energy, but it's also using glucose to expand the biomass of the tumor. So it becomes the primary source of energy.

And we knew this for some time, and that sort of underlies the basis of using what's called a PET scan for imaging the location and the aggressiveness of a tumor in imaging, an FDG-PET scan. So it basically shows sugar metabolism or glucose metabolism.

So now, investigators understand that the amino acid glutamine is also used at a fairly high concentration relative to other amino acids, I guess I would say, by cancer cells. And we call that glutaminolysis. So cancer cells can use glucose, primarily glucose, but they can also use glutamine. And this is understood now and kind of well-defined in the literature.

But we know that glutamine, I mean, some formulas actually promote or hospitals will promote giving IV glutamine or oral glutamine to cancer patients. That's not necessarily proven to be a bad thing, but I think I was airing on the side of caution by removing the glutamine from the XTEND product, at least for our studies. And we wanted to go back and do a parallel study with the glutamine actually to see if the −

Tim Ferriss: And the IV glutamine in the hospitals is for waste − for an anti-catabolic purpose, or is it for some type of recovery purpose? Why are they doing that in the first place?

Dominic D'Agostino: Yeah, glutamine is −

Tim Ferriss: Because I know a lot of people take glutamine post-workout, for instance.

Dominic D'Agostino: Yeah. If you're ingesting it, the gut pretty much − the gut and the liver, I think, probably are pretty greedy and take their share. I'm not sure how much glutamine you're actually getting to the muscles when you do that.

But glutamine, I would say, is a conditionally essential amino acid, so under periods of high stress or catabolic physiological state, your body will use more glutamine.

Glutamine is also an important amino acid for maintaining your immune system. So it plays a − I would say if you're deficient in glutamine, it can compromise your immune system.

So you want to make sure that if your immune system is challenged, which it would be if you have cancer, or you're getting chemotherapy, if you're a burn patient, you're going to want − you might want glutamine, although we're testing a hypothesis that we want to metabolically starve cancer cells in our experiment and preserve muscle at the same time.

So the XTEND product that's out there by Scivation is a remarkable product. I think people like it because it tastes so good. So the people who formulate the product really know what they're doing with taste. So it tastes really, really good.

And if you want a successful product, it doesn't matter if it cures cancer or enhances your performance ten times over. If it doesn't taste good, people are not going to take it. So the Scivation branched-chain amino acids, they taste really good, but they're also very tolerable and very palatable.

But this particular product had glutamine, so we removed it from the formula for our studies, and we ran a study with a ketogenic diet, and we added the branched-chain amino acid to the ketogenic diet.

And we looked at survival of mice with advanced metastatic cancer. And adding the branched-chain amino acid to the ketogenic diet, we had like a 50 percent increase in survival with the ketogenic diet alone.

And when we added branched-chain amino acids to the ketogenic diet, there was trends for an increase in survival, but I think the big thing is that we saw the animals were maintaining their weight better with the branched-chain amino acids added to it.

So, with branched-chain amino acids, one of them is leucine, and we know leucine can activate mTOR, and mTOR has been

associated with driving, a major driver for cancer growth and proliferation.

And there's cancer biologists out there that would say, well, if you give leucine, you're just going to drive cancer because you're stimulating an anabolic process that can drive cancer growth and proliferation.

But I would kind of argue that that's not the case here. We definitely don't see it in this model, and some of the other studies out there do not show that branched-chain amino acids cause cancer to grow faster, and some of it shows the opposite actually.

But I think branched-chain amino acids have − their effect on anabolic processes are relatively specific to skeletal muscle, and I think that's really important to understand is that stimulating anabolic processes is not a global effect, is that it's kind of similar to anabolic steroids right? So there's specific receptors on the muscles. We think that the −

Tim Ferriss: Right, and that's also why if you take a sort of less selective growth agonist, you end up looking like you're seven months' pregnant as a bodybuilder because your intestines are the size of your forearms, yeah.

Dominic D'Agostino: Yeah, IGF-1 is great for growing your skin and your organs, yeah, so it has a pretty global systemic anabolic effect, whereas − and we haven't proven this yet, but I think just based on literature and we're really delving into it, we think that the branched-chain amino acids will be relatively specific for skeletal muscle.

And to look at this, we're going to feed animals the branched-chain amino acids, and then we take the actual tumor tissue out, and then we do a series of metabolic analysis and assays and everything to look at the signaling and the insulin signaling, the metabolomics, the growth factors and whatnot and compare it to the groups without the branched-chain amino acids.

So we're really delving mechanistically into this.

Tim Ferriss: Which is something I love and enjoy about your research and our conversations is that, I mean, you have a lot of expertise in

neurochemistry, neurobiology, cancer chemistry, but would you consider yourself a nutritionist?

Dominic D'Agostino: You know, as an undergrad, I enthusiastically went into a nutrition science program at Rutgers University, and my − who would you call it? I guess my guidance counselor at the time just wasn't a very interesting person. And it was like, well, I kept going to her, and I said, well, direct me to labs that are doing interesting nutrition science research.

And there wasn't a whole lot going on. I mean, I like Rutgers and everything, but there just wasn't a whole lot of stuff going on there that really interested me.

And the more people I talked to − I was kind of going the pre-med route, and people were like, well, yeah, you should probably major in biology too. So I double-majored in nutrition and biological sciences.

But I really had a passion for nutrition. And then when I went into a PhD program, it was neuroscience because I was really fascinated with the brain but also did physiology, and I studied the neurocontrol of autonomic regulations, so how the brain controls our body, our physiology.

And then I started − did my postdoc in looking at physiological resilience and the oxygen toxicity thing, and it brought me back full circle because when I started − I was basically a pharmacologist as a neuroscientist trying to find a drug that would mitigate oxygen toxicity seizures.

And I'm looking at all these drugs, and I realize that they're not very good. They would be good if you give them at a dose that would sedate a warfighter and basically put them into a coma, and it's not very [inaudible] −

Tim Ferriss: Wouldn't be a way to prevent seizures.

Dominic D'Agostino: − ideal situation, yeah. But then when I discovered the ketogenic diet, and I wasn't really excited when I first discovered it. I was like, let me see the research on this. There's a lot of things out there.

But the research on it was so cut and dry. I mean, there was an on overwhelming amount of scientific research showing the efficacy of the ketogenic diet for drug-resistant pediatric

seizures and now in adults too. And I realized, wow, this is like the most powerful metabolic therapy out there for seizures, like bar none.

And I was, like, I realized this was grossly underutilized, and if I could harness the power of this and apply it to something as esoteric as CNS oxygen toxicity, that would be really cool.

So I could kind of bring back my passion for nutrition, which was always there. I always, even throughout grad school and postdoc, I was totally into working out and nutrition and understanding different diets and trying lots of stuff on myself.

It allowed me to kind of come full circle and incorporate nutrition research into my research now. So our entire research program is really based on the ketogenic diet. So we do ketogenic diet studies, exogenous ketones, but we also do metabolic drugs. So we do Metformin and a few other drugs.

Tim Ferriss: Well, and a lot of − I mean, you mentioned Metformin as sort of a regulator of liver glycogen, hepatic glycogen.

Dominic D'Agostino: Yeah.

Tim Ferriss: And there are plenty of folks who take Metformin − is it still called Glucophage or Glucophage − I'm not sure the brand name − but the Metformin prophylactically?

I mean, these are otherwise what you'd consider healthy people who are taking it primarily to prevent cancer growth, if I'm not mistaken. I mean, is that fair to say, or are they using it for other purposes?

Dominic D'Agostino: Yeah, you can use it for a variety of reasons. You could use it as kind of a metabolic prophylactic to prevent you from getting Type 2 diabetes down the road.

But when it comes to cancer, yeah, it definitely activates or dampens or activates signaling pathways associated with cancer growth and proliferation. And if you're activating ampakines, which it's well known to do that, and activate various downstream signaling processes, it mimics in many ways calorie restriction and fasting, the same processes that would be activated.

It comes with some side effects, and some people have intolerance to it, you know, GI issues with it. But overall, it's a really safe drug. I mean, so many prescriptions have been written for it. We know what it does and what it doesn't do.

We don't really − the cancer − there's a lot of research in cancer right now. And when you go to a cancer conference, you hear there's a lot of discussion, a lot of buzz about Metformin, but there's also a lot of debate as to how it's working.

So some people think it's toxic to the mitochondria and it's inhibiting Complex 1 of the mitochondria. And other people are saying it works purely by activating ampakines, and other people by its ability to regulate hepatic glucose output or a combination, and some people through other mechanisms.

So we don't know how it works, but I think − I did a run where I took 1 gram of Metformin for − I think it was 12 weeks, and I got bloodwork.

And the only thing I saw was that my testosterone was lower. So I think that's a side effect. I have since got off of it, and I rechecked and my testosterone levels are back into the normal range that they were. And that's the only thing −

Tim Ferriss: Did you feel any fatigue?

Dominic D'Agostino: No, I didn't. Well, I felt − I don't know how to describe it − a little − maybe a little less anxious, a little bit − kind of like you kind of set the governor. Like, my highs weren't as high.

And I would kind of dose it − I'd dose it twice a day. And my bigger dose would be at nighttime before I went to bed because that would be my bigger meal. So I would kind of dose the Metformin according to my food intake, which I think is important.

But, yeah, I didn't really notice any side effects. I went up to 2 grams a day initially and found out, okay, that's about my tolerance to it, so I backed down to one.

Tim Ferriss: Now, so to gut tolerance, meaning to disaster pants, like, risk? Is that −

Dominic D'Agostino: Not the MCT effect, not what I would describe as the MCT effect.

Tim Ferriss: Okay, all right, all right.

Dominic D'Agostino: But it's kind of like a dull kind of aching feeling in the stomach. But, yeah, there were, like, loose stools a little bit, and then I just kind of − the next day, I backed off, and I played around with it for probably two or three weeks. And then I realized, okay, 1 gram is about what I can do safely and comfortably, I thought. A

And, yeah, I did that for three months, and I tried to take nothing else at the time. I wasn't experimenting with any other things. And I took that, and my testosterone went down. But my other − like, my triglycerides were the lowest ever. My HDL was, like, 98.

Tim Ferriss: Wow.

Dominic D'Agostino: It bumped up from, like, 88 to 98. And other things, like my C-reactive protein wasn't even measurable.

And I tried not to calorie-restrict or even change my diet at all. So some things went in a positive direction, but I really thought that it suppressed my testosterone. And there was a couple publications that would indicate that it does that.

You know, maybe if I took 500 grams a day, it wouldn't − or 500 milligrams a day, it wouldn't have that effect. But I felt [inaudible] a gram a day. And I had, like, a powdered version, so it was probably, like one to 1.5 grams a day. I was kind of measuring out with a powdered version. So it was at least 1 gram a day I was taking.

So that's my experience with it, and I know a few people out there − if cancer runs in your family and you are concerned that you may be at risk or maybe had cancer in the past, I think it's a pretty safe drug to take.

One of my students is a PhD student, and his entire PhD dissertation is on Metformin. So we're looking at it, you know, very deep kind of understanding of Metformin as much as you can in a PhD dissertation.

So we delve over the literature. We're running studies in individual cells in isolation in advanced cancer models. And we have a pretty good understanding of what it does and what it doesn't do. And in our metastatic cancer model, we have survival times increased almost 40 to 50 percent increase in survival. And you have to give a pretty big dose.

Tim Ferriss: Now, metastatic, is that with some − you're talking about Metformin?

Dominic D'Agostino: Yeah, it's Metformin to a standard diet increases the survival times of animals that have metastatic cancer. We've presented this at several meetings, and we're finishing up the data now to publish it, which will be published pretty soon.

Tim Ferriss: And does that include in the animal models − I'm not sure if this is in the animal, but, like, glioblastoma multiforme, like, the GBM, sort of the uniformly − what are considered kind of the uniformly fatal cancers, is that also − do you still see the 40 to 50 percent?

Dominic D'Agostino: Yeah, so it's interesting. So the metastatic cancer model that we have, the primary tumor is derived from a tumor that pathologists confirmed was a glioblastoma.

What's interesting about these cancer cells are so aggressive that we have them in culture, right? We have isolated subcultures of these cells that are metastatic and very aggressive. And they're transfected with a gene that makes the protein luciferase. So it basically makes the cells glow in the presence of luciferin.

So not to get too complicated, but if we take these cells in culture, right, we harvest them and we implant them inside the flank of the animal or underneath the skin, the cells metastasize to all the organs and even the brain.

So, typically, a glioblastoma is thought not to metastasize the other organs of the body, and it stays in the brain. But I think we don't typically see people with glioblastoma with liver cancer because they die of the glioblastoma before it metastasizes.

So we've basically − and this is a model that was generated by Thomas Seyfried from Boston College. He wrote the book,

Cancer as a Metabolic Disease. It's a really, really good book. It's, like, required reading for all my students.

But he developed this model and made the cover of International Journal of Cancer. And it's probably the best model out there, so it's why we chose the model. But it's a model of advanced metastatic cancer.

And the primary tumor had a glioblastoma kind of cell type to it. And these cells were kind of described as tumor-associated macrophages, so they can travel along blood vessels. They can metastasize to organs very aggressively.

And it makes it a convenient model to use because when you implant the cells, the experiment goes real fast, right, because the animal succumbs to the tumor burden within about 21 days. So we can test and we can basically test a lot of things really fast because the tumors grow so fast. Within 21 days, we have to put the animal down because it'll succumb to the tumor burden. So it allows us to test various drugs and diets and ketogenic agents.

And when we tested Metformin with a standard high-carbohydrate rat chow, and we formulated it into the food, so it would be equivalent to a person taking about 2.5 grams a day − so Metformin comes in, like, 500-milligram tablets, I think even sometimes one-gram tablets, so with the 500-milligram tablets, it would be taking, like, five tablets a day would be the human equivalent to that.

The animals lived about 50 percent longer, about 45 to 50 percent longer survival time. So, instead of living 21 days, they lived almost 40 days.

Tim Ferriss: That's amazing.

Dominic D'Agostino: So what we're doing now − so we have to tediously test all these things in isolation, and then we have to do different dose ranges too, right? So we've got to do a variety of dose ranges and make all these dose curves and everything.

But I just want to jump right into it. I want to do a calorie-restricted ketogenic diet with ketone supplementation and Metformin and hyperbaric oxygen. I want to jump right to it.

And we're kind of doing some of these things as pilots, but we're testing − I think it's really important to get a handle on what each of these things do at different dosages.

Tim Ferriss: No, definitely. Let me − I apologize for interrupting, but if you − and you would figure this out earlier of course − but if you found out you had relatively advanced cancer of some aggressive type, what are the tools that you would throw at it that you have a decent degree of confidence would have a beneficial effect?

So you mentioned a few things, right? You mentioned calorie-restricted ketogenic diet, so I'd love to hear what calorie-restricted means, right? You mentioned Metformin. You mentioned hyperbaric oxygen treatment. You mentioned exogenous ketones. We talked earlier about fasting.

But let's just say you found out, oh, shit, I'm in a bad situation here, and this is a very, very aggressive cancer. Putting aside the chemotherapy and some of the other therapies that you might have administered, of the toolkits that we've been discussing, what would you do?

Dominic D'Agostino: Okay. Well, so I'm not the kind of person − some of my colleagues are kind of very anti-standard of care, some of them for some ways. But I think you have to − I know you told me not to talk about chemo, but if you have something like testicular cancer or leukemia or lymphoma, there's a variety of cancers you'd be crazy not to do the standard of care.

So, when I talk about this, one could potentially use it as a standalone therapy, or one could use it as a way to further augment the efficacy of standard of care, which we plan to do.

Tim Ferriss: For sure.

Dominic D'Agostino: So, say, worst-case scenario, like glioblastoma, right, a glioblastoma, in some ways it's really a good model to look at because your survival time is, like, one year, give or take a few months. So it's almost − if we do a study with glioblastoma patients, it's almost like you have historical controls that you can refer to.

So the ketogenic diet, I think would be absolutely like your base therapy, right? And it would be not just a macronutrient ratio. It would be the sources of the macronutrients itself. Like,

you would have to − you would do a macronutrient ratio that would put you in ketosis but take extra care to get fish that was from a natural source or grass-fed beef.

And I think these things would probably be important because we know the fatty acid composition changes dramatically from a corn-fed cow than a grass-fed or a salmon that's farm-raised or wild.

So the ketogenic diet would be kind of the base. And instead of the normal three-day or three-times-a-day eating pattern, I would go to an intermittent fasting personally. And I think that would be − you could further harness the power of ketosis by fasting throughout the day and then having a ketogenic meal once a day.

Tim Ferriss: So your single meal would be like a dinner?

Dominic D'Agostino: It would be dinner, yeah. You would eat probably within a window of four hours [inaudible]. And I've experimented with that, and that's possible. I just like eating though, so I like sitting down and having a social breakfast, and I don't eat during the day, and then I have a nice sit-down social kind of dinner at night. So I like that. So, either way, I think ideally I would probably do one meal a day.

And ketone supplementation, I think − I mean, we've shown, independent of even the ketogenic diet that ketones have an anti-cancer effect. They not only do − our ketones cannot be utilized as an energy source by aggressive cancer cells that have defective mitochondria.

So cancer cells cannot use ketones effectively as an energy source because they have defective mitochondria structurally. They're defective. If you look at the mitochondria of cells of a glioblastoma patient, the inner cristae, the little folds inside the mitochondria where ATP is actually produced is completely screwed up. And they're also deficient in various catalytic enzymes that would allow the cancer cells to make energy from ketones.

So ketones as a source of energy is a very poor energy source for cancer. So putting our body into a state of nutritional ketosis would be a way to marginalize the fuel source to ketones and enhance the energy capacity of our healthy cells. So exogenous ketones −

Tim Ferriss: Yeah. For you personally, how much would you take? When would you take them?

Dominic D'Agostino: Yeah, I would take a level of exogenous ketones that would put me above whatever baseline I was at, between 1 to 2 millimolars. So, if I'm cruising along at, like, 1.5, staying on a modified Atkins-like diet, I would further boost that to, like, 3 or 3.5 with exogenous ketogenic agents.

I think the easiest could be medium chain triglycerides, you know, MCT powder, which will be available soon, the KetoCaNa product. There'll be some products coming out pretty soon, ketone salt products that'll taste really good and will allow you to easily achieve this.

Tim Ferriss: How much would you have to take, you personally, to jack your ketone millimolar up 1 or 2 millimolars like you described? Is it three times a day, twice a day? What type of dosing and frequency are we looking at?

Dominic D'Agostino: I would do twice a day, probably twice a day or maybe three times a day depending. See, the MCTs kind of allow you to maintain the levels up a little bit higher. But I think it's okay to not continuously provide an exogenous source of ketones, but maybe just use them when you need them if you need a boost in energy. So you might want to ---

Tim Ferriss: But if you had the glioblastoma, you would do two to three times a day?

Dominic D'Agostino: Yeah, I would do two to four times a day probably because the way kind of our experiments are panning out, it just looks like the stronger you stay in ketosis, the higher levels you get, the better tumor suppressor effects that you get.

So, yeah, I would use them to the extent where I was pretty much constantly from the time I wake up keeping my ketones more or less artificially elevated. Well, I guess it wouldn't be artificial if you're adding MCTs, which are a good carrier for the other forms of exogenous ketones, to keep it further boosted an additional 1 to 2 millimolar minimum.

Tim Ferriss: Got it. And what about other things that you might do?

Dominic D'Agostino: Yeah, the Metformin. I would titrate Metformin in to where it starts causing side effects and then back off from there.

Tim Ferriss: So titrate meaning you'd just start low and increase the dosage?

Dominic D'Agostino: Yeah, even, you know, you can get it in 250-milligram tablets or break the tablet in half and keep, you know, start out one week, maybe start at 500 and then go up to 750 and then to a gram, and then bump it up to where you start to get some GI discomfort and then back it off and then stay there.

Metformin's pretty cheap, pretty remarkable drug in our hands. And I think it would synergize with the other things that I'm describing.

So DCA is another drug that we're looking at, and one could simply get on Google and do a search for dichloroacetate, DCA and cancer, and find a lot of interesting information. I think there's registered clinical trials going on right now with glioblastoma. And we think it may synergize with some of the things that I'm talking about, even Metformin.

So DCA activates a particular enzyme metabolic pathway, pyruvate dehydrogenase complex, and for reasons we don't completely understand, it can cause cancer cells to − it kills them. It triggers apoptosis in cancer cells by reasons we don't completely have a handle on yet.

But it's used clinically for lactic acidosis. And lactate can drive − or in the micro environment, lactate can drive tumor growth. So DCA can actually make your body more alkaline, right? I mean, it's used clinically for that application.

And maybe its therapeutic effects may have to do with that, but we know that if we just grow cancer cells in isolation, like a dissociated cell prep and put on DCA, the cancer cells start to die and at levels that are relatively nontoxic to healthy cells.

So dichloroacetate at − you know, I don't like to give recommendations, but if I was to − this is all theoretical −

Tim Ferriss: No, this is for you and theoretical, yeah.

Dominic D'Agostino: Yeah, I would start at, like, 10 milligrams per kilogram, and I'm a little over 100 kilograms or whatever, so you could do the math on that.

And so I would start up to 10 milligrams per kilogram and probably not go higher than 50 milligrams per kilogram because once you get above 50 milligrams per kilogram of DCA, you start to get peripheral neuropathy. And we see this in our animal models, and it's also reported in patients.

If you go onto the forums of patients that have glioblastomas, they'll report tingling in the fingers and the toes at, like, once they start reaching about 50 milligrams per kilogram. I think the clinical trials use 20 milligrams per kilogram if I'm not mistaken.

So DCA activates pyruvate dehydrogenase complex, so that complex makes the mitochondria − it activates the mitochondria. And if you active the mitochondria of cancer cells, which have defective mitochondria, it causes the mitochondria to, like, explode and the cancer cells, it triggers apoptosis.

So it probably triggers the release of cytochrome c from the mitochondria, which is part of apoptotic pathway.

Tim Ferriss: Apoptosis, meaning cell death.

Dominic D'Agostino: Yeah, programmed cell death.

Tim Ferriss: Programmed cell death.

Dominic D'Agostino: Yeah, yeah. And that's kind of like a theory that I'm throwing out there, but it's based on kind of what we know, what we see in the lab and what we know from the literature. But it's relatively a nontoxic drug, I mean relative to the chemotherapeutic agents that are − chemotherapy is − are highly carcinogenic.

So when you're giving chemotherapy, you're giving a highly carcinogenic substance. So does it make sense to treat cancer with something that we know is a powerful carcinogen? It doesn't. In some cases, it does. Like I mentioned, some of the −

Tim Ferriss: Testicular cancer.

Dominic D'Agostino: − cancers I mentioned before, yeah, and there's application for it. But I think we have to view this in perspective. DCA, I don't

think you can patent it. It's like a really simple molecule, dichloroacetate, right?

You can kind of visualize it if you're a chemist. It's a pretty small, simple molecule. And it has a pretty powerful metabolic effect. And again, it works well by itself with a high-carbohydrate diet.

So just think about how it may synergize with a ketogenic diet, exogenous ketones, you know, Metformin, intermittent fasting. It's working through overlapping mechanisms. So you are further compromising sort of the energetic state of the cancer cells by adding it to the mix.

Tim Ferriss: And if you had this − you're using this portfolio of techniques. So you're on a ketogenic diet. You're intermittent fasting. You're consuming exogenous ketones two to four times a day, enough to jack up sort of your ceiling by 1 to 2 millimolars. You're perhaps taking Metformin in combination with DCA.

Would fasting be additive to this, or would it be redundant in your mind?

Dominic D'Agostino: I think it has its place, you know, and you may not want to do, depending on your overall health − like, my health, I can tolerate fasting pretty much every day. Intermittent fasting would be no problem.

But I think you could derive benefits by fasting two or three times a week, even once a week, I think could be beneficial. But I would try to do it − you know, some people do every other day fasting, but I think one meal a day is one way to go about doing it, or alternatively if that's too stressful, you could eat two or three meals one day, and then Monday, Wednesday, Friday do one meal per day.

But I think that gap in time, that 20-plus hours that you're not eating and that you have Metformin in your system, you have DCA in your system, and you have exogenous ketones kind of flooding your bloodstream, I mean, it's putting your physiology − it's putting your metabolic physiology into a state that's compromising the tumor tissue.

And I always − and I discussed this with my colleague, Thomas Seyfried, he thinks that if you don't have cancer and you do a therapeutic fast once or twice a year or maybe three

times a year if it's a shorter fast that it would purge any precancerous cells that may be living in your body.

So, if you put your physiology into a state of fasting ketosis, that puts tremendous metabolic stress on cancer cells that are highly dependent for survival and growth on high levels of glucose and insulin. By subtracting them of those growth needs, they can trigger apoptosis autophagy, and you could potentially purge yourself of some precancerous cells.

Tim Ferriss: Precancerous cells, which pretty much everybody has by age 35, 40, right, I would imagine?

Dominic D'Agostino: Pretty much, yeah. Our immune system is kind of a surveillance mechanism that detects them and takes care of them. In our animal models, the cancer cells are kind of − they've evolved to evade the immune system, so that's one of the hallmarks of cancer, right, that it can metastasize, evade the immune system.

Now, in 2011, thy finally added that it has an aberrant metabolic phenotype, but they ignored the whole metabolic thing for a while.

But, yes, so our immune system kind of becomes overwhelmed or declines in its capacity with age. So that surveillance, that immune system surveillance over our bodies of these potential neoplastic cells can be overlooked.

And I think one way to reset our body and even stimulate our immune system is to do therapeutic fasting.

Tim Ferriss: Definitely.

Dominic D'Agostino: And I think it can build us up in ways that we're just really starting to understand now.

Tim Ferriss: So I'm trying to − or I'm not trying; I am fasting at least once per quarter. And the question of duration is one I'd love to ask you about because I can go seven days if need be. I've done that already.

Last time, I wanted to see what it would be like just from a starvation standpoint, you know, crash in an airplane, going from high-carb intake to no food, which I would not do again. I would induce ketosis as quickly as possible nutritionally and

then do it because I had excruciating lower-back pain. I just was like in a fetal position with − I think my uric acid levels −

Dominic D'Agostino: I've seen that.

Tim Ferriss: − were just through the roof, among other things. So I'd like to avoid that. That was really shitty.

But my question is: If the therapeutic fast is, say, two to three times a year, what duration might those fasts be? What is the sort of minimum effective dose in your colleagues' mind, or I'm not sure if it was colleague or student, but −

Dominic D'Agostino: Yeah. If you want to do it kind of hardcore −

Tim Ferriss: Yeah, that's kind of my MO.

Dominic D'Agostino: − and be resilient, yeah, yeah, okay − and this would apply to someone on a high-carbohydrate diet, too. But what I've seen, I mean, you just described it very nicely there, the back pain. You know, your body goes into kind of more or less a stress −

Tim Ferriss: Shitty, shitty sleep, like, horrible −

Dominic D'Agostino: Yeah.

Tim Ferriss: − I guess that's − is that a cholinergic response? I don't know. But every − I was in a location where there were 40 people fasting, 50 people fasting, some of whom had been doing it for two weeks, three weeks, four weeks or so.

Dominic D'Agostino: Wow.

Tim Ferriss: But everyone reported horrible insomnia and, like, tachycardia, like, rapid heartbeat when they were trying to sleep.

Dominic D'Agostino: Yeah, so, yeah, that's an activation of your sympathetic nervous system.
It's your body saying, hey, this is a stress response, so that's lack of fuel flow to your brain will trigger brain fog; it'll trigger headache; it'll trigger activism of sympathetic immune system.

Your insulin levels will go down very rapidly, right, and when insulin goes down, it has a natriuretic effect, which means that you lose sodium, so you're peeing out all your sodium, so your

blood volume drops. You become hypovolemic, and your blood pressure will drop and that'll contribute to your headache and just feeling crappy and −

Tim Ferriss: Dizziness when you stand up and all that, yeah.

Dominic D'Agostino: − some people faint, yeah. I've seen several women − it seems to be more pronounced in women that try this, that they faint and I had a couple of them, they called me up, and it made them go crazy. Like, they thought they were going to die.

So, if you can get past that, if you can get past the feeling of − and that's usually the second and third day. I've got reports as early as the end of the first day, but I think they were kind of wimps.

But usually the second and third day, you're kind of hurting. If you can cruise through that, and I think cruising through it would be a lot easier with exogenous ketones −

Tim Ferriss: I would totally 100 percent agree, yeah.

Dominic D'Agostino: − so if you're giving your body some kind of cheat through that. So this is something that I'm kind of working on, like, developing, thoughtfully developing protocols that would make this whole process easier and even enjoyable potentially.

So, okay, in a perfect world if you can tolerate fasting, I would do it ideally, yeah, like, maybe once every quarter for five days. I think five days is sort of the point where you start to level off everything, five to seven days.

Some of the − that work by George Cahill at Harvard showed them kind of leveling off at about ten days, but they were severely obese people starting from absolute baseline.
So I would say a five-to-seven-day fast, two to three times a day or maybe two to four times − not per day, per year would be −

Tim Ferriss: I was, like, wow, this is a real interstellar moment. You were really doing some funny stuff with time. Okay, yeah.

Dominic D'Agostino: No, sorry −

Tim Ferriss: No, no.

Dominic D'Agostino: − per year, I think would be something to do. And you'd want to, you know, I would kind of say time it so it would fit into your schedule, but when I fasted, I did it right in the middle of writing grants and teaching and all this other stuff.

And it didn't − I think it increased my productivity because think about all the time that you spend preparing food, eating food, cleaning up, eliminating, and shopping for food and all these things associated with our fixation on food.

Tim Ferriss: It's a lot.

Dominic D'Agostino: And that's kind of time that you save. And I also realized that I was, prior to doing this, and this goes back five, six years ago, I had a preoccupation with food.

And even going back maybe a little bit longer, I thought I had to eat, like, five or six meals a day. And I would prepare my food, like, all my food on a Sunday and put it in bags, in Tupperware and have it in there and have it labeled, and I was kind of neurotic about it.

And that's okay if you're into that sort of thing, and I think it's good, and it actually may be more efficient throughout the week, and no offence against people who do that. But I find that not doing that makes me more productive.

And I find that eating a ketogenic diet also sustains me − sustains my energy levels to where I just get more out of life. I'm more productive. I'm not fixated on food because I don't have to eat as frequently but because my energy levels are stable. So I can spend the time doing the things that I think are more productive.
And I'm in the process as we speak − this is like the week that I submit everything for my tenure, so it's been super crazy as far as 18-hour days preparing for all this and traveling and stuff on top of that. And I can't imagine doing that living the way I used to live, eating five, six meals a day and having it timed and everything. I just couldn't do it. So this makes it easier.

Tim Ferriss: Yeah, it is very liberating to realize that you don't have to eat on the clock three times a day and that in fact you'll be fine and in some cases even better.

Dominic D'Agostino: Yeah.

Tim Ferriss: I was astonished when I went through my very unpleasant plane-crash simulation starvation. I was miserable from − well, miserable's exaggerated. I was fatigued in Day 2, and then I had the low back pain and so on Day 3 and part of Day 4, and then I was fine.

But the latter part of Day 4, 5, 6 and then before breaking the fast, I felt fantastic. I mean, I went for long walks. I felt extraordinarily cognitively sharp.

Have you found that you or other people, subjects in ketosis, require less sleep because when I get past a certain millimolar point, for whatever reason − and I love sleep, and I tend to sleep quite a bit, you know, eight to ten hours a night − but I found that I would wake up after six hours, six and a half hours and not have any morning fog and be able to go about my day without fatigue. Have you observed that in other people, or is that just a Tim thing?

Dominic D'Agostino: Yeah, I have. I've gotten emails about that. I found it in a couple kind of articles on discussing that. And I found that in myself that, like, last night, I got to bed at 2:00 a.m. I try to get to bed about, like, midnight, and I woke up at 6:30, 7:00, so I'm running on four and a half, maybe five hours, and I feel totally fine. I've been pretty productive today, did a lot of work in the morning.

And I typically run better, best on about six hours, as opposed to maybe seven or eight that I felt I required. And that depends on my activity level and kind of what's going on. But generally, I feel like I need about one or two hours' less sleep, that my requirement for that is less now.

And I think there's different reasons for that, and I think when we're in a state of nutritional ketosis, we have better fuel flow to our brain without the fluctuations in glucose throughout the day. And I think that our astrocytes actually kind of spare − our astrocytes have −

Tim Ferriss: What is an astrocyte? I apologize.

Dominic D'Agostino: Oh, I'm sorry. There's different brain cells, like neurons and glial cells, and among the glial would be astrocytes.

And it's thought that astrocytes are − they actually store glycogen, a form of carbohydrates, a form of glucose for the

neurons. And it's thought that that may be their function and that when we go to sleep, the astrocytes can actually build up their glycogen levels. So there's a couple studies that indicate this.

And I think sleep is a restorative process obviously, but I think we restore neurotransmitters, and we restore the bioenergetics of the brain when we sleep, and I think that process is more − is enhanced or is augmented when you're in a state of ketosis or if you've adapted to living in a state of ketosis. I think our brains are better able to restore homeostasis of our brain chemistry.

And I think that metabolic − so enhancing global brain metabolic activity or preserving brain homeostasis or metabolic homeostasis in the brain is a reason why the ketogenic diet is so effective for all these different seizure disorders independent of the etiology.

So, whether it's a glucose transporter deficiency or temporal lobe epilepsy −

Tim Ferriss: What does etiology mean?

Dominic D'Agostino: Oh, etiology is like independent of the cause of the disease. So, for example, glucose transporter deficiency syndrome is actually there's a defect in the transporter that gets the glucose across the blood-brain barrier for the brain to use glucose as an energy source.

So, if a child has glucose transporter deficiency, the only therapy that's offered is a ketogenic diet, and it restores fuel flow to the brain so the child can live a normal life, right?

So, even in the presence of a persistent molecular pathology, like the glucose transporter deficiency − and we know the cause; we've identified the gene and the protein product − so even in the presence of that persistent molecular pathology, the ketogenic diet can completely silence the symptoms of that disease.

And it's doing that by restoring homeostasis in the brain, not only the energy to the brain, but the neurotransmitter levels are restored; there's a balance of glucose − or of glutamate to GABA, so the GABA levels are restored.

And I think that's what's happening too when it comes to sleep. So we know if we do a cerebral, you know, a CSF, the cerebral fluid of the brain in people that are on a ketogenic diet, it shows that there's a higher GABA to glutamate ratio. So glutamate is excitatory, whereas GABA is kind of like inhibitory. It's kind of like the chilling out neurotransmitter.

So there's various things out there that you can take, like Phenibut or GABA that you can take before bed and helps you sleep. So the ketogenic diet elevates these things naturally, so that may be offering some sleep-promoting potential.

But I do think that being in a state of ketosis and having ketones elevated and having them available for your brain can enhance your restorative processes that occur when you're sleeping in the brain.

Tim Ferriss: So I am looking to shift gears a little bit. I'm looking at some goodies that I'm making a cocktail with in front of me. And I've been fasting since I got up, and it's about 1:30 my time, and I can feel my brain starting to get a little grumpy, even though I'm in ketosis. And so I'm inspired by our conversation.

I have KetoSports KetoCaNa calcium and sodium beta-hydroxybutyrate, and the label says dietary ketone supplement for enhanced physical and mental performance. This one is not for resale, for R&D use only, so this must be an early one. And then I have the branched-chain amino acids. And then I have a Parillo MCT oil, CapTri, which is the caprylic acid.

Now, on the side of the calcium sodium beta-hydroxybutyrate, the KetoCaNa, they have the directions, you know, consume 15 minutes prior to cardio-intensive exercise; maybe used with carbohydrate supplements if desired, blah, blah, blah; do not exceed three servings per day.

So I want to ask you about the risks or toxicity of consuming exogenous ketones. And part of the reason I'm wondering is because I think of consuming these while on a standard American diet or a high-carbohydrate diet, and it just seems like a very unnatural combination to me, but I could be totally off.

So I'd love for you just to talk about the toxicity risks or other risks associated with exogenous ketones.

Dominic D'Agostino: Okay. So it says do not exceed three servings per day, so you will − the GI intolerance will far exceed sort of the biological intolerance that you'll get from [inaudible].

Tim Ferriss: So your body will stop you through diarrhea before you get close to anything that'll hurt you? Is that −

Dominic D'Agostino: Exactly. I mean, that's the same thing with MCT, right? You're limited by your ability to transport it across the gut. So the mineral load that you would get from the KetoCaNa product would cause an osmotic issue in the gut. And it's great if you want to stay regular.

So it stimulates peristalsis in the gut. So you'll get that side effect probably if you exceed − for me, I could probably do up to five or six servings a day and be okay.

But as far as toxicity, and this is where we can draw off some of the rat studies we're doing, we just finished a 15-week study in rats, and it's equivalent to, like, a year or two years in humans where we fed a variety of ketone supplements from esters to the salts to combinations thereof at 25 grams per kilogram per day. So that's really high, right?

So we did that − this is part of the toxicology studies that we are doing to get FDA approval for different things.

So they actually just required 2.5 grams per kilogram per day. Well, I was, like, well, let's increase that tenfold, and we formulated it. I come at this from the FDA may see this as a drug, but I see ketones as a fourth macronutrient, right? You have fats; you have proteins and carbs. Ketones are an energy-containing molecule, and they're like water-soluble fat molecules.

So we formulated them into the diet, and we fed it − we fed our rodent models this, and we did clinical chemistry. We were doing metabolomics. We do histology. We did actually some anxiety studies where −

Tim Ferriss: What is histology? I'm sorry.

Dominic D'Agostino: Oh, histology is where we, at the end of the study, we harvest all the organs, right, like, the kidneys, the liver and heart and everything, and we weigh them out. And then we take the

organs, and then we basically treat them in a way where we can section them and make slices of them and look at the cells.

So we can look at the liver, for example, or the kidneys, and then we can examine at the level of the mitochondria inside the cells. We can examine these cells to determine whether the agent that we administered caused any toxicity to the animal, to the organs.

Tim Ferriss: Got it.

Dominic D'Agostino: And if there was toxicity, we would be able to pick it up most likely in the clinical chemistry, which we've done that. And we've also, on top of clinical chemistry and the histology, we also looked at about 27 different types of cytokines.

And we didn't see anything relative to the control, relative to the standard rodent chow. There were no abnormalities to indicate liver or kidney stress.

And on top of that we did, kind of parallel to this in the same group, we did some −

Tim Ferriss: And that was at 25 − what was it, 25 grams per kilogram?

Dominic D'Agostino: 25 grams per kilogram, so instead of delivering it like they do in drug studies with one dose, we formulated it into the diet. So we figured out how much − how many grams of food the animal ate, and then we took that and we formulated it in a way that we know that if they ate this amount of grams per food a day, they would be getting this amount.

So, instead of getting it at a big dose once a day, they would eat it − they'd nibble on it throughout the day.

Tim Ferriss: Got it.

Dominic D'Agostino: And that's kind of a more realistic way to give it instead of doing like most drug studies, or even food studies are done with food additives. They just give it in a bolus.

Tim Ferriss: So is the − I'm sorry.

Dominic D'Agostino: And we didn't see anything, no negative effects.

Tim Ferriss: Okay. So you haven't observed any toxicity then, no known toxicity? Like, there's no, like, LD50 of − sorry, lethal dose 50, like a dose that'll kill 50 percent of the subjects or anything like that or produce some nasty effect. You guys just haven't observed it?

Dominic D'Agostino: Not when administered that way. So, in taking a step back, if we were to give 25 grams per kilogram as a single dose of our most potent ketone ester, that would cause ketoacidosis in the rats for sure.

Tim Ferriss: Got it.

Dominic D'Agostino: And then that would be hard to reverse actually, but that would be such − I don't even think that volume is possible. I think the IACUC wouldn't even allow us to administer that dose because the volume would be so high for the stomach, you know what I mean? So it would be really, really high.

So we haven't seen any side effects at doses that would even approach kind of what's on the label there. And you have to figure, when these things are ingested, it's bioidentical to what our body makes anyway.

And even if we eat an egg or a piece of − if we eat muscle from an animal that's in ketosis, we're getting ketones, exogenous ketones. We're just not getting it at the level that would really put us into ketosis, although I think milk, there's some ketones in milk and different products that could kind of boost your ketone levels a little bit.

So we sort of looked into that when we were trying to understand for FDA regulations, are ketones in our food? And, yes, they are in our food if an animal's in ketosis and we're drinking milk from an animal or meat from an animal that's in ketosis. We're technically consuming exogenous ketones.

Tim Ferriss: So are there any unusual foods or beverages or anything that increase ketone levels dramatically in animals or humans that you've seen?

So I'll give you an example, and this could be a complete − well, it is speculation, but it could be just completely erroneous. So I've gotten a bunch of my friends kind of hooked on using the Precision Xtra device to track their millimolar

levels. And some of them have really gone kind of nuts where they're taking five to ten readings a day and so on.

And one of them observed − this is Kevin Rose − that artichokes seemed to spike ketone levels. And he replicated it for himself, I think, two or three times. I've been doing some experimentation with it, but I was, like, huh, interesting because artichoke extract, I've seen it used as a − what is it? − PDE4 inhibitor because PDE4 breaks down cyclical AMP, as far as I understand, blah, blah, blah.

But is there any − I mean, you could talk to artichoke specifically − I don't know if you've ever looked at it, but are there any foodstuffs or things that people can use to jack up ketone levels besides exogenous ketones or MCT oil, etc.?

Dominic D'Agostino: Yeah, that's an interesting observation with the artichoke. Artichokes are mostly fiber really, and I guess that could lead into the next question, right? Soluble fiber breaks down into short-chain fatty acids, which are ketotic.

Tim Ferriss: Oh, interesting.

Dominic D'Agostino: So I was actually at NASA a few weeks ago, and it was brought to my attention by a former astronaut, Rick Linnehan, who's also a vet, that cows are ketotic, and this gets back to sort of the thing we were talking about, about short-chain fatty acids being formed from the breakdown of soluble fiber.

And short-chain fatty acids can be a form of ketones, can contribute to ketogenesis and also the generation of butyrate in the gut, which can enhance and contribute to our gut microbiota.

So, yeah, so I think that needs to be appreciated that we were talking about foods that could enhance ketosis. And I think that one could formulate a ketogenic diet with the intention to further enhance ketosis by adding certain types of fiber, soluble fiber that are broken down into short-chain fatty acids, which are potentially ketogenic, like your friend that had the artichoke and had a big bump in ketones. That's really interesting.

I love artichokes, and maybe that's why I get levels − I'm looking at the macronutrient profile of artichokes now, and I see that, yeah, they're primarily carbohydrate but mostly fiber. And that fiber can be ketogenic.

And fiber can also assist in helping us stay in ketosis by being a buffer when they're eaten with protein because it helps slow the digestion, assimilation and utilization of protein. So you get less of a spike in amino acid levels, which can help − a quick spike in amino acid levels can shut off ketogenesis. And if you attenuate that spike, it can help promote your body into staying in that state of ketosis longer by −

Tim Ferriss: I'm sorry to interrupt. Is the spike knocking you out of ketogenesis because the liver is using gluconeogenesis to convert those amino acids into glucose, or is it something else entirely?

Dominic D'Agostino: Yeah, if you get too many amino acids getting into the liver as a source of fuel for gluconeogenesis, but also protein can stimulate a release of insulin, and insulin is very anti-ketogenic.

So it's the combination of attenuating the rise in amino acids, which will attenuate the rise in glucose, which will attenuate the bump in insulin that you could potentially get from that. So fiber is a pretty − fiber is actually really useful.

Tim Ferriss: What would be good sources of fiber that are going to have very low net carbs?

Dominic D'Agostino: Yeah, I think the staple ones that I like are − actually, artichoke is on that list − spinach, kale, broccoli, asparagus is probably at the top of my list, celery a little bit, so any kind of green leafy vegetables, like salad. I have a salad every night with mixed greens and a lot of olive oil.

And always eat your vegetables with a source of fat. I think it helps promote that you're getting the most nutrition out of the vegetables.

And also, if you mix your food so you're eating your protein with − obviously, high fat and fiber will definitely help you stay in ketosis because if you just bolus protein, a lot of people say they're on a ketogenic diet just by eating no carbs, but a chicken breast will quickly kick you out of ketosis.

But a chicken breast cut up into a green leafy salad with a lot of olive oil and maybe some feta cheese and some bulletproof coffee or something like that combined will not kick you out of

ketosis. You can just stay cruising in ketosis. So this, I think, needs to be appreciated if you're −

Tim Ferriss: Just to fill in the blank though, the blanks for your sort of typical day then, if your breakfast is sardines, half a can of oysters, four eggs, and then some asparagus or some other green, what are the rest of your meals for a typical day?

Dominic D'Agostino: Okay. I do get a lot of MCT in the day, so −

Tim Ferriss: Those are just tablespoons of MCT oil or the powdered MCT oil?

Dominic D'Agostino: I have the powder and the oil sometimes, and I cook in coconut oil. And I'll cook with a combination, coconut oil and butter, so I'll put a pat of butter with a spoonful of butter in a pan and cook my eggs in that. And the sardines, if I have sardines in the morning, it's packed in extra-virgin olive oil, which I like a lot of.

I was eating a lot of dairy fat, and I noticed my LDL went really high, and my LDL particle number went up. And that's kind of like a whole other conversation, but I was kind of doing an experiment on myself. So I haven't phased out dairy completely, but I've backed off on it a little bit and been using more coconut cream in place of regular cream.

Yeah, so in the morning, I kind of described my breakfast already. But at nighttime, what I like to have would be I always have a salad.

Tim Ferriss: So you're skipping breakfast and having intermittent MCT oil instead − or I'm sorry, you're skipping lunch and having −

Dominic D'Agostino: Yeah, yeah. And when I have my breakfast, I will make − I'll have a cup of coffee, but I have a Thermos that I bring with me to work. And in that Thermos I cut a stick of butter in half and throw it in it, and then I put a scoop or two scoops of MCT powder, and then I pour the rest of my coffee that I make in a French press in that. And then I just kind of shake it up or zip it up so it's all mixed up, and then I bring that with me to work, and that's the coffee that I sip on throughout the day.

Tim Ferriss: I see.

Dominic D'Agostino: And basically, I make, like, three cups of coffee. It's not super strong, probably less strong than Starbucks coffee or something, but I have, like, one cup in the morning and then two equivalent cups in my Thermos. And sometimes I'll brew a cup of coffee at work, or I have a product that my friend makes. It's called Utopian. It's a really good product by De Novo Nutrition. I'll do that instead of coffee, and then I'll −

Tim Ferriss: What is Utopian?

Dominic D'Agostino: Oh, Utopian, oh, there's a company − my friend has a company called De Novo Nutrition.

Tim Ferriss: How do you spell that?

Dominic D'Agostino: De Novo is spelled D-E-N-O-V-O.

Tim Ferriss: Oh, okay, got it.

Dominic D'Agostino: Like, made de novo, you know. So De Novo Nutrition makes some really interesting products, and I'm really particular about products that I use. And the one product that they have is called Utopian, and they also sell probably the highest quality whey protein too. But Utopian is a product that I use sparingly. I have it packed in my bag now because I'll be traveling in Europe.

And it's basically like a cognitive enhancement agent that also promotes sort of a wellbeing, and you might call it − it's a mild nootropic and a mild stimulant. And it's just got some standard things in it, like Huperzine. You might be familiar with that.

Tim Ferriss: Sure, yeah, the acetylcholinesterase inhibitor, right, Huperzine?

Dominic D'Agostino: Yeah, it has that. It's got, like five ingredients that are formulated really well that enhance acetylcholine transmission, enhance dopamine. There's just enough caffeine to get a stimulant, I think about 100 milligrams of caffeine.

And it's just − it's a good product too that I keep on hand. And a lot of thought went into the formulation of it with the ratios of things. So I definitely − if you're looking for a lift, a boost, sort of a nootropic, Utopian is definitely something that I keep at the corner of my desk. And I use it kind of sparingly, but I'll use it a couple times a month.

Tim Ferriss: And then dinner is a large salad? What does the salad composition look like for you?

Dominic D'Agostino: Yeah, I usually get, like, mixed greens, two or three different types of salads, usually spinach, a mixed green, and two different types of mixed green-bagged salads, and I mix them together.

And I get a good-quality extra virgin olive oil, and I will − what else do I put in it? Artichokes actually, avocado, artichokes, olive oil, and I put MCT oil on as salad dressing too. And so I'll make a salad and maybe a little bit of Parmesan cheese on it or feta. And we have typically chicken, which would have the skin on it, beef, or fish.

And it's usually the fattiest versions that we can get. And I don't go too overboard on the protein like I used to, so pretty moderate amount of protein, maybe about 50 grams of protein and then some kind of −

Tim Ferriss: 50, five zero?

Dominic D'Agostino: Yeah, like, 50 grams. That would be like my bolus, like, probably one of the larger protein meals. And if I work out, if I happen to work out, which I did yesterday, I would probably eat a little bit more, maybe about 60 or 70 or 80 grams of protein. And that'll be kind of my larger meal of the day.

And then I'll have a salad, some kind of fatty protein, and last night I cooked Brussels sprouts, and I kind of cut them in half facedown and cooked them in butter and olive oil − no, butter and coconut oil, so they suck it up.

And so I think of vegetables as like a fat delivery system, so the same thing with collard greens or asparagus. They're usually cooked in a lot of butter, olive oil, coconut oil, and I'll have that. So I'll have some kind of fatty protein, some kind of vegetable cooked in fat, and salad.

Tim Ferriss: Got it.

Dominic D'Agostino: And then I always have dessert that's kind of unique actually. I call it my − I don't know − keto mousse or keto ice cream.

And what it essentially is, is it could be sour cream or coconut cream, and I take sour cream − so the easiest thing, take sour

cream or coconut cream and take maybe about a cup of it or two cups, cup and a half, and then I put a tablespoon of dark chocolate baking powder in it, some cinnamon, a pinch of salt, and stevia and stir it up until it's like a thick mousse, and then I stick it in the freezer.

Then I go kind of do my things, shower, get ready for the day or whatever. Then I take it out of the freezer or refrigerator, and it's basically like ice cream to me.

Tim Ferriss: That sounds amazing. So it's one cup sour cream, one tablespoon dark chocolate powder − hope that's right −

Dominic D'Agostino: Yeah.

Tim Ferriss: − pinch of salt. How much stevia?

Dominic D'Agostino: Stevia, just sweeten it to whatever you like. I mean, I have the super concentrated stevia, so I just put literally a pinch of it in there.

Tim Ferriss: What brand do you use? Do you know offhand?

Dominic D'Agostino: I have to go back and look at the brand, but you can get it on Amazon if you just go to bulk stevia powder, and it comes in, like, a two-pound or a one-pound container.

Tim Ferriss: Got it.

Dominic D'Agostino: And, yeah, it's kind of like the generic − I've tried every brand of stevia, and this is − it's powder; it's pretty good. It travels well and everything too.

Tim Ferriss: And cinnamon. Cool. That's nice.

Dominic D'Agostino: Yeah, a little bit of cinnamon. And it's like a fat bomb.

So people ask, like, where do you get all your fat? You know, this is a lot of fat to eat to get in about 300 grams of fat a day for the diet. So, yeah, so that's like a fat bomb. It's about 80 grams of fat, I think.

And you know what? If I eat that at nighttime, and if I work out or if I haven't gotten any carbohydrates during the day, I usually put in, like, a third of a cup or even a half cup of wild

blueberries, which are higher in fiber, not real sweet but higher in fiber, and I stir that into it.

And sometimes I'll do − it'll be a pretty big bowl − I'll do, like, two cups of coconut cream or two cups of sour cream. So I was doing a lot of − I have a whipped cream maker that I put heavy cream in, and I would put whipped cream on top of that.

And in my whipped cream maker, I would put the heavy cream, and then I'd put stevia in, so I'd sweeten the whipped cream a little bit, shake it up and charge it with the little things that they have and make my own whipped cream.

And I would put whipped cream on top of that. So it's like a 100-gram fat bomb.

Tim Ferriss: Wow.

Dominic D'Agostino: And I was getting in extra fat throughout the day with heavy cream, and I did an experiment because I wanted to determine what happens if you have surplus amount of calories in the form of dairy fat, and if I did that for two weeks? So I got, like, 1,000 extra calories per day, 500 to 1,000 extra calories per day for two weeks.

Then I went in and got an NMR lipidomic profile of everything. And it really shot up some things remarkably, like my LDL-P particle, and I'm still analyzing it right now. I'm kind of still doing experiments on myself. But I went back, and I cut out the dairy and I replaced it with coconut cream. And all those numbers came back down.

But I still get dairy in the form of butter, and I just don't go too overboard with it −

Tim Ferriss: Got it.

Dominic D'Agostino: − because people ask me that question a lot, like, can I have dairy? And I do have dairy every day, but I've switched out my nighttime snack, switched out the sour cream to either a mix of sour cream and coconut cream together − and sour cream's really not sour, right?

I mean, especially if you have − I buy the dark chocolate baking cocoa, the extra dark, and it's a little bit bitter, and if you add it to it, it sort of neutralizes any remote little sourness

that sour cream has. And it makes a really delicious chocolate mousse.

Tim Ferriss: I'll have to try that.

Dominic D'Agostino: And it's, like, purely ketogenic. And, oh, yeah, I also will take a tablespoon of coconut oil, and especially if it has the frozen blueberries in it, and then if I drizzle it around and stir it up, the coconut oil will sort of harden and make these little crunchy chocolate things. So it actually tastes like you have chocolate chips in there if that makes sense. You know how coconut oil −

Tim Ferriss: Yeah.

Dominic D'Agostino: Yeah, and then my fiancée's totally not ketogenic. I mean, she has an enormous carbohydrate tolerance, and she just thinks what I do is really strange. But if I make this − and she's a big fan of regular Breyers or Haagen Dazs chocolate − and if I give this to her, she thinks it's incredible. So even someone who's not ketogenic and doesn't eat this way and has a sweet tooth thinks this is really good.

Tim Ferriss: Cool. I'll try it out. So I would love to ask some rapid-fire questions. I know we're wrapping up. We could talk for many more hours.

But for people who want to dig into ketosis further, give it a shot, what resources should they start with or books should they start with?

Dominic D'Agostino: Yeah, I think probably the best place to go would be Ketogenic Diet Resource, and that's a website. Ellen Davis has that website, and literally that's the name of it, KetogenicDietResource.com. And it's like a ton of information on there, pretty much every question you'd ever want on there.

We even − she put together a book for ketogenic diet and cancer, one for the ketogenic diet for Type 2 diabetes. It was coauthored by a doctor that's actually in my area that has Type 1 diabetes that uses the ketogenic diet for that. So that's an incredible resource.

Tim Ferriss: Excellent, Ellen Davis.

Dominic D'Agostino: Yeah, Ellen Davis, Ketogenic Diet Resource, definitely one of the go-to places.

I have a website, KetoNutrition.org, and basically it's like a skeleton website. I just compiled a lot of useful links that I thought − and her website's on there; her book's on there. So that's KetoNutrition.org.

Tim Ferriss: Awesome. What is the book you've given most as a gift, not necessarily related to ketosis, just any book that you've given often or given before as a gift?

Dominic D'Agostino: That's a good question. Yeah, I would have to − well, going back in the college days, I would say Anthony Robbins, I listened to his stuff when I was − my senior year in high school, and I listened to these 30-day tapes back when we listened to tapes.

Tim Ferriss: Oh, the Personal Power?

Dominic D'Agostino: Yeah, Personal Power. So I bought the book too. And I liked it so much, I bought it and I gave it to all my lifting buddies. And they went off to college and everything, and years later, two of them contacted me and they're, like, you know that book you gave me? It changed my life. I did better in college and everything.

So I would say, going way back, Personal Power, Anthony Robbins' book, was kind of influential from back in the day.

And then, as I got into science and became a scientist, and my advisor was funded by the NIH, and I was always told that I needed NIH funding to be a career scientist. And then I met the NIH director, Francis Collins, at a Society for Neuroscience meeting. And I was, like, well, I should understand the mind of Francis Collins and understand, what is the director of − basically the president of science thinking?

So I went to try to find some biographies on him, and when I did a search I found a book, The Language of God, and I thought that was really − I had no idea of his sort of − his spirituality or his kind of worldview, besides − outside of science. I knew he spearheaded the human genome project and was pretty instrumental in finding the gene for cystic fibrosis.

But so The Language of God, it really inspired me because I had no idea that a scientist of his stature could have such a devout faith. And that kind of influenced me and got me to

reread some older books I read by C.S. Lewis, The Screwtape Letters.

Tim Ferriss: Screwtape Letters is great.

Dominic D'Agostino: Yeah, yeah, The Screwtape Letters is really good. And I don't think I've given that, but I gave The Language of God to some of my friends, and they really enjoyed it, so that would be one.

And then a required reading for my students would be Tom Seyfried's book, Cancer as a Metabolic Disease. So that's a really − I mean, I think it sold pretty well on Amazon, and it's highly, highly technical, and unfortunately it's really expensive, so it's about 100 to 130 bucks, I think.

Tim Ferriss: Wow.

Dominic D'Agostino: Maybe you can get it cheaper. You can get used versions for probably, like, 50 bucks online.

But if you want a really good kind of description of, I guess, cancer as a metabolic disease, the science, the history, I mean, it's really well written. Tom did − he's a collaborator of mine. He worked a lot on that book, and it shows, so that book.

And, oh, another book by a guy that I'm actually working on a project with him now, his name is Travis Christofferson. He wrote a book called Tripping Over the Truth.

Tim Ferriss: Quite the name, yeah.

Dominic D'Agostino: Yeah. And he wrote a precursor to the book. He wrote an article that appeared on Robb Wolf's blog, and I'm actually − I have an article written with him that's going to appear on the blog on Thursday. It's about the history of the ketogenic diet, and I think Robb's going to put it on the blog on Thursday, I believe.

But Travis is a brilliant − he's probably one of the most gifted writers I've ever known. So Tripping over the Truth is basically the story of cancer really. I mean, it's a great history of the story of cancer that comes at it from a different perspective from the Mukherjee book, The Biography of Cancer that is pretty popular, New York Times bestseller, it's been on.

The Emperor of All Maladies is actually the name of the book, The Biography of Cancer. That book kind of talks about the history of cancer.

Tripping over the Truth is similar to Mukherjee's book, but viewed from the perspective of understanding cancer as more or less a metabolic disease and how we could develop therapies to target it from a metabolic perspective.

And I've given that book, probably bought seven or eight copies of that book over the last year and given it away. And everybody has come back to me and said that book was fantastic. I mean, not only is it informative, but Travis is an unbelievable gifted writer.

Tim Ferriss: Awesome. Let me ask you one − I have one more question, and then maybe we'll do a Round 2 if people demand it by popular request.

Dominic D'Agostino: Sure.

Tim Ferriss: But you mentioned Robb, so Robb and I are friends, Robb Wolf, and we've talked about Lyme disease on and off for a while now because I was out of commission for about nine months or at least operating at about 10 percent capacity after contracting Lyme disease on Eastern Long Island.

And what appears to have made the biggest difference for me, in terms of getting back to feeling like myself and having the cognitive function that I had pre-Lyme disease was the ketogenic diet.

And I was very puzzled by this, and I wasn't sure exactly why that would be the case. And so I just hypothesized that perhaps either Lyme disease or the subsequent antibiotic treatment caused some type of carbohydrate metabolism dysfunction.

And I was chatting with Robb about this because I didn't know the mechanism, but I had recommended to a few people with Lyme that they test ketosis. And literally 100 percent of them, if they entered ketosis properly and stayed there for more than a week or two, reported the same results.

And Robb sent me an interesting research abstract which showed how antibiotics such as doxycycline could cause

mitochondrial dysfunction or degradation because my understanding is that mitochondria are very similar to bacteria.

And how would you explain ketosis making me and these other people feel better after Lyme disease? And I don't know if you're familiar with Lyme disease −

Dominic D'Agostino: Yeah, yeah.

Tim Ferriss: − but how would you approach thinking about that and investigating that?

Dominic D'Agostino: Well, I'm from New Jersey −

Tim Ferriss: Yeah, you're in Lyme country.

Dominic D'Agostino: − so Lyme disease is really, you know, I knew a lot of people, especially growing up in a family that was hunters and knowing most of my friends were hunting and in the woods. I grew up in the woods. Somehow I didn't get Lyme disease, never been tested for it but never really had any symptoms for it.

So Lyme disease really produces pretty profound inflammation. And the spirochetes can cause everything that you described, fatigue.

But I think they can cause, you know, from a neurological perspective, they can cause encephalopathy, and that essentially is resulting from neuroinflammation.

And ketones, the ketogenic diet and ketones in particular have pretty profound anti-inflammatory effects and especially in relation to the nervous system, since ketones are freely permeable to the blood-brain barrier and kind of bathe our nervous system.

So I think that may have something to do with it. Also, the spikes in blood glucose, higher insulin levels all can contribute to inflammation and inflammatory processes.

So putting a dampening on that situation with a ketogenic diet and having elevated levels of ketones could impact the primary malady that's causing the symptoms, which would be the inflammation, the encephalopathy, the inflammation of the white matter, I think.

There's memory attention. Cognitive, emotional states are altered in people, and I think it can just help bring your nervous system back to a state of homeostasis, similar to what it's doing for other disorders.

But inflammation is really − did you happen to get bloodwork and look at − because the spirochete really − that's how it wreaks havoc in your system, I mean, by activating your immune system, but also just wreaking havoc, as far as causing systemic inflammation in the body.

Tim Ferriss: Yeah, I could go back. You mean looking at things like C-reactive protein or whatever?

Dominic D'Agostino: Yeah, or cytokines or something like that.

Tim Ferriss: Yeah, cytokines. I'm sure I have the bloodwork.

I mean, the inflammation was so clear to me that I didn't really need the bloodwork to confirm it. I mean, my knees were so swollen that I could barely get up in the morning, and I had very slow, almost slurred speech and felt like I had early-onset dementia. It was really scary as an experience.

What effect does ketosis have on mitochondria, if any?

Dominic D'Agostino: Yeah. So ketones are very efficient metabolic fuel, and in studies that were done in animal models − and we're looking at the muscle biopsies too − shows that if you're in a state of ketosis relative to a higher carbohydrate diet that it can increase the mitochondrial biogenesis and mitochondrial efficiency.

At the level of the cell, when we talk about efficiency, I don't want to get down into too much specifics, but the electron transport chain is kind of how our cells, the mitochondria make energy.

And there's a site between Complex 1 and Complex 2 and Complex 3 called the semi- ubiquinone site, and ketones have the ability to oxidize Q basically, and that can prevent by − ketone metabolism can enhance the energetic flux through the mitochondria to produce NTP or energy currency.

And at the same time that it's enhancing the bioenergetics of the mitochondria, it's also preventing the formation of

superoxide anion, which is an oxygen free radical or reactive oxygen species. And that's the precursor to more reactive oxygen species like hydroxyl radical and peroxynitrite and things like that.

So by kind of fundamentally turning down the generation of superoxide anion by enhancing mitochondrial efficiency, not only do we make more ATP through ketone metabolism, but we're also enhancing the flux of substrate utilization and energy production from that substrate, even glucose substrate, by enhancing mitochondrial bioenergetics.

And the ketones, we know can do that through a variety of mechanisms that I can get into. But basically, yeah, I mean, you can derive more energy per oxygen molecule −

Tim Ferriss: Got it.

Dominic D'Agostino: − with ketone metabolism.

Tim Ferriss: Is it conceivable that ketosis could aid − it sounded like the answer is yes. You mentioned biogenesis. If one had damaged their mitochondria through 8 to 12 weeks of doxycycline or even using harder antibiotics for longer periods of time, is it conceivable that the ketosis could help repair that damage?

Dominic D'Agostino: Yeah, yeah, I think so, especially in certain tissues. We know muscle is incredibly plastic, but if you're exercising and in a state of ketosis, that you can build up your mitochondria, and you'll do that more efficiently if you're on a ketogenic diet.

And I think even in the central nervous system, which may have taken a big hit from doxycycline or Lyme disease, the central nervous system is running more efficiently in a state of ketosis, I believe, especially if you can dampen some of the neuroinflammation that's associated with the disease.

And I think that would ultimately contribute to − I don't know how you would quantify that. I'm trying to think of studies that we've done sort of in parallel. We did some work in an Alzheimer's model, and I think that the Lyme's has been associated with tau and amyloid plaques and neuroinflammation that can contribute to those plaques.

And I think being in a state of ketosis − even there's some work with exogenous ketones and calorie restriction or even

intermittent fasting type things − can limit the accumulation of some of these plaques that are associated with neuropathology such as Alzheimer's disease, the amyloid and the tau plaques. And this can be shown in animal models that are genetically kind of predisposed to accumulating those plaques.

And I think that would be − you could probably draw some parallels from that work with the neuroinflammation and the neurotoxic effects that Lyme disease kind of has.

And Lyme disease is not something that I study, but I just come across it a lot because hyperbaric oxygen has been used to sensitize sort of the bacteria to the antibiotics.

So a lot of people ask me questions, and I have to go − I've been staying up on top of the literature kind of in a peripheral sense because it's not my kind of core of study. But everything that I read really focuses on the neuroinflammation that's resulting from the spirochetes.

Tim Ferriss: Got it. Well, Dom, this is so much fun. There are so many other things that we could talk about, the hyperbaric oxygen treatment, the brilliant Patrick Arnold, we didn't have a chance to get into.

Dominic D'Agostino: Yeah.

Tim Ferriss: And, I mean, not to mention your own training and the approach that you no doubt bring to that. So I want to let you get going, and if fans enjoy this, then maybe we can do a Part 2 sometime.

Dominic D'Agostino: Okay.

Tim Ferriss: But what is the best way for people to find you online in terms of websites, social media, if they want to say hi to you online. What's the best way to do that?

Dominic D'Agostino: Okay. I think probably the best way would be the KetoNutrition website, dot org. And I have that and, yeah, Facebook, and I probably use that more than Twitter.

Tim Ferriss: What are you on Facebook?

Dominic D'Agostino: My Facebook handle, you mean?

Tim Ferriss: Yeah, your Facebook handle. I could pull that up too. I can put that in the show notes if you don't recall it offhand.

Dominic D'Agostino: Yeah, it should be obvious, right, but −

Tim Ferriss: I think it's − oh, wait, here it is.

Dominic D'Agostino: Yeah, it's Dominic.Dagostino.1.

Tim Ferriss: Got it, all right.

Dominic D'Agostino: Yeah.

Tim Ferriss: So I will link to the skies, so Facebook is Facebook.com/Dominic.Dagostino.1. And I will link to all of this as well as your USF page in the show notes, so everyone listening can find links to many of the things that we talked about in this episode and more at FourHourWorkWeek.com/podcast all spelled out or just go to FourHourWorkWeek.com and click on Podcast.

But, Dom, I really appreciate the time. I always love chatting. And how much do you weigh these days?

Dominic D'Agostino: Weigh? Man, I haven't weighed myself in a while, but about − I always say between 220 and 230, probably about 222, yeah.

Tim Ferriss: Is that ever a challenge? I found when I − like, for every additional millimeter of neck diameter that I have, the perceived IQ that people have of me drops by five points. Do you ever have trouble being taken seriously by people who are not sort of a nerd wrapped in a meathead body?

Dominic D'Agostino: I don't have that problem too much now, just because I have my diet under control. But, yeah, I think sometimes I face that resistance a little bit. But generally, it was a little bit more apparent when I was a younger scientist, but now that I'm working my way up and have a lab, I think people are starting to take some of this stuff seriously.

I am in a totally oddball area of research though, as far as being in a pharmacology department doing this weird high-fat diet stuff. It raises some eyebrows. So I feel like I kind of have to prove myself still.

Tim Ferriss: Well, I think I would like to collaborate more in the future. We'll talk more about that.

Dominic D'Agostino: Okay.

Tim Ferriss: But this is enough for one big session. So, Dom, I really appreciate you taking the time, so thank you.

Dominic D'Agostino: Thanks for having me, Tim.

Tim Ferriss: Of course.

Dominic D'Agostino: [Inaudible].

Tim Ferriss: This is a good time. And to everyone listening, as always, thank you for listening, and until next time, experiment, be well. Check out the ketogenic diet.