Introduction to ketogenic research

When we look at the research to actually see that Parkinson's was arrested dead in its tracks, it was a pretty breathtaking result. And now we're seeing, you know, slowing of decline in Alzheimer's patients, and even in diabetic patients a 70% risk reduction in the risk of developing Alzheimer in that case, in established diabetic patient, the comparison part of that study to the use of insulin.

We're hearing a lot about the ketogenic diet lately, that's for sure, and with good reason. There is so much to be gained by looking at this science and in fact engaging our bodies in a diet that lowers our intake of simple carbohydrates and actually welcomes back the consumption of dietary fat.

And who better to tell us about the benefits of the ketogenic diet and his research than Dr. Dominic Dagostino. We've had him on the program before. Let me tell you a little bit more about Dr Dagestino Dominik Dagstino is a PhD and he is tenured associate professor at the University of South Florida, Morsani College of Medicine in the Department of Molecular Pharmacology and Physiology.

He teaches medical neuroscience, medical physiology, nutrition and neuropharmacology. And he is also a senior visiting research scientist at the Institute for Human and Machine Cognition to assist with their efforts towards optimizing the safety, health and resilience of the warfighter and astronaut.

His primary research focuses on developing and testing nutritional and metabolic-based therapies for a variety of disease states and advancing the use of metabolic based therapies into human clinical applications.

So I'm really looking forward to our time together with Dr. D'Acostino. I've known him for many, many years. He's really a leading voice in how we understand things like the ketogenic diet.

How we regulate our blood sugar and how can really increase insulin sensitivity, which is a very important goal. Let's get right to our interview. Dominic, how are you doing?

I'm doing very well. Great to be here. It's good to see you again. There's a lot of talk about ketogenic diet. People are wondering what it's all about, why it is important.

We're going to unpack that, that's for sure. You're the man to do it or the person to it. How did you get started? What made you so interested in metabolism?

Yeah. Uh, well, I've always been interested in nutrition and I did major in that as an undergrad, uh, along with biology. Um, and then I focused on, was mentored by a physiologist and a neuroscientist.

So I, did my PhD in both of those things and just knew.

Dr. D'Agostino's background and path into metabolism

Fundamentally, I did my PhD in a pulmonary critical care division and many of the people even in there were, many these things, treatments could have been a nutritional intervention for that.

And I my postdoctoral fellowship mostly focusing on drugs that could mitigate seizures, oxygen toxicity seizures which limit Navy seal diving and hyperbaric oxygen therapy.

So our lab is very, we have a hyperbaric research center at the lab, so I do a lot of work on that front. And then, you know, were using drugs that essentially were not working to block the seizures, and then I discovered that, the ketogenic diet had been used for, since the 1920s.

I transitioned into that and really that changed the trajectory of my career, as did your books soon. About four years into this, you had published Grain Brain and Brain Maker, Brainwash, and then more recently Drop Acid.

So your books have really provided me with the fundamental principles and reinforced a lot what I was doing at the medical college. Yeah, I was in a tenure track position.

So it was not really looked favorably transitioning from drug research to nutrition research. And, um, but it all worked out. Yeah. How, how does nutritional research benefit the institution per se?

Yeah that, well, that's a question. yeah. so, uh, there's not a whole lot of an age. We leave that one hanging in the air. Yep. So ketogenic diet and you've become kind of the godfather of ketogenetic diet, the go-to guy to really break it down, explain it to people.

I mean, you know, there's certainly plenty of influencers talking about aspects of ketones and various diets, time restricted eating, actual full on fasting.

But what is it about being more into ketosis and maybe we should first talk about what that means. What I want to do is ultimately get to the place that that seems to be a good thing for metabolism Then we'll look at why improving our metabolism is a good thing and maybe relate that to the brain.

Why not? But let's just first talk about what it is that you're trying to do. Yeah. Well, there's even a debate within the epilepsy world as in regards to the levels of ketones and their, you know, how they correlate to seizure control.

And now I think the data is emerging that if we look at beta hydroxybutyrate and acetyl acetate and also acetone, which these are all things that we measure like with mass spec, in the lab in our early studies, we find that the degree of ketosis is, there's good evidence to suggest that that's associated with the therapeutic efficacy of this nutritional intervention.

And the ketogenic diet being a very calculated macronutrient ratio that shifts your physiology from burning Primarily glucose for energy to fatty acids and ketone bodies for Energy and then the ketones more or less become the alternative energy substrate.

In addition to glucose, we're still burning glucose or fuel, but then they become an alternative Energy substrate that not only have metabolic effects, of signaling effects and they're being used for, you know, at least two dozen different clinical applications.

And I know them off the top of my head. I can kind of run through them all and why, and you 10 years ago, there might've been three or four like, Lennox-Gastaut syndrome or Dravet and, different forms of epilepsy.

But there's 439 registered clinical trials on clinicaltrials.gov right now for ketogenic diets. And actually that dropped very slightly from last year, which was like 450 or something, mostly because there's about a hundred or more clinical trials on ketone supplementation.

So many people that are coming to this field kind of see that an innovative path of using various forms of ketones supplementations for some of the same disorders.

Actually exogenous ketons that ingested and I'm wondering, if there may be less interest in studying a dietary intervention that targets metabolism in our current climate, in that now we're seeing such an overwhelming representation in the research and certainly in in clinical application of GLP-1 agonist drugs.

Yeah. I mean, I think that's kind of like a good example, right? Our medical college has a nutrition science course, and we're one of the maybe less than 20% of medical schools that have a Nutrition Program.

And within the various speakers, there's quite a heavy interest, i would say, on GLP-1s. But also, Nutrition with GLP-1s, but also the off-ramp to coming off of GLp-ones and how you manage nutrition with that.

But, you know, GL p-one's have are they're amazing drugs. My course director, Dr. Barbara Hanson, has worked with Gerald Schulman. She spearheaded the original insulin research, and diabetes.

And she did the originally research in GL P-ONEs all the way back in the 1980s. in 1990s. I think maybe people don't even know this research was going on back then, but she was involved in that research and they have remarkable effects on metabolism primarily through dietary energy restriction, right?

So the gastroparalysis, and and, they do come with a host of side effects.

What ketosis is and why it matters

i think in some cases they can be even life-saving for that, you know, obese type 2 diabetic and really add years to their lives, Uh, but I think they, they need to be used cautiously.

And I. Yeah. Um, it's really sweeping, uh, through like wildfire, you know, an interesting metaphor. I would choose that in these times, But nonetheless, in our world, your world and my world related to the brain, I think we're really starting to see some, and I'm not arguing in favor of widespread usage of GLP-1 agonists off-label for brain issues, but when we look at the research that the New England Journal of Medicine article from April of last year demonstrating in a one-year interventional trial of, 153 Parkinson's patients, that placebo group declined on the UPDRS scale by about three and a half points as expected.

the intervention group getting lixacenetide not only stabilized but had a slight improvement. You and I have never seen that. I mean, we've seen slowing down of the decline on the ketogenic diet.

Matthew Phillips' work in New Zealand has demonstrated that, but to actually see that Parkinson's was arrested dead in its tracks, that was a pretty as a pretty breathtaking result.

And now we're seeing, you know, slowing of decline in Alzheimer's patients, and even in diabetic patients a 70% risk reduction in the risk of developing Alzheimer in that case, in established diabetic patient, the comparison part of that study to the use of insulin.

So, I bring these points up because it keeps you and me focused on the pivotal role of metabolism. your work in dietary intervention as it relates to metabolism and gets us back.

to ketogenic diet. So let's just, for a moment, unpack the notion of ketogenetic diet, the production of key tones versus pretty much the higher carb approach of the modern day, what used to be called the standard American diet than the Western diet now the global diet where we're pretty running on glucose day in and day out.

How does metabolism look different when people are more ketagenic, i.e. cutting way back on the provision of carbohydrates and actually welcoming a diet that brings some fat to the table.

Yeah, I think it's important to recognize that the ketogenic diet is a pretty restrictive, and some may say severe, some say draconian, dietary approach that restricts carbs typically under, in kids it is under 10, but in adults under 20 grams, of carbohydrates per day, no added sugar, and no starch, maybe a small amount of fiber you would get from green vegetables.

So with the balance of the macronutrient energy coming from fats. With a classical ketogenic diet, it's about 87% fat, with a modified ketogenetic diet upwards of about 65% of fat.

And then there's different categories of ketagenetic diets from classical to modified Atkins, MCT, based diet, there's a low glycemic index diet developed by Elizabeth Teal from Harvard.

So, which is not ketogenic, but may have some therapeutic effects like for autism and other disorders. But the primary thing is that you're suppressing the hormone insulin and a suppression of the hormones insulin is required for hepatic ketogenesis for your body to make ketones.

And essentially what happens is that with carbohydrate restriction and protein moderation, there's a depletion, a decrease in hepatic glycogen. And the liver is more or less like an energy sensor.

When levels get low enough, that stimulates beta oxidation of fatty acids in the livers. Then the accumulation of acetyl-CoA will form acetoacetate and then that makes beta-hydroxybutyrate, which is the more stable ketone molecule in circulation.

And we have different ratios of acetylacid to beta hydroxy butyrates in the blood, and it's sort of an interesting area. of science and research to sort of look at that.

But the definition, the clinical is that your elevation of blood ketones is about 0.5 millimolar and above, but we can measure ketone in urine and blood and also in breath.

And I've experimented with all these different measurement tools, many of them commercially available. And when you achieve and sustain that, we know that ketones are neuroprotective, they're cardioprotective.

They're anti-catabolic. We've published on cancer cocaxia. we have models where we inject lipopolysaccharide, LPS, and create massive systemic inflammation that we can mitigate a lot of that with elevating ketone levels.

they have antioxidant effects, have anti cancer effects. So we've, we researched these and we published, you know, multiple, uh, dozens of publications, like on all these different applications.

So there are a lot of popular diets now, a time restricted eating full on ketosis. Uh, Dr. Walter Longo talks about fasting, mimicking diet. And are these all kind of nuances of allowing the body to be trending more, at least directionally towards more ketoses?

I think that's one of the benefits, you know, with time restricted eating, intermittent fasting, time-restricted feeding, whatever you want to call it.

Essentially what's happening is that you are creating an eating window and a fasting window. And during the fasting. You are putting your body into typically a mild state of ketosis.

reducing the level of insulin to levels that would otherwise not happen. Maybe if you were even calorically restricting the same amount, at least during that window.

So the benefits from them are derived largely from the energy deficit. I would say like maybe 80%, it's hard to put a number, but then there are probably additional benefits.

For example, you're letting the gut rest in repair. You're enhancing maybe You know enhancing gut permeability or reducing gut Permeability by giving your gut some time to rest So I think there are some additional you know benefits by having that fasting window independent of calories and that seems to be the debate Within within people in the field that study time-restricted feeding And, you know, and other people looking at energy models will say, well, all those benefits can just be, tied to the caloric deficit that you inadvertently eat less food if you're eating within a restricted window.

And I think that's true too, but I there are some additional benefits as Dr. Walter Longo, Dr Sachin Panda, have talked about, I've interviewed them for various podcasts too.

The work is breathtaking. And, you know, when you take a deep breath and step back, it seems true that what we are doing is emulating our hunter gather forbearers who must have had times when their hunting and gathering was not as productive and they had to be a bit more resilient.

I think that you're really presenting here is a hormetic stress that when we're calorie deprived, energy deprived that it is a bit of a stress and what we're then taking advantage of and activating are these mechanisms whereby we ultimately become more resilient and stronger metabolically by stressing our bodies in this way that by restricting

the carbs and allowing our body to utilize our endogenous fat or as is popular today providing exogenous in the form of supplementation.

I think there's also all great points that you make and I also think that there is probably a behavioral component. When you do that, that it changes your relationship with food and that maybe it instills in you a level of discipline around food, around restriction.

And the more you it, the easier it gets and the benefits you derive from it. a feed-forward sort of thing is that once you start to experience the energy and quite frankly, the dietary control that you have once your insulin is suppressed and you started making ketones.

So the ketone's do, I talked about, we study the neuroinflammation, and we studied anti-cardiac, anti cancer effects and things like that. But I think just by virtue of being an energy molecule that your body has access to, It keeps your brain in a state of preserved metabolic energy production, even in the face of hypoglycemia, which is associated with a caloric deficit.

GLP-1 drugs and metabolic effects on the brain

So I think achieving and maintaining a level of ketosis makes Being in a caloric deficit more easier so you don't the hypoglycemic lows do not trigger a craving for food and overeating and going off the rails and you know the early work by George Cahill and Oliver Owen at Harvard when they fasted subjects for 40 days and injected them with insulin.

they were asymptomatic for hypoglycemia which is just was in 1967 they published that it was just a very dramatic demonstration that that ketones could largely replace glucose as an energy molecule and so that's you know the neuroprotective component to that really interested me but I think more practically if you have low levels of ketones, even one millimolar is providing your brain with 10% of its available energy, just one.

So pretty much, I remember talking to Dr. Cahill and Dr Beach about this, and it was like, you know, one one million molar was, like 10 percent of brain energy.

Two million more is like 20 percent, a brain, energy largely speaking. That's very important in the context of many disease processes. Well, i think it's interesting from from that research that even at the 40 day point with those subjects, actually they were medical students and I think perhaps some pre-med students who got paid for this.

Even at that point, there were still utilization of about 20% of what was powering the brain was still glucose. I mean, we have a notion that while you're shifting over to full on ketones and the reality is there's still residual glucose power in the brand.

And I thought that was quite interesting. Yeah, that's important because that gets confused a lot. That's right. It's often framed like you switch from glucose to ketones, but there's a transition more.

But there are very powerful homeostatic mechanisms that maintain our blood glucose. And the ketone can fill that energetic gap. Even when you fast for a week, which I've done, my glucose still stayed at about 60 millimolar.

or 60. No one's gonna say that fasting is easy. It is a challenge. I mean, I, you know, we've all done it. We've tried to walk the talking. To be fair, it isn't easy, but being on a more ketogenic diet is certainly a lot easier.

And especially if you cycle, I don't mean bike, if cycle between keto, being in keto and not being keto. What would a consumer use to measure his or her depth of ketosis?

Do you think the breath analysis is adequate? Yeah, I have lots of things right around my desk that I'm doing experiments now. I don't market any brand, but the Abbott Precision Extra, we've published a lot with that.

The more recent is the Keto Mojo device that has the glucose-ketone index that we can go into that, that's the

millimolar concentration of glucose over ketones.

It's a very important biomarker. Uh, I got lots of tools here. Lactate meter. I've got your, uh, you are sure the, the uric acid presenting that I'm still measure that.

And then I keep mine handy. Actually I correlated my, your shirt to the a, to a blood test. Just, and I get the results yesterday and it looks like it's right on target.

Uh yeah, 4.6 at the lab and then 4 7 on the finger stick. So. I did. Yeah, I got 4.6. I don't know if you could see it from there. There you go. Great minds think alike.

Yep. And that was sort of after a meal too. So yeah, also validated mine with Quest diagnostic labs and it was like plus or minus 0.2 or 0.3. It was pretty close.

You mentioned how ketosis is really a good way of restoration for insulin sensitivity by reducing insulin, reducing the challenge of higher levels of insulin in the body and good for insulin sensitivity, why should we care?

Well, you know, broadly speaking, most Americans are insulin resistant. And after, especially after 50 in the 60s and 70s, you know, pre-diabetes or diabetes, people have overt diabetes.

It's a large percentage of the population. So the fastest way to bring down your insulin and to restore insulin sensitivity is to restrict carbohydrates and restrict to some extent total calories too can help augment that process, but fasting, time restricted feeding combined with a lower carb.

I like to do time-restricted feeding with the ketogenic diet, but you could do with Mediterranean pattern. You know, I liked to use the word low carb Mediterranean style diet.

you know I'm still confused about what a Mediterranean diet is and how it's defined in the literature, But simply eating a hundred, 50 to a 100 grams of fibrous carbs per day and following a Mediterranean style diet would probably restore most people's health.

We tend to target like disease processes and everything from genetic disorders to epilepsy to other things. And then a bigger lever for that would be ketogenic therapy in the form of diet or supplementation or maybe even time restricted feeding.

So, but it's that insulin, it all kind of focuses, just to get back to your question, reducing the level of insulin or restoring insulin sensitivity through carbohydrate restriction.

Well, hi everyone, Dr. David Perlmutter here. We hope you're enjoying this content. And if you would do so, go ahead and hit the like button. If you are not already a subscriber to our channel, please consider doing so.

Uh, we're really grateful to have you as part of our community. So let's get right back the presentation. I think a question that a lot of people have is on how much protein they should be consuming.

Ketogenic diet, insulin sensitivity, and protein intake

And you indicated earlier that, you know, if you're consuming a lotta protein, that might help keep you out of ketosis, which is not the goal. We're hearing the protein recommendations kinda across the board.

You know some people are saying as much as 1.5 grams per kilogram ideal body weight, seems like a lots. Others 0.8 grams per kilogram, ideal body weight.

So through the lens of trying to maintain some degree of ketosis, how much protein do you think is best for an individual who's not necessarily trying accomplish anything in terms of disease reversal, but just for maintaining good health?

Yeah, everybody will have different protein requirements based upon, you know, their level of muscle mass or activity level and things like that. And I know Dr.

Walter Longo kind of advocates for a lower protein approach. We've had that conversation before, but I kind point to the research by, Donald Lehman and Stu Phillips where Let's do grams per pound, upwards of one gram per pounds of protein, I think, especially as we age, we have age-related sarcopenia that we want to mitigate.

That means loss of muscle mass for our viewers. Go ahead. This may sound very extreme, but even one to two grams per pound may be helpful for some people.

If you're in a caloric deficit, then the proportion of protein in your diet, the ratio would be higher, I think, because you want to mitigate some of the muscle loss that can accompany weight loss.

So obviously, we don't talk about exercise enough. If exercise was in a pill, it would be blockbuster. It would more effective than anything we currently have available.

Or sleep in the pill. Yeah, sleep is super important too. Good sleep hygiene and light and yeah, just the balance of those things. But if you are, your protein requirements will increase with resistance training, with exercise to help rebuild.

And so I'm of the opinion that if we do the metric scale about, you know, 1.6 to even two grams per kilogram. Of ideal body weight. Yes, of ideal, bodyweight.

Yeah, important to say ideal. Well, to be fair, that's kind of on the higher side, correct? Yep. in comparison to what others are saying. Plenty of people are right there with you.

But then again, does that tend to help steer us away from our ability to engage ketosis? It can, yeah. So this is like clinically for kids, one of the side effects, I guess most serious would be, well, there's kidney stones.

And then we figured out if you do potassium citrate, you can like, like there is no higher risk of kidney stone. Early studies show a bit of a stunting of growth, like, you know, growth metrics were a little bit reduced and some of the early studies with clinical classical ketogenic diets were limited.

And if you have children need higher protein and we were in ketogenetic diet studies for epilepsy, the protein was restricted to increase ketones more.

and to control seizures. So we know now that a modified higher protein ketogenic diet can have the same anti-seizure effect, especially if that diet is formulated with specific types of the early fats were like Crisco and hydrogenated oils.

These are in like shakes that, that kids would drink. But now we know a lot more, you know, monounsaturated fats, but also medium chain triglyceride or MCT oil can be incorporated into the diet.

And you can get levels of ketones that are even above a four to one classical ketogenic diet with a 1.5 to 1, which essentially means, getting about 20% of the calories from protein and the early diets were like 8%. And that was too low.

That created side effects and growth. Do you think their growth issues might have been just from an overall reduction of protein, or could there have be a more specific targeting that might've obviated it by adding in higher levels of branched-chain amino acids?

Yeah, I think I mean typically like these are formulated with like a casein or whey and they have high amounts of EAAs and branched chain amino acids with the leucine content being the primary driver for skeletal muscle protein synthesis so that it was probably sufficient but you still need you know, an increase in the total amount of protein.

And you, know with that level of routine restriction, you're probably not getting to that leucine threshold for, stimulating protein synthesis. So I think essentially amino acids can be really important for maybe women or other people that don't like to eat as much protein and that if you were doing more of a plant-based approach, EAAs, Essential amino acids and branched chain amino acid could be added to a meal.

That's for example, more, plant centric or plant based approach. And I think that's usually the only time that I would advocate for that because like an egg, you know, even if you're a lacto ovo vegetarian or something, or just get a little bit of dairy, You can do okay.

But if your vegan or vegetarian, I've worked with different registered dietitians to formulate those meal plans. that is where we go to essential amino-acids or branch chain.

In that inflammation seems to be such a central player in the degenerative conditions and certainly let's just go neurodegenerative of conditions. What is the mechanism whereby we are reducing inflammation by getting more of a ketogenic program going?

Yeah, I think it's multiple mechanisms working in synergy, right? So a ketogenic diet is by its nature a restrictive diet. So it is probably restricting things like grain and maybe certain types of fiber and helping to change the microbiome in a way that probably enhances the tight junctions and reduces gut permeability.

So there's that going on. Initially though, what you may see, we see this in rodent models and also in humans, sometimes the stress of the initiation of a ketogenic diet could make certain biomarkers jump up like HSCR and then it comes back down at plateaus.

lower than baseline if you stick into a state of nutritional ketosis. But you have many things going on at the level of the gut, at glucose coming down, insulin coming, ketones going up.

and everything I just sort of mentioned with a properly formulated ketogenic diet that does have fiber in it. And I think I'm a proponent of a higher fiber, like 20 to 30 grams of fiber I feel should be important and we could talk about the different types of fibers.

But yeah, it's a great, great point, though, that people who are eliminated carbs and fibers, by definition, a carb, uh, That's risk. That something that I think is really part of the induction education that, Hey, yeah.

It's. But you're desperately in need of a fiber. Yeah, and some people do thrive on a carnivore diet and I get quite a few people will email me and they're essentially eating no.

And I think fiber is not, to my knowledge, not essential. But, you know, in most of the data, people point to is epidemiological data, but it's really good data.

And there's a number of studies showing that prebiotic fiber can enhance butyrate and really help to restore gut health, fermented foods. In some cases, maybe probiotics are helpful.

But I think certain types of fiber are important for most people. I can't let this go. I mean, this is really very interesting. You know, the messaging has been, well, we need to eat a lot of fibers, vegetables on our plate, various colors for the polyphenols on and on.

And yet what you just said is, is it's really quite interesting that people who are full on carnivore at times tend to, when you metricize them, they're in pretty good shape.

Obviously their microbiomes are quite different, but when we look at, for example, the Inuit who have very little plant fiber in their diets and yet are existing on ocean type protein and certainly fat, And that's, you know, for many months of the year, that the mainstay of their diet and yet seem to be pretty resistant, at least to cardiovascular disease.

Maybe that is the offset by the omega-3s, who knows. But, I think this is an area that needs further unpacking, or atleast exploration. Yeah, it's not being studied rigorously right now.

I think Dr. Belinda Lenertz might be tracking a number of carnivore followers and she's published something out of Harvard to just more of a retrospective observational study looking at the different biomarkers.

And I've, you know, at least maybe a half dozen people will, have emailed me with longitudinally like sending me their blood work.

Inflammation, fiber, and carnivore diet questions

And, I would basically say, the LDL is elevated often in people, but with other, insulin, HSCRP, hemoglobin A1C, triglycerides, You know, even B12 status is up, but that APO-B does elevate, you know HDL, APoA1, will go up and that's a good thing, But you see this elevation of APB or LDL cholesterol and should we be concerned about that?

I think that is an area of ongoing debate and research. Well, I think it's a question of how, you know, as well, the personalized medicine approach, how much can that individual tolerate?

I know for me, i cannot tolerate any further elevation of LDL. So I guess that's where the personalised medicine comes into play and certainly genomics aswell would factor into that.

Yeah, there's a, you know, I was at a conference and I said I thought genomics was, genetic testing was important for cardiovascular health. And that was quite debated with me on that.

But personally, did a GB health watch. I don't advocate for any specific testing. company or anything, but it did. And someone said, I think you are a hyper responder of cholesterol, you know, just based upon what I've seen in your dietary patterns.

This is someone that looks at thousands of patients. So I have a mutation for the MPC1L1 transporter. That's the transporters in the gut. Zetia, also a generic name, azetamide, blocks that and I could take a baby dose of that, and it literally cut my APO-B like in half and trended to increase my HDL.

And my triglycerides went down a little bit too. I didn't change anything. So that was, I'm not in favor for my situation for taking a statin, but azetamide monotherapy five to 10 milligrams per day had a remarkable effect on me.

Other people have told me that and I said, well, you should go get tested to maybe see if you, but I think, there's a lot of different drugs. We have very good drugs for lipid lowering.

And I they should be considered for people that have a history, or maybe if they have APO, APoA is elevated like APa. And really on the basis of their cardiac workup as well.

I mean, what is the calcification score? That's the big one. What is their CT angio looking like? And, you know, these are very valuable. But, I would also think it's important to rein them in metabolically as it relates to insulin and glucose as Yeah.

I think, you know, we have to look at it more, uh, get the whole picture. And I. You know having a calcium scan and a CT angiogram or something like that is really important, especially if you have a family history of obviously had a heart attack or.

Yeah, um, but, yeah, I, think we need to be cautious at this point in time, when it comes to carnivore diets and that, cause I get a lot of questions.

Completely agree. I would add to the data set that looking at epigenetic expression or tags, very important. I just did a test called True Diagnostic and it's very helpful in terms of indicating where you are epigenerically in term of

risk moving forward.

The good news is to some degree you can change your epi genetic expression based upon lifestyle intervention. based upon pharmaceutical intervention as well.

Let me get back to the notion of ketogenic diet and its role in insulin sensitivity and it's role and glucose metabolism. Can we just momentarily touch on Glute 1 and Glut 4 transporters and how that's influenced, what they do and that influence in the presence of a ketogenetic diet?

Yeah, let's start with Glut1. And we actually have the glucose transporter type 1 deficiency mouse model. You know, but maybe your listeners don't know that the standard of care for a deficiency in Glute1 is the ketogenic diet.

So that is like this, literally the, standard to care, for that rare inborn error of metabolism. So the glut one is, you know, it's in the blood brain barrier and it helps to transport glucose, into the brain and its on a wide variety of different tissues, even in cancer tissues.

We're developing drugs to potentially target that. So, Glut 1 is not insulin activated, whereas the Glute 4 transporter can be translocated. It probably has its most profound role on skeletal muscle and activity, resistance training, cardiovascular, stretching the muscle, and an increase in You know insulin and different things can translocate that receptor to the muscle and make it can enhance glucose disposal and that can be done sort of independent of insulin to that you there's like a insulin independent trans location of the glut for.

that's sort of an activity dependent thing. So if you're like a type one diabetic and you eat a carby meal and then go exercise, some can even like inject way less insulin or no insulin at all because that response is so powerful.

You had also mentioned that There's some signaling activity associated with the production of ketone bodies, specifically beta-hydroxybutyrate. I think it kind of gets to our brief discussion on epigenetics.

What are some of the important signaling aspects of this ketones, beta hydroxy butyrates that we increase as we're in more of a ketogenic diet? Yeah, that's really like the hub, the main focus of the lab.

And it started over 10 years ago. We looked at just looking at the brain, and the neuropharmacology of brain changes with the ketogenic diet and with exogenous ketones.

So it increases the GABA to glutamate ratio by activating GAD65 and 67 are proteins that are glutamic acid decarboxylized. convert glutamate to GABA. So there's, you know, the brain neuropharmacology.

We published a paper in 2015 and I helped formulate the diet in Nature Medicine that showed the beta hydroxybutyrate can function as an NLRP3 inflammasome suppression.

Actually, and then if we look more into it, the activation of the complex that's an inflammasome and the assembly and activation, both processes are regulated in part by beta-hydroxybutyrate.

reduce and suppress that and downstream that would reduce IL-1 beta. It's independent of the enantiomer. Your body makes primarily D beta-hydroxybutyrate, but also makes L beta hydroxy butyrates as a mirror image and enantimer.

And what's interesting about L, and now there's, you know, a bunch of people patented it. I think the Buck Institute and other, there was a number of different patents on the L but that simply sold as racemic.

You have a 50-50 mixture. The L seems to retain that signaling property. And if you consume a racamic mixture, the D gets burned up quickly as energy and then that L stays elevated in the blood about four times longer and retains that signalling effect.

So there's a GPR109A receptor, the NLRP3 inflammasome and different sirtuins that too are sort of activated and

that's epigenetic. And then my student just graduated about a month ago with her PhD dissertation.

Her focus was metabolic control of epigenetic regulation. So, there is something called beta hydroxybutyrolation where beta-hydroxy butyrate can interact directly with the histones.

Ketones as signaling molecules and epigenetic effects

uh to activate different genes and we started looking at this in the context of something called kabuki syndrome we had the kabuky syndrome mouse model uh but you know i'm convinced that these metabolites especially ones that are robustly elevated with a ketogenic diet have epigenetic effects.

And it's probably not just beta hydroxybutyrate. We know that there's something called lactylation too. So lactate can also, lactates very interesting and was my original interest before ketones actually.

These metabolites that are changed profoundly by our diet, by fasting, but ketone supplementation have very remarkable epi genetic effects in a positive way.

Respectfully, let me just step some of this down for our viewers. One of the byproducts of getting into ketosis from a ketogenic diet is the production of something called beta hydroxybutyrate, which can be used as a fuel.

But the question was, it also acts as signaling molecule. Why is that important? What does it do? And what you describe, one thing that you described that I think is really very important is It binds to certain cells in the immune system, receptors on certain cell that activates something called the NLRP3 inflammasome.

Why is that important? Because that then causes genetic changes within the cell, these immune cells, in brain, for example, the microglial cell. that subsequently then will, when it's activated, will increase the production of damaging inflammatory chemicals called cytokines, but also influence the mitochondrial function within that cell, the energy metabolism part of what goes on within the cell and can help propel that otherwise helpful immune cell the microglial cell to becoming a harmful phenotype, M1 phenotypes such that its metabolism is affected and its production of inflammatory cytokines is effected.

And the worry there is that those inflammatory cytochines can then feed back and through the same pathway influence neighboring microglial cells and convert them from being friend to foe, to becoming the evil twin as it were.

So basically what we're saying then is that aside from the fuel aspect of ketone providing great fuel to produce energy, that they are producing at least beta hydroxybutyrate, most gets most of the attention, is acting as a signal molecule in terms of gene expression through modifying epigenetics, through what are called histone deacetylase activity, but also through influencing, through this inflammation pathway we just described, NLRP3 inflammasome, a reduction of activation, influence the level of inflammation in the brain.

And that's key. When we recognize the role of information in Alzheimer's and Parkinson's, multiple sclerosis, autism, that this is really what we're looking for.

This is pretty much the home run. Let me shift our conversation for a moment it to something that you and I have been exploring, and that is the use of allulose.

And it's a new player for us. We've only been looking at it for a few years. So there's lot of excitement about alluose, tell us what this is and what you have found in your research on alluleose?

Yeah, alulose is really fascinating. So it's a rare sugar. It's found in nature, things like fig and it even in wheat, I think, you know, in various fruits.

Yes. so it is a rarer sugar that is an epimer of fructose. So very similar molecular structure like on paper. It also uses the Glut5 transporter to get into cells.

And it's very low calorie. I think it is like 0.2 to maybe 0,4 calories per gram. So, very essentially like no calories. Its absorbed in the gut, its excreted primarily I thing in urine.

non glycemic, non insulinogenic, you know, compared to other has very minimal insulin response, very minimum, if at all, glycemic response. Actually a lowering effect.

Some studies coming out in animal models and maybe there's, I think there is about, there at least a half dozen randomized controlled trials for allulose.

And we are, full disclosure I guess, multiple medical students were working on a systematic review of natural sugar alternatives with erythritol, alluolose, monk fruit, stevia.

Allulose seems to shine for many different reasons. It seems have functional effects, perhaps anti-inflammatory effects on the gut. Generally recognized as safe by the FDA.

Again, it is found in nature. If you take large amounts of it, which I did the very first time I tried allulase in 2014, I dumped a bunch into my coffee.

It's about 70% as sweet as sugar. And if you put 30 grams in your coffee, on an empty stomach, you'll likely have some intestinal bloating and things depending.

So I think it's good to start out with maybe five grams. I can now tolerate 30 to 40 grams per day if the Iolus is taken with food, but it also has some GLP-1 releasing effects, which is very interesting.

Allulose, CGM effects, and exercise response

sweeteners out there so it can when I consume allulose I wear a continuous glucose monitor my glucose goes down even if it's the alluose is in a chocolate bar like an arc sugar bar and I've measured insulin it has essentially no insulin response and i have not measured my own glp1 but there's research out their nature communications showed that me someone my size taking an equivalent of 30 grams of alluvose they had like a a three to 500% increase in GLP-1 secretion in a rodent model.

And that has not been fully replicated, I think, in human studies, but there's research around that. Very exciting. I mean, you know, there's every month that goes by, There's another popular sweetener, it seems.

And I think lately we've seen some concern, at least from a cardiovascular risk perspective with respect to erythritol, a sugar alcohol. Um, I that, by and large, the more we can do to help people not cater to their sweet tooth, I think it's a good thing.

But I too, as you know, am using Iulis. We've talked about this quite extensively. And I'm very happy to say that. I am taking in about 10 grams a day in the morning.

It's clear that it is having an effect on my continuous glucose monitor. There's no question about it. Especially what I've noted is that You know, there's generally, I find when I run that I get a little bump in my blood sugar as I'm starting my run.

Well, within the first 10 minutes or so. And I found that that bump seems to be a bit blunted when consume Allulose ahead of time. Any thoughts? I have the same same response.

I've even like posted about this on social media. You know, if you engage in really intense exercise and I think there's a threshold for heart rate stimulating, you know their sympathetic nervous system activation and same can be said for exogenous ketones too.

It seems to for reasons I don't fully understand, I think it's decreasing hepatic gluconeogenesis and maybe decreasing hepatoglycogenolysis in a way, and probably perhaps enhancing glucose disposal in peripheral tissues,

which is kind of maybe more exciting.

So nonetheless, this has been reported by, I mean, you just reported it, and I think it's also in the literature that when, yeah, probably the most profound thing in literature is that, when you consume allulose with carbohydrates, with glucose, it significantly attenuates the glucose-induced elevation when it is coupled with alluose.

And allulose may be delaying gastric absorption, but even the area under the curve is reduced. And that's remarkable. I don't know of any other sweetener that has that functional property.

Well, again, it's a great argument in favor of using a CGM. Yeah. Yeah, you wouldn't know it. You never know without that. So yeah, I think for the diabetic population, type 2 diabetes, Type 1 diabetes.

I know, allulose could be, especially if you have a sweet tooth, could like a really important component. You can bake with it, you can cook with, it you, can incorporate it into various things.

And it can make, I'm working with the Moffitt Cancer Center because ketogenic diets can augment the adaptive immune system to perhaps make checkpoint inhibitors work better.

So we're working like the big kind of pushback is the unpalatability of and the lack of not having sweet foods, but you know with things like alulose, their dietitians and their metabolic kitchen that they just built, they can formulate foods and a whole array of different food products that could incorporate aluose and be, you palatable to that person who's uninitiated to low carb or ketogenic.

And that's really important. Need we say more of Walter Longo? I mean, he's made it very clear as an adjunct to standard care, chemotherapy, radiation therapy, surgery, that challenging the body with a ketogenetic diet goes a long way to enhancing outcome and great work.

MCT oil and closing thoughts on metabolic health

Let me ask you as we close, what is the efficacy, the role, and the utility of MCT oil in hopes of pushing people to a better metabolic state? You know, I love MCT oil and I think it's like the poor man's ketone ester, right?

Some of the ketones esters on the market, they're kind of derived from a 1,3-butanediol, which has some questionable things. I'm more inclined to use ketona electrolyte salts.

But one thing that we observe is that when you take any exogenous ketone and couple it with MCT oil, the therapeutic effect of that is greatly augmented.

And MCO alone by itself can elevate ketones levels in the blood independent of diet, meaning that you could be eating a standard diet consume MCC oil and you have about 20% I think more if you're fat adapted and you are making lots of ketones, a significant percentage of that oil is converted to beta hydroxybutyrate and gets into circulation.

Also, MCT oil can cross the blood-brain barrier. So they can actually, unlike long-chain fatty acids, when you consume MCTs, those fatty acid can directly get across the brain barrier and into cells and neurons.

In addition, they help your body to stimulate fat oxidation in the liver because they go directly to the livers via hepatic portal circulation. It's almost like the live is getting a big hit of fat, which could be uncomfortable for some people.

So I think it's important to titrate it in slowly over time, but I they are inexpensive. They're remarkably therapeutic. And I thing they're a cornerstone fat for a ketogenic diet.

Dominic D'Agostino, we've covered the waterfront today. Thanks for spending time and sharing your wisdom. It's always great to see you. Great seeing you, David.

Yeah. Thank you for having me on and I appreciate it. You bet. We'll talk soon. Bye for now. Well, I'm sure you all learned a lot today. I know I did.

Dr. D'Agostino is a wealth of information. Again, the value of cutting back on simple carbohydrates, getting ourselves into a state of ketosis from time to time.

We talked about fasting, intermittent fasting. All the potential inroads to better health, regaining insulin sensitivity, and really overall improving our metabolism, which is essential goal for us.

as it relates to our brains and even overall health. Thank you for joining us. I'm Dr. David Perlmutter. We'll be back soon on The Empowering Neurologist.

Bye for now.