Introduction and background in ketogenic research

I am Doctor Sanjeev Gupta and you're listening to the advanced Anti-Aging summit with Doctor Poff. Hi, Angela. How are you? I am great, how are you? How are you?

Thank you so much. I'm really looking forward to today's talk. So maybe just take me through. Before we get into more detail about your research, how did you actually get involved into into this field of ketogenic medicine or therapy?

Yeah. So I, had always planned on, being a scientist. I wanted to be involved in research, and, I did my undergraduate work in biochemistry and molecular biology, and I graduated and, started looking for PhD programs.

I landed on the University of South Florida here in Tampa and moved down here and started that program. And that's when I met Doctor Dominic D'Agostino, and he was starting up his lab.

At that time, he was a junior faculty member, and he was looking for his first PhD student. And, he was funded by the Office of Naval Research to look at mitigation strategies for oxygen toxicity, seizures.

And he had a big interest in, nutrition and specifically ketogenic nutrition at that time. But he was interested in expanding his research into cancer.

And, there was a little bit of data at that time looking at, ketogenic diet as a potential therapy for cancer and in particular brain cancer. And, I remember, you know, my first conversation with Dom kind of on this topic, it was really just incredibly eye opening to me.

I never thought about nutrition as being a powerful tool in the face of something, you know, very serious, like cancer. And, my father had had brain tumors, when he was young and then again when I was young and, you know, he thankfully went through therapy and respond to them, but he had, you know, some lifelong consequences from the radiation therapy that he was given.

You know, it saved his life. But it also, you know, had some, long term problems. And I just remember thinking like, wow, what a cool idea. You know, that we might be able to contribute to finding, some therapies that can impact cancer in a way without some of these classic side effects that can come along with standard of care therapies.

And, so I just really got kind of enthralled by this idea. And I ended up joining Don's lab, and and I did my, PhD research based on ketogenic diet and hyperbaric oxygen as a potential nontoxic, metabolic targeted therapy for cancer.

And then I've stayed on, and worked with, Dominick, ever since then. And, we continue to do a lot of research on the topic of ketogenic therapies, in cancer, but also in various neurological diseases as well.

Well, so now are you, run your own lab or are you still work with doc? Doc? So I still work with, Dominic. Yeah, I'm a research associate, which is like a research faculty position, but I work within Dominic's lab, and, we have, a variety of students and some, postdocs that that do a lot of the work that's going on.

So, you know, we had, we just had, guest talking about hyperbaric and, and we're actually going to be opening a center here in Toronto for that as well.

So I'm curious about what did the what did the results of the initial your PhD show what it was that. Yeah. So that was really interesting. We found in the mouse model system that we were using, which was a brain tumor derived model of metastatic cancer.

We found that the ketogenic diet alone, and we use two different formulations where it was able to slow tumor growth and prolong survival in that model, we found that on its own, hyperbaric oxygen did not, result in a significant, slowing of tumor growth or, or extension of survival.

But when we combined it with ketogenic therapy, both the diet and then actually also exogenous ketones, we found a really nice synergy there. And so the results were actually greater than the additive results individually.

And so there was some kind of synergy happening between ketosis and hyperbaric oxygen in that mouse model that we, that we, studied it in. Oh, wow. Okay.

I did a couple of things I definitely want to talk about, maybe before we even get into into ketosis, what are your thoughts about just so hyperbaric oxygen on its own?

How would you what are what are the effects on brain health like? I'm just curious. Yeah. So it's interesting. Hyperbaric oxygen has a long history of research.

You know, I'm most familiar with the literature, surrounding its potential use in cancer.

PhD work on ketogenic therapy and hyperbaric oxygen

So, of course, with hyperbaric oxygen, you know, you're breathing, 100% oxygen at elevated barometric pressure. And this allows more oxygen to become saturated into the plasma of the blood and allows for a greater diffusion of the oxygen into the tissues.

Now, this is very helpful in conditions where oxygen diffusion or oxygen carrying capacity is limited. So it's used, clinically for things like, carbon monoxide poisoning.

It's also used for, diabetic foot ulcers and chronic wounds or radio necrosis of the type of necrotic, tissue damage that can occur following perhaps radiation treatment for, for cancer.

And, but it has, you know, oxygen. We in the field of hyperbaric medicine kind of describe oxygen as a drug. So it has drug like effects in the brain.

And we interestingly, our lab kind of is very involved in and hyperbaric medicine research from kind of the alternate perspective of when too much hyperbaric oxygen can be dangerous to the brain because too much can result in, central nervous system oxygen toxicity, which has a lot of signs and symptoms, but the most concerning of which is seizure.

And, we are funded by the Navy to look at mitigation strategies, for that condition because, of course, a seizure underwater can be fatal. And so this really greatly limits the amount of time that a naval war fighter can spend on a mission.

And so, you know, but interestingly, within the, kind of, realms of a more therapeutic range of hyperbaric oxygen, you do see, you know, changes going on in the tissues, obviously, more oxygen getting delivered to the tissues.

And, changes in excitability of the brain. And so it is being studied as a therapy in a few different, conditions related to neurological damage. And then, you know, from my perspective, it was interesting because it was historically viewed as a potential radio sensitize or for cancer, because, tumors have hypoxic areas that actually drive tumor growth and drive, resistance to both chemotherapy and radiation.

And so soaring oxygen levels in the tumor is thought to maybe, inhibit some of those beneficial effects that the tumor is receiving from the hypoxia. So there's a whole lot to do with, hyperbaric medicine.

It's a very fascinating, because it's really impacting the tissue on a very, cellular level. The hypoxic response within the cell is, is play a topic influencing hundreds of genes simultaneously?

So there's a lot going on. Wow. Yeah. That's a I guess a whole other topic. But, I guess it seems like it's not. So it's not so straightforward is what they're saying.

The answer is yeah. Yeah, I would say so. Like so let's leave it and let's, let's start moving into then. So you, you, you started getting involved looking at, at ketosis and how that can have a treatment in cancer.

And then, you're also working on its effect on, metabolic dysfunction, chronic disease and neurological disease as well. So if you want to tell me, how did you pivot to that and why did you you know, I just say that.

Yeah. I mean, it's so it's been fascinating to see the field of ketogenic, therapy research over the past decade. It's really exploded, you know, within the public conversation, even, which is coming off the heels of really some pretty amazing advancements in our understanding, both, molecularly and clinically, in terms of what's happening in a physiological state of ketosis and, you know, we've seen just this explosion of interest and, and ketosis is really now being studied kind of across the board in terms of metabolic disorders.

So some of the more obvious potential applications, things like obesity or diabetes, but also for things like neurological diseases, neurodegenerative diseases in particular is a very fascinating area of research.

And we have a strong interest in the brain, as I mentioned. Our lab is is, very strongly studied in, and neurological research with our, we have a strong interest in seizure disorders.

Of varying etiologies. And, and so it's kind of a natural transition or continuation, really to continue this kind of work. In neurological conditions.

There's been a lot of research looking at how in especially neurodegenerative diseases. So things like Alzheimer's or Parkinson's or multiple sclerosis, you see kind of these common threads when you start looking at the tissue level of what's going on in those cells, you see some of these things like neuroinflammation is a very common theme, high levels of oxidative stress.

And then things like, aberrant energy metabolism. So like glycolysis or glucose, hypo metabolism, and insulin resistance and all of these areas are things that there's data to show ketosis might be able to target therapeutically.

Hyperbaric oxygen, brain effects, and cancer research

So that's really fascinating. You know, even just within the past year, there's been research. A lot of it is pre-clinical, but a lot of, research has come out looking at ketosis as a potential therapy for things like spinal cord injury.

Autism even, that's very fast. And mental illness. So depression and anxiety, depression, anxiety, even schizophrenia. So there are kind of these common themes that we're seeing in these chronic diseases, that might be targeted by ketosis.

So it's a really hot area of research. So maybe let's, let's I know that not all the viewers to completely understand, what's happening during ketosis.

So maybe if you don't mind, do it to kind of explaining that piece in a, you know, kind of a short manner. And then I'd love to talk more about Parkinson's and Alzheimer's specifically.

How does this how do we think this is happening? This what is your understanding so far from the research of how it's impacting those so slowly? So, you know, I would say ketosis is first and foremost a natural metabolic state.

So this is in my kind of view, just a very normal part of our physiology. That is initiated when glucose and insulin are suppressed. Now if you think about it, our ancestors were not eating three times a day, every day.

And they weren't always eating these very high carbohydrate load meals. So they had some carbohydrate in their diet, but they were often, you know, came with a big load of fiber along with it.

Right? Like natural sources of carbohydrate. These very processed carbohydrates that are basically stripped all fiber, from them is very new in terms of human evolution.

And, and so our, our ancestors were regularly going in and out of ketosis, and ketosis is just can you just give an example of what is what is being a way, what would be a food now that we could eat that would be similar for like a high fiber?

Yeah. So well, I guess, you know, kind of what it's like. Yeah. I mean, so natural sources of so like things like berries, for example, berries are they have carbohydrate, but the glycemic load is much lower than a lot of, other fruits and they come with a higher amount of fiber.

So this is a more kind of natural form, I would say, of carbohydrate, especially compared to like, you know, cane sugar, like these processed, added sugars that are now added into every food that's on the, supermarket shelf.

So, you know, when I view kind of, carbohydrate choices, I tend to view. And in that regard, I'm from for my perspective, I'm not scared of whole food kind of sources of carbohydrates, especially when they come with, fiber and and, or otherwise, you know, nutrient dense type foods.

But some of these processed forms of, of carbohydrate are quite new, to human physiology. And so, you know, historically speaking, our species was not constantly consuming food.

You know, we might have a meal and then it might be, you know, even days or a week before, you know, we secured another large meal. And so the human body is set up in a way that we have plenty of calories on board to, you know, carry us through those, those times in between meals.

So we store calories primarily in the form of fat. And when we don't eat, sufficient calories or we don't eat a significant amount of carbohydrates, we start breaking down that stored fat.

And fat is converted in part to ketone bodies. And the whole reason our bodies do this is actually to support the brain. So most of your body can is perfectly happy to run on fatty acids that come from the stored fat when it gets broken down.

But fatty acids are not sufficient fuels for the brain, because a lot of them can't even get into the brain. They can't cross the blood brain barrier, and we need to be able to fuel our brain in these scenarios.

And so ketone bodies are small, like water soluble fat molecules. And they are indeed the only other molecule energy molecule that our brain can really use to support its high energetic, needs and is no different.

Different people have different, ability to use ketone ketones in their body like the other do. The nerve cells is there. So, you know, people have different receptors or.

That's an interesting question. So the type of transporters that carry ketones into the cell are called mono carboxylate transporters. They're ubiquitously expressed because they're they also carry some other very common molecule.

So things like pyruvate and lactate. So other really common metabolites. And so you have a baseline expression of ketones, regardless of if an individual has ever been in a state of ketosis.

And it's possible that someone who, you know, eats very regularly and perhaps eats a fairly high glycemic load diet has never or barely ever been in a even a mild state of nutritional ketosis.

But studies show that even in individuals that are not consuming a ketogenic diet, they can take up ketones into the brain. So Doctor Stephen Kunin has done a lot of work looking at, Pet imaging showing ketone uptake in the brain of adults, with, healthy brains, also mild cognitive impairment all the way up to Alzheimer's disease.

And it's very fascinating because individuals across the spectrum do are able to take up ketones into their brain, even in cases where perhaps glucose uptake is impaired, such as in Alzheimer's disease.

Ketosis as a therapy for neurological and metabolic disease

And we can talk about that in a minute. But yeah, study is absolutely show that, everyone for the most part, you know, unless you have some kind of like very specific, unique, maybe inborn error of metabolism type disease, you express these transport and are able to take in ketones and utilize them.

But as people are adapt to a state of ketosis, you become more efficient at taking up ketones. And that's why you see, you know, sometimes, people might be tracking their ketones with urine strips or they might be measuring in their blood.

And after a few weeks of being in ketosis, they see their levels start to drop and they get worried. You know, that something's wrong, but that's normal because your tissues have actually just become more adapted.

Actually taking up those, those, those molecules to use them. So you do so in the brain that can happen. Is that what's happening is, I mean, everywhere in the body or just in the brain.

So everything so there are only a very small amount of tissues that don't, take in or utilize ketones. The liver is one. So the liver is where you make ketones.

And because of that it lacks, enzymes that are required to actually utilize ketones, which makes sense. You wouldn't want, you know, the area that's making them to just turn around and use them immediately.

So the liver makes them and ships them out to circulation to be used by almost all of the rest of the body. I mean, just a few kind of tissue types that are thought to maybe not be able to, for example, like red blood cells and mature, erythrocytes, they don't contain mitochondria.

And ketone metabolism happens exclusively in mitochondria. So those cells can't use ketones. But yeah, most most tissues in the body can and do very efficiently.

So you mean by the people who are who are more like, their body are used to being ketosis. Are you saying that they become more efficient? And is this because of the receptor, or how what how are they becoming more efficient at this.

Yeah, I so I think largely you see like an upregulation of receptor expression and transport. There might be other things at play, but that's kind of generally speaking, the thought process.

So we can train our bodies to become better at this. Yeah, I would say so. Yeah. Yeah. Okay. That's really interesting. So, so yeah. Tell us about that.

You're about what's happening in Alzheimer's and Parkinson's or. Yeah. So this is a very fascinating area of work. There's been it's been known for quite a while that, a very consistent hallmark characteristic of Alzheimer's disease is reduced glucose uptake.

So you can actually look even in individuals who, are at high risk for developing Alzheimer's and end up, you know, developing it decades down the line even very early on.

So before there's even, any symptoms of cognitive impairment, these individuals will show reduced glucose uptake in the brain. And, Doctor Kunin and others have really shown that as, you know, the dementia increases and mild cognitive impairment turns into Alzheimer's disease that becomes even more and more severe.

And so by the time an individual has full blown Alzheimer's disease, their glucose uptake, capability is significantly reduced compared to a normal, healthy, individual.

And so, you know, being that ketones are the only other primary fuel for the brain, it's kind of an obvious idea that, well, potentially ketones could could, you know, support brain energy metabolism in this, condition.

And there's been research that shows very interestingly, while glucose uptake is reduced in these individuals, they're they still retain very normal ability to take in ketones.

So and it's probably just because it's a different type of, of transporter and, and kind of a different way that these molecules are metabolized. But for these reasons, ketosis is a very, you know, at least from a theoretical standpoint, it makes a lot of sense to study this.

And, there has been both animal research and some preliminary, human research to, to to show that it does seem to be therapeutic in some cases. And so, there's work in a variety of animal models of Alzheimer's disease.

And then, and then some work in humans to support this. So we need larger trials before it can be, you know, proven that this is therapeutic. And there might be some, you know, some subset of the population that doesn't respond.

That's pretty typical for almost any therapy. But the preliminary preliminary evidence that we do have is very encouraging. So let's so you're saying that these patients who have early Alzheimer's or they have problems getting glucose into the cell, is that right into the neurons.

So are you saying that then they're basically the cells are being starved. And so this is that's another progression. That's what we think. Yeah, essentially.

So I mean, you know, we have to keep in mind that the brain is a very energetically demanding organ. So it, you know, uses about 20% of the energy that we consume and use on a daily basis.

But it only makes up 2% of our body weight. So, in neurological diseases, you very consistently see kind of an energetic crisis where the neurons are not getting adequate, amounts of energy.

And so, yeah, there's thought processes that perhaps with chronic, you know, impairment or energy deficits, over time, you start to see, you know, cell death or, you know, just a reduction in the viability of these neurons that that leads to this impairment.

How ketosis works and fuels the brain

And so what if, let's say, if a patient has diabetes or metabolic syndrome and does this impact how fast Alzheimer's is progressing or, this question uptake?

I don't know of any research, specifically looking at that. I do know that, we now know that, you know, these are common comorbidities. So if an individual has diabetes, they have a much higher risk of also developing Alzheimer's.

So there is some sort of link. But honestly, I can't think of many chronic diseases that are not. Also, your risk is increased if you have diabetes. This is a very it's like a, to me, it seems like a central hub, right, that this insulin resistance is playing this role and linking, to the development of all of these chronic diseases that seem completely, you know, separate.

You wouldn't necessarily think that something like Alzheimer's disease might have anything to do with insulin resistance, but people are even now calling it type three diabetes.

Insulin resistance of the brain. So, there's clearly a link and and that's why I think there is so much research looking at ketosis in such a variety of areas because these common threads of insulin resistance, hypoglycemia, oxidative stress and inflammation are really seen in a lot of different disorders.

And so and we think that maybe ketosis can target these therapeutically. How what about in patients who have ApoE4, LDL. Yeah. Yeah. Is there any studies looking at ketosis in those individuals or the disease.

Yeah. There is. Yeah. So there in and right now also it's unclear. So there's definitely some research that may have suggested that they might not be as, benefited by ketogenic metabolic therapies, but there's actually also case reports of ApoE e4 individuals who responded very, very well.

Now again, those are case reports. So take that as well. But you know, in a field like this, all of this is kind of informing the direction of the research next.

So I would say it's hard to say. But conflicting I guess, ideas there. So, how does the kit, keto genesis, ketosis state, change the insulin resistance just for review?

Yeah. How does that happen? Yeah. So really, the biggest impact of ketosis on insulin resistance is just removing the primary substrate that is contributing to, high insulin levels.

So, ketogenic diet is a low carbohydrate diet. Carbohydrates are the macronutrient that most significantly contributes to your blood glucose levels. So about 100% of the carbohydrates you consume get converted into glucose in your blood.

About 50% of the protein that you consume is made up of something called eugenic amino acids. That can then contribute to a rise in blood glucose and fat is can should be considered basically a negligible source of blood glucose.

So it makes sense when you consume a diet that's more, based on fats and proteins and less on carbohydrate, you're simply removing reducing glucose levels.

And so when glucose drops, insulin drops because insulin is produced by the pancreas in response to glucose. And, you know, this is this is a very interesting area of work.

And there's certainly been, a lot of research in the past couple of years, especially looking at low carbohydrate or perhaps ketogenic diet as a viable tool for diabetic patients, specifically type two diabetes.

Although there's interesting thought processes with type one. But that is a very, very kind of special condition, situation because, and I'll say in all of these senior videos, people tend to kind of think about like, oh, it's a diet change.

You know, it's it's benign. But from my perspective, this is a medical intervention. So if anyone is interested in a ketogenic diet or ketosis for a medical condition, it's very important that they work alongside their physician.

On that because you can have, you know, effects that you just, you don't even think about as being, you know, potentially, something that needs to be considered cancer patients, for example, I know a lot of people are interested in this very important.

They work with their oncologist because, you know, there could be specific interactions with chemotherapy that individuals are going on. Weight loss. And that scenario can be dangerous, for late stage cancer patients.

There's just a lot going on. It's not just a simple, oh, just a diet change when you're talking about someone that has a medical condition. But regardless, there are a lot of clinical trials now kind of validating that this is a, feasible, you know, method of, of perhaps treating insulin resistance and people that have historically not been able to reverse this disease.

I think type two diabetes has been viewed as a chronic progressive disorder that does not get better. And maybe you can slow its progression, but you don't see improvements and, Berta health, for example, has done an incredible, job showing that, you know, published this data that their, their patients using these low carb ketogenic

diet are able to reverse their symptoms of their type two diabetes, and come off medications and reduce insulin requirements.

And, you know, so it's been a fascinating kind of area, I think, of hope for a lot of people that maybe otherwise didn't think that they had hope in certain situations.

I wouldn't mind, if you could maybe just talk about the different types of ketogenic, diets, like, you know, I mean, is there also differences, a type of fat that you're using and, yeah, absolutely there.

In fact, I don't have. Yeah, that it almost certainly has a big impact.

Ketosis in Alzheimer's, Parkinson's, and insulin resistance

And it's something that, you know, I'm sorry to say we don't have enough research on. And it's something that complicates the field of ketogenic therapy research because, you know, if you're talking about, you know, a new, pharmaceutical agent that's being studied and you say, okay, give five mics per gig of this, this medicine, any time that studied in any lab, you know, you're getting the exact same thing.

But when you say, okay, they went on a ketogenic diet, what does that mean? Right? People set their standards all across the board. And for an individual, it can mean something completely different.

So, you know, for example, a sedentary older individual, perhaps with a higher, BMI, they might really require a much lower amount of carbohydrate to get into a state of ketosis, meaning where their blood ketones rise above this kind of threshold that we've agreed upon, which is, 0.5 million molar.

And that's kind of considered state of ketosis. But I, perhaps a younger, leaner, you know, highly active athlete could probably eat a lot more carbohydrate and protein and still, you know, enter kind of this, this zone of ketosis.

So it does matter. And, and we and there are a few different kind of formal formulations of ketogenic diet. You know, when I'm talking about the research that's being done as, you know, a control application for medical conditions, I'm almost always talking about the classic ketogenic diet, which is this, therapeutic version, which is like a 4 to 1 ratio of fat to protein and carbohydrate.

That's like 90 plus percent of your calories coming from fat. That is not easy to do. That is not something that someone on the street but just, you know, is, oh, I'm doing keto. They're not doing a 4 to 1.

You know, it's almost it's very difficult to even get patients in, you know, serious clinical trials to adhere to a 4 to 1 ratio or ketogenic diet. Right.

But that's where most of the research is actually coming from. So that's an interesting point. But, you know, people will do 3 to 1, 2 to 1 ratios. People will do forms Thai called like MCT supplement and ketogenic diet.

So MCTs medium chain triglycerides are a type of fat that is ketogenic and will actually, cause, ketones to be produced regardless of carbohydrate content.

And so people can use this in their diet to kind of up ketones while maybe being able to be a little more liberal with their protein and carb content.

There's formulations used where people just simply only eat, low glycemic index carbohydrates. So foods that have a glycemic index of 50 or below and that's being used, for example, in pediatric epilepsy.

And it's been shown that in some cases it's as effective as this very strict therapeutic ketogenic diet. So and then that's not even touching on the types of fats.

And you know, in the types of other food, you can almost certainly eat a very unhealthy ketogenic diet if you're

loading yourself up with really low quality fats and, and some of these processed oils and things like that.

So, you know, it all matters. But, you know, we unfortunately are not in a place where we have really good tabs on kind of what all is going on. And what are the best recommendations.

It might seem that's one of the biggest things that, you know, people have this vision about, you know, go keto and then all of a sudden they're going to like, you know, McDonald's or having ice cream and things like that.

And I think that's, you know, I mean, some of the criticisms, absolutely, of people of the ketogenic, lifestyle, yeah. Is it possible to be and you were kind of mentioning the kind of fit, athletic person to be producing ketones and eating carbs.

Like, I guess you're saying that that is possible, like some people, some people, it's not an all or nothing phenomenon. Like, do we know it's not? And and it really is very dependent on the individual.

And both from like probably some genetic, component as well. But also especially lifestyle. I mean, the more active you are, I would say the more, you know, carbohydrate and protein you can consume the larger amount of muscle mass you have.

Because muscles really love ketones. They suck them up pretty quickly. And yeah. So, you know, I think I think it's totally dependent and, and this is one of the cool things about the ketogenic diet, though, you can actually test if you are in ketosis.

So a lot of diets or you know, some of these, you know, people like to supplement with all kinds of things. And, and you don't actually know if you're reaching whatever your goal is, right.

But with ketosis, there's actually, you know, objective end points you can measure and you can say, oh yeah, I'm in ketosis. Either a a breath meter or a blood meter or urine strips.

So that's a that's a kind of cool part about, ketogenic diet that isn't really something that a lot of other diets or supplements can, can really. And so you mentioned at the beginning that you, you also had, added some exogenous ketones.

Yeah. In your study. I'd love to hear your thoughts on that. What are the different types of, Yeah. Ketones. I'm, I'm, I'm having my prove it. Okay. Right now. Yeah.

Like super. But, I'd love to hear your thoughts on this. Yeah, I think it's a very good idea. Exogenous ketones as another tool in the ketogenic therapy's tool belt.

Right. So I, am very aware that there are, you know, from my perspective, I'm always kind of thinking of like the clinical potential applications of ketosis.

And I recognize that there are always going to be some part of the population that is not able or interested in consuming a ketogenic diet. And, you know, exogenous ketones might provide an outlet in those situations to open up this line of therapies to those people that otherwise wouldn't have had that opportunity.

Ketogenic diet types, exogenous ketones, and personalization

And, you know, just even thinking, you know, sometimes kids with epilepsy also have other, you know, sensory, processing issues. So epilepsy and autism, for example, are often found, together.

And it can be really hard, for families to get their children to stick to a very strict diet, understandably so. There's this thought process, like, well, wow, maybe exogenous ketones could supplement, you know, a low carb diet or even in some cases might be good enough.

And, to kind of get the job done in this comes from a lot of research showing that the beneficial effects of ketosis are, at least in part thanks to your direct roles of the ketone molecules themselves.

Ketones are far more than just an energy metabolite. They have very potent signaling properties that we're only now really being able to understand. They can influence gene expression, and they have dedicated receptors that they bind to and initiate cell signaling cascades, and they intersect with our immune cells to, you know, modulate inflammation.

All of these behaviors, at least those that are coming from the role of the ketone themselves, is not necessarily dependent on carbohydrate restriction, as long as ketones are present in the blood.

I mean, even the example of, Alzheimer's disease. If this idea is just simply to get ketones to the brain, which there's definitely research to show, that might be the major, you know, impetus there.

That might be a situation where exogenous ketones are going to be a great fit. So, it's been really cool to see these ketones in. You have like a whole host of them, things like ketone salts, ketogenic fats, like these medium chain triglycerides.

I can consider them a form of exogenous ketones because you just consume them. And then you have a mild elevation in blood ketones and then ketone esters, which are the most potent.

And these are synthetic molecules, that either are ketones themselves or they're, they release ketones or they're converted by the liver into ketones.

And they can really at least the the preclinical research suggests they can kind of elicit a dose dependent elevation in your blood, ketones. And so maybe in conditions where kind of a higher level of ketosis is needed to elicit, you know, the desired outcome, you know, ketone esters might be kind of the most promising tool there.

But yeah, that's that's how I view it. Exogenous ketones are just something that might work in certain cases for certain people and more options is better, in my opinion.

So are all ketone esters the same like some? No. I mean, there are different ones that are available. A lot of them are only, there's not a lot that's commercially available there are some there are others that are in development or in pre-clinical testing.

Largely they're not all exactly the same. Some specifically only produce beta hydroxybutyrate. Some produce both beta hydroxybutyrate and acetal acetate.

Those are the two primary ketones. And there might be, you know, specific scenarios where one is more desirable than the other. So, you know, these are synthetic molecules.

So they can kind of be designed to fit your needs, which is pretty cool. And is there like ketone salts or is it's the same as it's different. So they're different. Yeah. Ketone esters are different.

Thank you. Two insults just in the composition of the molecule. So ketone salts or a more simple molecule. They're pretty much just beta hydroxy beta eight.

You know, with a an iron attached like sodium, for example, sodium or potassium or magnesium or calcium beta hydroxy beta eight. And it's, that's why they're called salts.

Because of the type of bond that they have with those, those ions. And yeah, it's pretty much just like consuming straight ketone molecules with some of these other, minerals.

Okay. Not perfect. Where do you think, like, where do you see the field going? I mean, in the next a year or so, like, what's the next big question that you're, you're looking at or you think it's awesome this time?

Yeah. I think it's, really incredible to kind of think back on where we've come from in the past. You know. Well, actually 100 years. So this year is the 100 year anniversary of the ketogenic diet, which a lot of people would be totally shocked to know that, because I think, you know, because of the public conversation around this diet, it kind of gets viewed as this like fad diet now.

But it was developed at Mayo Clinic, in 1921 as a therapy for epilepsy. And it's been used clinically essentially ever since then. So it's not just a fad diet.

There's 100 years of science behind it. But in the past decade, there's been this huge resurgence in interest. And, and people are really just seeing it go kind of all over the place.

I'm probably most excited about the, research being done in neuro, neurological diseases. So things like Alzheimer's, you know, as our population ages, we have a lot of people that are thinking about what can I do now to keep my brain healthy as I age?

And, and I think ketosis is a very promising tool in that regard. So I would say, you know, that's where I'm most optimistic about seeing the most progress being made.

How do you think that we can help, make these, these, recommendations and, but how to, incorporate ketogenic left on or, like, more personalized, like what can what do you think?

Can we be learning about our genetic makeup and, and such that could, you know, potentially give us more ideas on how to make this more suitable? It's hard to say.

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You know, I don't think there's a lot of understanding exactly about how, for example, genetics plays in, and the potential application of ketosis, for a specific individual.

We certainly need more research for that regard in that regard. I mean, we just need more, long term clinical studies across the board. And and that's, you know, probably the biggest and obviously the most, valid kind of argument against, ketogenic diet being used so ubiquitously is that we do want to see longer human trials, really kind of like sussing out some of these nuances.

But, you know, it's hard to do those kind of trials. Diet trials are hard to design. They're hard to get someone to stick to permanently. I mean, can you imagine, you know, convincing 100 people to follow a very regimented diet for ten years just so we can see what happens?

You know, it's very it's difficult. So we kind of have to take what we have and, and improve from there. But, yeah, I mean, just without more research, we don't really know, exactly where and when and if these therapies or these lifestyles are going to be, the best option for all different kinds of people.

And again, people are different. You know, there's probably people out there that won't respond, you know, super favorably to a ketogenic diet, may have some wonky, you know, blood lipids happen.

I've definitely heard of that happening. So it's all has to be individualized. And I think more than anything, I would love to see greater education in the medical community about nutritional therapies, and nutrition in general.

So I'm sure you probably, you know, could speak to however much nutrition education you got in medical school. I know my husband's a physician, and he got one three hour lecture.

And nutrition should be a pillar of health education and prevention of disease and maybe even treatment of disease. So we need more education for the health care community and for the individual.

Yeah. Thank you so much. That's that's amazing. I really appreciate your time, Angela, today. This is great. Work in

our viewers go if they want to learn more information.

I know that you run the Metabolic Health Summit, but any other that you want to tell them about that, that would be great. Thank you. Yeah, we, we host an annual scientific conference called Metabolic Summit.

And it's the next one is going to be May 5th through eight, 2022, in Santa Barbara, California, and will be in. So we'll all be back together, which is awesome.

And we have, you know, a lot of, research presented related to metabolic health in general. But we do have a strong kind of interest in ketogenic therapies.

And we have about, you know, 30 presenters from around the world, both scientists and clinicians, talking about the cutting edge research, and implementation of these kind of, ketogenic and other metabolic therapies, everything from neurological diseases to cancer to metabolic disorders to just human optimization and, aging and longevity.

And, it's a really cool experience. We have lectures all day, and then we have mixers and events. We have a big gala dinner one night to support Max Love Project and Charlie Foundation.

These are some really incredible nonprofits in this space. And so we also aside from that, you know, once a year in-person event throughout the year, we put out a lot of, high quality education content.

Our kind of heart's desire is to be a platform for evidence based education related to metabolic therapies like the ketogenic diet. And, we constantly put out on our social channels at Metabolic Health Summit, put out lots of information about new research and just cool stuff like that.

We even recently put out a, 2020 Year in Review e-book. It's completely free. You can find it on our website. Metabolic Health summit.com, on the videos tab.

And it's, it's a overview of the metabolic therapies research that came out in the year 2020. And we've addressed and presented the key findings of over 100 research articles.

And it's all in one spot. So that's a cool, cool asset, especially for health care providers, because I think, you know, they want to be able to know what's happening without having to do these long, expensive PubMed searches.

And so that's a cool, a cool asset, I would say go check that out if you're interested in that like Health summit.com. Right, right. Want to make sure you got that right.

Thank you so much I really appreciate your time. Thank you. This is great. Thanks.