DANNY LENNON: Hello and welcome to another episode of Sigma Nutrition Radio. As always I am your host Danny Lennon and you are very welcome to another episode of the podcast. Today we are at episode 186 and I'm just going to be joined in a few moments by Dr. Jake Kushner, who is a pediatric endocrinologist, who is involved in both frontline care of patients as well as research. So he has been leading up the efforts in diabetes in endocrinology at Texas Children's Hospital for a number of years now as well as being the Chief of Pediatric Diabetes and Endocrinology at Baylor College of Medicine as well, looking at some things within research. And some of the things he started implementing in practice have been related to looking at the nutritional and lifestyle interventions we can use in the care of type 1 diabetic patients.

And one of those strategies being is carbohydrate restriction, a viable option for someone with type 1 diabetes. So of course there has been a lot of talk for those with type 2 about how maybe a lower carbohydrate intake could potentially be favorable, but in type 1 there has been a lot more course to be, a bit more skeptical or a bit more concerned about using this due to a variety of reasons that I'm hoping to bring up with Dr. Jake Kushner. And he has been looking at this idea of using carbohydrate restriction within type 1 diabetes and

has used it with certain patients, certain circumstances and, so it'll be interesting to dive into those views. Before we get into the episode, just one announcement I wanted to make because something that I think I've mentioned a few times before and is concerning a question I get asked extremely frequently from those of you wondering about nutrition courses. So whether you are a nutritionist or a personal trainer or someone who has not yet gotten into the nutrition field but has a passion for it and is thinking of getting into nutrition, the big question a lot of people ask is, "I'm looking to do an online nutrition course, which one should I do?" And if you've been listening to this podcast for a while, you've probably heard me mention that pretty much my default recommendation across the board for people looking to do a online nutrition course has been Mac-Nutrition Uni, the evidence based course developed by my mentor and now friend, Martin McDonald. And having known the quality of content that's within the course and having seen it, having seen the ongoing interaction that there is from students with Martin and the other speakers that are involved and just how the whole course is structured and how sound the information and learning is, I could a 100% vouch for this being the outstanding choice when it comes to an online evidence based course.

So with the upcoming intake of students for the next intake, enrollments have just started for that this week. So enrollments are now open for the next batch of intake of students for MNU and if you're interested in that then Martin has kindly organized a 50 pounds starting discount for anyone within the Sigma Nutrition audience. So if you listen to this podcast, you can get a discount code that will allow you to get 50 pounds off the usual enrollment fee. So if you just want more details about that course and you want to see some of the course options available and overview what's included, how it runs, the topics, all that type of stuff, I'll just put all that together over on the website. So just go to sigmanutrition.com/MNU, so it's sigmanutrition.com/MNU and you'll have all the details about the course there. So I just thought I'd mention that because it's something that gets asked extremely frequently. So with that let's get into this

week's episode with Dr. Jake Kushner showed on – this episode is going to be over at sigmanutrition.com/episode186 and let's welcome Dr. Jake Kushner. Dr. Jake Kushner, thank you so much for joining us on the podcast today. It's my pleasure to have you on and really excited for this conversation.

JAKE KUSHNER: Thank you so much for the opportunity to speak and to get together and talk about these ideas.

DANNY LENNON: Yeah, I think there's a lot of important topics that we're hopefully going to get into some detail. But maybe before we get really into the nitty-gritty, just as a background for people listening, can you briefly introduce us to the work that you do both in practice and academia and maybe a bit about your background that's led you to that point?

JAKE KUSHNER: Sure. So I'm a pediatric endocrinologist and I got into the field because of my love of basic Science and Molecular Biology. And I thought I was going to end up working on some sort of esoteric disease and I found myself as a young doctor in training working with children who are newly diagnosed with type 1 diabetes. And I realized that I wanted to spend my career focusing on trying to address their needs. And, so my background in Molecular Biology and Developmental Biology led me to become a Beta cell biologist. I trained in a basic Science research lab, focusing on these cells that make insulin, the beta cells. And I realized after a few years that I wanted to start a lab of my own, focusing on finding ways to expand or grow Beta cells.

And, so for the most of my career as a independent scientist, I've been focused on trying to find new ways to increase the ability to make insulin in the human pancreas. So we use mouse as a model, we do various experiments around that. Okay, so my clinical interest is around these children with type 1 diabetes and by the way, that's a huge problem, right? It's the most common life threatening chronic illness of childhood that requires medication and it's just a big deal. There's over a million people in United States and there's many millions of people worldwide and injected insulin is the only available therapy at the moment. It's really

challenging! So I have this clinical interest and I care for patients with type 1 diabetes. I'm a scientist and I'm trying to find ways to expand Beta cells and about 6 years ago, maybe 10 years ago, I went through what my wife calls 'my midlife crisis' where I began to worry that my basic Science career was going to never actually translate to helping patients. And I went through this weird anxiety over it and I didn't buy a red sports car and I didn't take up skydiving, but I decided I want to do something really practical with my career. So I became the Chief of a very large diabetes service here at Texas Children's Hospital and once I got here, I started just trying to look for creative solutions to help people with type 1 diabetes, sort of out of the box kinds of things.

Okay, so I'm now – so this is precisely 6 years ago, I arrived at Texas Children's and I'm trying to learn from people who have type 1 diabetes. And I met a nurse practitioner named [indiscernible 00:08:46], who has type 1 and she was telling me about this method and this book called 'The Bernstein Method' and this is about Dr. Richard Bernstein, who had come up with a really interesting way to treat type 1 diabetes that focuses on carbohydrate restriction and insulin to cover protein. And I had never heard of it and I discovered it was really amazing and I started asking questions about it. So basically my – the past 6 years, my interest in nutrition and type 1 diabetes has led me down this path to learn more and more. And I'm a constant reader and learner, so I'm always asking questions about how things work and why. I just completely fell down the rabbit hole on this topic of nutrition and type 1 diabetes.

DANNY LENNON: Awesome. And I certainly want to dig into a whole host of things related to the nutrition component of that and definitely get into the whole aspect of diet and what you found in the area. But maybe to start us off on this conversation, we should first set the scene here by considering type 1 diabetes just as a disease first.

JAKE KUSHNER: Yeah.

DANNY LENNON: And in that, a lot of people listening will of course be familiar with the fact that type 1 diabetes – they probably most know it for being this failure to be able to produce insulin right?

JAKE KUSHNER: Yeah.

DANNY LENNON: And then comes up with these images of people with shots and injections, but to get a more comprehensive view here and really set the scene for the rest of this conversation, what details beyond that should people be aware of when it comes to the actual disease of type 1 diabetes?

JAKE KUSHNER: Great question! So this is an autoimmune condition whereby the T cells and also the B cells are targeting the Beta cells, the cells in the pancreas that make insulin. And, so for reasons we don't understand, genetics and environment, a bunch of things conspire to force the immune system to destroy this central component of the pancreas that makes insulin. And the genetics are multi-factorial, there's no one single gene. There are a bunch and bunch of genes and the environmental factors are very, very poorly understood and it almost seems to be random. So when I sit down with a family of a child whose newly diagnosed and the parents are like, "Why did this happen to our kid?" The first answer is, "We don't know." And I feel really confident saying that in a sense what I say is, "The person who can look you up in the eye and tell you why this happened is showing they're naivety." My general model of how this works is the immune system is charged with protecting us from viruses and bacteria and fungi and also immune surveillance from cancers and other bad things. So the immune system is trying to protect us from these terrible things and it has these really big guns that it deploys to protect our bodies from these terrible things. And perhaps, not surprisingly, these guns are so big and so potent and so lethal that on occasion, they get confused and they began to attack ourselves. And this term in the military 'friendly fire' sort of applies here. Now that's not very satisfying to parents of a child who's been newly diagnosed with type 1 diabetes, but that's about the best we have.

DANNY LENNON: Yeah. And that tends to throw up a lot more topics on that. And I think one question it brings to mind is, when we're talking of this autoimmune destruction of Beta cells and maybe even beyond that if we're just considering Beta cell function, there's obviously something dysfunctional going on in type 1 diabetes. Does that exist on a spectrum? In that do we have some individuals with virtually zero function whereas others have a greater degree of function, although maybe still largely suboptimal compared to a normal state? But is there a variation in how well the Beta cells are functioning among different diabetic individuals?

JAKE KUSHNER: Yeah. This is a great follow-up question. So it turns out that it depends. So the younger you are at diagnosis, the less insulin you make. So we are involved even in some extreme cases of babies who're diagnosed at seven or eight months of age and when they present – by definition they've only have type 1 diabetes for a few months and they almost invariably make no insulin, like almost none. And another hand, I've also been involved in the care of young adults with type 1 diabetes, who had this autoimmune process probably going on for many, many years and they have dramatically elevated blood sugars and they have – it seems like pretty severe diabetes and yet they're sort of walking around and they feel okay, but they are super thirsty. And when we begin to give them insulin, all of a sudden they recover their ability to make insulin on their own. And this has been termed the 'Honeymoon' and we think the reason is that very high glucose actually inhibits the ability of the Beta cell to make insulin.

So the function of the Beta cell is glucose stimulated insulin secretion and when glucose is very, very high the Beta cell simply gets overwhelmed. So it's like, you can't hear anything when you're at a rock concert, it's like when you walk out your ears are ringing. You could never hear the subtlety of String quartet after going to see Metallica. So that process of glucotoxicity interestingly is reversible. And in many people, young adults who're diagnosed with type 1 diabetes, they begin to make enormous amounts of insulin on their own. There's even a thought and this is kind of controversial, it's really new, but that there may be forms of

type 1 diabetes that affect people all the way into middle age and even the elderly. And, so because they make so much insulin when they're diagnosed, their diabetes maybe confused with type 2 diabetes and very difficult to differentiate one type from the other. There's a new research coming out by a close friend of mine, Dr. Richard Oram at the University of Exeter, who is brilliant young physician scientist and his unpublished data suggests that there are a large number of adults who have type 1 diabetes, but simply don't realize it.

DANNY LENNON: That is fascinating. So just to clarity a couple of things and again, correct me on any of this is it's incorrect, we're saying that type 1 diabetes is itself, of course is not reversible as a condition, children don't outgrow this or you don't get rid of it through treatment.

JAKE KUSHNER: That's right.

DANNY LENNON: But in terms of the actual Beta cell function, some patients can start to restore at least some amount of that capacity to produce the insulin once they initiate the insulin treatment, right?

JAKE KUSHNER: That's right. And by the way, I should just say there have been many clinical trials to try to permanently forestall the destruction of Beta cells and every one of those trials have failed its primary clinical endpoint. So we have no ability to poison or modulate the immune system and shut down this destruction, but we can at least see in many people a continued production of insulin for at least a few months, in some cases years, in some cases even more than that.

DANNY LENNON: Okay, cool. So I think that gets us to the point now where as you said, when it comes to treatment options there's very little outside of giving exogenous insulin, which we can maybe talk about. But you mentioned right at the start that what you've started to look and practice and what you've more dealt through in the research in the past few years that's really piqued your interest is around the nutritional management and the lifestyle advice given around type 1 diabetes and you mentioned, for example, carbohydrate restriction. So when it comes to the typical lifestyle advice

and nutritional management of type 1 diabetes, at least from the outside from where I can see the standard, conventional advice that might be given is quite different to this approach that you've mentioned about actually restricting carbohydrate for type 1 diabetic.

JAKE KUSHNER: That's right.

DANNY LENNON: We can maybe talk about the conventional care and then maybe the ways that are a bit new ones that you're approach or your thoughts in this are slightly different.

JAKE KUSHNER: So the conventional care around the world involves very fixed concentrations of macronutrients. So the World Health Organization for healthy adults says, you got to eat I don't know, 55% carbohydrates and less than 30% fat and then also some protein. And there are many players in this field, who have claimed without evidence that people with type 1 diabetes must eat the same diet that "healthy people" do. But if you dig deeper, you find that there isn't strong evidence for this, but regardless we, as a field prescribe the so called healthy balanced diets, whatever that is, to virtually every patient. It involves like the MyPlate from the US government, it's like a bunch of carbs, some protein, some fiber, some vegetables and the claim is that that's the best diet that nutritional Science can come up with. And because people with type 1 diabetes are set at such great risk for cardiovascular disease, we must afford them every possible opportunity to have the best possible cardiovascular outcome and this is the healthiest diet to do it.

So that approach, which again is based on consensus guidelines that were generated more than 20 years ago and all this again goes back to people like Ancel Keys, essentially claims that we must avoid fat because the fat involves saturated fat and the saturated fat involves cardiovascular disease. And of course, you can't even eat lots of unsaturated fat because you will get obese and, so we have to have carbohydrates, but they should be complex carbohydrates and a little bit of the other stuff. And that view has absolutely dominated the field and there are very few physicians or diabetes educators or nutritionists or nurse

practitioners, who believe anything other than that basic tenor. So that view has been so dominant that it's actually been very difficult to have an alternative conversation around it. And I became interested in this approach, again having talked to adults who lived with type 1 diabetes and I was struck by this paradox.

So I know these adults who lived with type 1 diabetes, some of them are my best friends in the world and they've said things like, "Well, I just learned on my own that if I ate carbohydrates I got sick, my blood sugars were too high." And I was really surprised by that. I thought, "Wait a minute, so you can't eat carbohydrates?" And they're like, "Yeah. I just can't do it. So what I've learnt to do is not eat them." I know a physician in Boston who I trained with at Boston Children's, who has type 1 and I vividly remember eating dinner with her one night and watching her pick the croutons out of her caesar salad. I said, "What are you doing?" She said, "I can't eat them. If I eat them my blood sugar goes high." I said, "What do you eat?" She goes, "Salads, lots of salad dressing." So basically what's happened is, some people who've really paid very close attention to glucose control and type 1 diabetes have learned on their own to avoid the macronutrient that they can't effectively metabolize. And this is really the heart of the issue. If your pancreas doesn't make insulin, you have to replace it and the problem is, the insulin replacement strategies for type 1 diabetes are hopelessly ineffective. We imagine that there is some ratio of the amount of insulin for a given amount of carbs, so we have this notion that someone would be able to very precisely determine the number of carbohydrates in a meal.

And based on their experience, they would inject insulin at some precise time point prior to eating that meal and that the amount of insulin would effectively counteract the glucose excursion, that is the elevation or change that would come from that meal. But the problem is, you can never get it right. It's only a question of how badly will you get it wrong? And that leads to a lot of frustration in people with type 1 diabetes. So let's imagine that you're the parent of a child with type 1 diabetes and you're told, "Well, you're kid

should eat 45 grams of carbohydrates for lunch and dinner and 30 for breakfast." And you're like, "How much is that? I can't even – my child is four. I don't know how much he's going to eat." Okay, so you come up with a number, you guess and then guess what, you're watching – if you check his/her blood sugar after the meal, you find out that you've got it wrong and it's very frustrating for families because they feel like they weren't able to do the right thing for their kid.

And it's only gotten worse recently with the advent of these continuous glucose monitors, so called CGMs. And the CGMs essentially can measure interstitial glucose continuously and give you a read out on your watch or on your phone, on your tablet. And families come away from CGM monitoring with a lot of frustration because they're like, "How is it that I can't get my kid's blood sugar to near normal? Why does this system work so poorly?" And out of that frustration has been essentially two responses. So some families basically take the CGM off and they put it in their sock drawer and actually the uptake of continuous glucose monitoring has been quite poor, in part because we haven't been able to figure out how to help families use this information. But the other approach is to say, "Well, wait a minute. If the carbohydrates are difficult for me to eat, maybe I should eat less of them." And that insight has led many people on their own to go down this pathway where they now began to view the type 1 diabetes as a disease of carbohydrate intolerance. And, so again, the essence of this is heuristic learning where people learn from their own actions and the beauty of CGM is it facilitates that. But it's really complicated because if you are on your own, you have type 1 diabetes, your child as type 1 diabetes and you have reduced your carbohydrate requirement, your carbohydrate intake in order to get better blood sugars and then you go to see your doctor or nutritionist and you're told, "Well, you're not eating enough. Your child maybe too skinny or you're too skinny." How do you respond to that? It's very difficult.

DANNY LENNON: Yeah. That's one of a lot of questions and I think from the outside at least there are probably two ways we can maybe talk about this. First I'm going to maybe to talk about something in a very simple manner just to make sure

everyone is on the same page here. And there is a lot of complex, more nuance things that I think we can get into.

JAKE KUSHNER: Sure.

DANNY LENNON: And there's certainly the opposite view that we can explore. But I think on a very simple, basic level and from someone who is not a pediatrician that's working with these people or that's within this research area, it seems that the main goal from a nutritional management standpoint is coming down with the glycemic control. If we can glycemic control we're going to help someone. And then it makes intuitive sense I think, when people hear what you're saying that we know that this carbohydrate amount is going to result in a certain elevation in insulin. And, so at this moment a lot of people will have a certain amount of carbohydrate and trying to match that with x amount of insulin to be able to account for that, whereas if we think of the view of – well, if you lower that carbohydrate altogether and have a very low overall incoming amount of carbohydrate, you're essentially able to manage that glycemic response better because you're not having these consistent increases in glucose for example.

JAKE KUSHNER: Right.

DANNY LENNON: So that's the kind of simple view I think that people are probably getting right now. Is that kind of ?

JAKE KUSHNER: Yeah. That's it, but I want to say that – so we come up with a formula that says you need this number of units for this many grams of carbohydrate. But the formula does not include the intrinsic error in the system. We never talk about the variants and, so we always have – in medicine there's a tremendous amount of false precision where we don't really come to grips with how ineffective or variable some of the responses are. And certainly the [indiscernible 00:27:21] hopelessly complex, so if you add more fat to a meal then you delay the absorption of carbohydrates because the stomach doesn't empty and everyone will recognize what that is. When you think about a really high fat meal and then if you burp afterwards, you'll smell the food that you ate hours beforehand. So high fat meal alters gastric emptying and it completely alters the way carbohydrates are absorbed.

Moreover, the actual amount of carbohydrates is just really difficult to estimate. So Dr. Bernstein and others have come up with this idea, Bornstein was really the key proponent to this what he calls ' the rule of small numbers' and the idea goes, small amounts of carbohydrates, small amounts of insulin, less opportunity for error in the calculation; larger amounts of carbohydrate, much more insulin, far graver the injured. So the analogy I view, it's like reducing the speed of your carbohydrate on a windy highway. It just makes intuitive sense that you'd want to slow down so that you don't drive off the road.

DANNY LENNON: Right. It's a matter of increasing that precision and I think even when you touch on there, just the simple fact that people can wrap their head around of, if you're taking this carbohydrate that means less insulin, that means less medication someone is taking.

JAKE KUSHNER: Yes.

DANNY LENNON: So that intuitively, at least at first glance sounds like a good idea. Just when you mentioned the inherent error, I mean we could even get into individual variation between people. I think there is a paper I read last year, I can't remember the author's name, but they were looking at glycemic responses and you see, one person can have a certain glycemic response curve. I think they compared a cookie and a banana. And you see, two people having two very different responses to the cookie and then you look at the banana is almost the flipside of that.

JAKE KUSHNER: That's from this group in Israel. That's a major paper.

DANNY LENNON: That's the one. That's awesome.

JAKE KUSHNER: And actually the other thing I would mention is that there's inter individual response and there is intra individual response. There's what happens from day to day or hour to hour and if you're sleep deprived, you're much more insulin resistant. And if you've exercised a bunch, you may be more insulin sensitive or if you're currently acutely exercising, you may be more insulin resistant. And all of this stuff just makes it way too complicated.

DANNY LENNON: Sure. And just for a moment let me play devil's advocate maybe because I think it's just a great way to address some of the issues I'm sure you've heard quite a lot before. Because at the moment, I'm sure it sounds quite simple to people, right? We have this thing where we can reduce carbohydrate intake that reduces the reliance of someone to use insulin, so the medication use has gone down. And now we're seeing a greater precision for glycemic control, so all sounds good. But like I said, to play devil's advocate, some of the issues that are potentially proposed as why maybe a very low carbohydrate diet could be unsuitable for type 1 diabetes, at least from what I have read. And there was one statement I've picked out from a publication I've seen online, not a pure reviewed piece, this was just again, something you've probably seen from numerous organizational bodies. And the statement reads, 'Ketogenic diets are suitable for someone with type 1 diabetes based on a few things: The unpredictable fluctuations in blood sugar, the increased risk in having episodes of hypoglycemia, therefore, need to be treated with carbohydrate and the lack of biological feedback on the liver's rate of glucose production.' Is there anything you want to get into on those particular concerns that at least are surfacing in some areas?

JAKE KUSHNER: Yeah. I guess, I would like to say that my interest in this topic comes from my role as a physician, but as a scientist, I'm very concerned about what we know and what we don't know. And I think what we don't know is vast in this topic and we need proper studies. So I have a role as a physician and I help people to think about what they can do, but if you ask me as a scientist, what I think about low-carb nutrition, I can tell you a very long list of things that we don't understand.

So I don't understand the impact of low-carb or high fat nutrition, long-term impact on cardiovascular disease or on survival. And we need to know those things because those are the primary in-points for people with type 1 diabetes. That is the major area that they ultimately succumb to their illness though they also have many other terrible things that can happen. But we also have these other things like the psychological impact and the burden and I hear things

around that as well. So I hear some – there's a physician and nutrition team in Australia that have argued that low-carb nutrition is simply too burdensome and outrageous of parents to ask their children. And they've implied that it almost amounts to some form of abuse where these kids are simply being asked to do something that is unreasonable and they want to just be kids. And, so the burden of expectations of their parents is leading to unnecessary and outrageous psychosocial trauma.

Now, I will also say that there is a counter balance to this that we have to really seriously consider, the lifestyle of type 1 diabetes, checking your blood sugar all the time, administering insulin, worrying about what you eat, worrying about what your blood sugar is going to be. That's a very serious burden and in its worst incarnation, people feel like they have to essentially manage their diabetes 24/7. You know these people who are always checking their smart phones for new messages, that sort of hyper vigilance? Imagine if the thing that you are checking is absolutely necessary for you to live and you can't – if you look down and you check your blood sugar and you discover that your blood sugar is low and going lower, it's terrifying. And similarly if you feel okay and you look down and your blood sugar is high and going higher, it's exhausting. I tried really hard, how is it that I have such a little control on my blood sugar? And we see at least in the pediatric population, a very high rate of mental health issues, about 40-45% of our patients are struggling with anxiety or depression. And I've wondered whether that is a direct result of our inability to provide effective therapies for our patient population.

So again, the psychosocial impact of these nutritional strategies must be studies and I suppose there is a potential burden of eating restrictive diet, but there is also a great burden of living with an ineffective therapy and the resultant variability and anxiety. So psychosocial aspects are enormous. There is another weird thing, which is that there is a stigma of eating a diet that's different than everybody else. And kids just want to be kids and no one likes to be judged for what they do. And for people who are eating unusual diets, there is some question. And just sidebar, I've

been low-carb myself for two years and people were like, "Oh, that's right! Dr. Kushner doesn't eat carbohydrates" They sort of wink at me and smile. So there is a potential stigma around eating a different diet and I suppose that that could be a negative aspect of this as well. Hypoglycemia, we talked about this, you mentioned this. So low blood sugars are potentially very serious with type 1 diabetes, even fatal and we know from the literature that lots and lots of people with type 1 diabetes struggle with frequent low blood sugar, so that's a big, big deal. And we also know that there is not relationship between your average blood glucose control and the frequency of low blood sugars.

If anything that, people with high blood sugars actually have episodes of hypoglycemia and I think it's just that they're having trouble controlling blood sugars just like you'd have trouble keeping the car on the road, either to the left or to the road if you're driving down a windy road and you're going really fast. So hypoglycemia is a very serious concern and some stakeholders, who are concerned about the possibility of sever hypoglycemia in low-carb people and the reason is if your blood sugars is close to normal all the time, the argument goes, you could have a reduced threshold to end up with a severe low and, therefore, could end up with terrible. So that's a very serious concern amongst the conservative proponents in this debate, but there is also an opposite and I want to mention that. So for people with type 1 diabetes, who are on these very low carbohydrate approaches, they seem to have less variability. They often require less insulin to correct high blood sugars and at least – and totally, what I've seen is a lot less hypoglycemia. It's surprising, it's sort of counterintuitive. They just don't seem to go low that often and I think the reason is, they're never that high, they don't each that much correction.

It's also that they're eating very few meals that require these big, vamping doses of insulin and, so they don't put themselves in danger. And there is even a potential third reason, which is pretty cool, so Dr. Stephen Phinney has talked about this. Dr. George K Hale did some experiments with ketogenic diets decades ago and found that they were quite tolerant of hypoglycemia without any obvious side

effects. And, so the suggestion is that once you adapt your brain to preferentially consuming fat as its primary macronutrient then variations in ambient blood glucose become far less important to the brain. The brain just continues to function, moving along. It's like it's unperturbed by hypoglycemia. Now, do I have any evidence for those things? I don't. I gave you a bunch of potential reasons and anecdotes around how hypoglycemia could be better at low carb, but we need to study this. We need proper, well controlled studies. We need randomized controlled trials funded by major stakeholders and the best minds in the business, so we can overcome these anxieties and really figure this out.

DANNY LENNON: Yeah. I'm so glad that you mentioned that and put that context around you answer because like you say, it's so important to realize that there is quite a lot we don't know. And that is again one of the issues that I was planning on bringing up that people tend to promote is that we don't enough long-term evidence, at least right now, to demonstrate that low-carb or ketogenic diet is suitable for type 1 diabetes, which you just eluded to. So with that in mind, where do you as both a scientist and someone who is working in the real world with people to trying to help them, how would you go about that kind of thought process of being able to influence change in that? You're now in a position where anecdotally, something that you tried with a few people, had these positive results, you're seeing benefits from it, there is potentially mechanistic reasons that you can point to as to why there is these benefits. Yet, on the other side as an academic, if we were looking at the "evidence based perspective", there's not enough there perhaps to back it or at least a consensus around it within this side of community.

JAKE KUSHNER: Right.

DANNY LENNON: So how do you even go about thinking on that as someone that's working with someone? How do you weigh up those two things and make the decision as what you think is going to be best practice for a given patient?

JAKE KUSHNER: Well, I try to take the holistic view of the whole diabetes ecosystem and my role as a scientist and physician around this topic is sort of multi-prompt. Number one, my first and foremost, I'm advocating for more funding and better studies and I have tried to reach out to key stakeholders around this. We actually put together a multicenter, randomized controlled clinic trial proposal with some of the best minds in the business and we sent it to a foundation, but unfortunately, it wasn't funded. But we're very eager to obtain this kind of funding and I have a team that signed up to participate in this clinical trial. These are literally some of the best minds in the business for type 1 diabetes. And by the way, many of them were not low-carb cheerleaders. May of them were simply type 1 diabetes clinicians, scientists, who are interested in finding creative, new ways to help people. So I am going to continue to try to apply for more funding and support others applying for more funding. I'm certainly not proprietary about this. I just want to see these kinds of research studies eventually done and though we have some very conservative organizations that are really anxious about funding this kind of work. There are other places around the world that are much more open to this. One prominent example is Sweden where low-carb high fat has become so popular that there is even a butter shortage.

And the Swedish government has taken a much more open-minded approach to low-carb approaches. So I think that there are some parts of the world that may be more open to innovation around low-carb and others. There are also philanthropic organizations that are interested in this. It's only a matter of time before good studies are done, let's face it. My hope is that within the next 5 or 10 years, there will be multiple well controlled, randomized controlled clinical trials with people with type 1 diabetes where you compare standard diet to a low-carb or alter low-carb approach. And of course the primary outcome would be hemoglobin A1c or glucose control. And then a bunch of secondary outcomes about all the things that we mentioned, cardiovascular disease and hypoglycemia and psychosocial impact and power ability and cost. So I think that that should and will happen and part of the reason why I say that is that current

therapies to help people with type 1 diabetes are not very effective.

And the stuff in the pipeline is similarly not very effective. So most people in United States have hemoglobin A1c around 8-8.3. People really struggle, people in elite clinics can get their hemoglobin A1cs down to near 7, but that's not a representative sample of the national population of adults with type 1 diabetes. Teenagers are similarly around 8.3, so many, many kids and adults fail to achieve their glycemic targets and have elevated blood sugars, which put them at great risk for cardiovascular disease and terrible complications. And we as a society has recognized that that situation is unacceptable, so there is funding through these very traditional scientific approaches of – find new ways to modulate the immune system with very precise and targeted poisons of the immune system. And perhaps some interesting combination of things will ultimately safely and permanently reeducate the immune system so it doesn't destroy the Beta cells. I'm open to that and would celebrate it and would celebrate it if that occurred. But then another possibility is technology, so maybe like an insulin pump that can measure glucose and administer insulin and is really smart. Well, there is one device already FDA approved, so the Medtronic 670G can do that, but interestingly, it can't really deal with meals.

So people still have these huge glucose excursions after means and at least anecdotally what I've heard is that people who're on low-carb approaches do better than the people who are eating of gobs of carbs. So I think that these so called closed loop insulin pumps solutions will always be vulnerable to the variable carbohydrate and therefore, the extreme glucose excursions that's around meals. And beyond that, you're left with some really sophisticated, incredibly ambitious projects around stem cells that make insulin and those projects are fraught with danger. You're going to find a way to take those cells and put them in some perfect cage where they can – where they are nurtured by the blood system and they don't communicate with the immune system and they make perfect amounts of the glucose. I

think we're honestly a decade or two or three or four or five away from those approaches ever becoming mainstream.

DANNY LENNON: Yeah. Thanks for that really comprehensive answer. Before we do start wrapping up Jake, one topic that I really wanted to make sure to bring up was that of ketoacidosis, which is obviously of great concern those living with type 1 diabetes.

JAKE KUSHNER: Yes.

DANNY LENNON: Can you maybe talk through that process of ketoacidosis? What's occurring, just how dangerous that actually is for a diabetic?

JAKE KUSHNER: Okay. So this is a really big deal. People with type 1 diabetes require insulin for life and the devices and the systems that we use to deliver insulin for them are not very good. So asking a teenager to do anything all the time is somewhat a variable. And, so we have kids who just forget to take their insulin. And then similarly we use these insulin pumps and the insulin pumps can plug or clog. Insulin, basically precipitates in the tubing and then it stops infusing. So we have, for a variety of reasons, this vulnerability that people will not get this life sustaining and when that occurs, when they have this crisis of no insulin all of a sudden their body goes from being anabolic, that's building to catabolic where it begins to break down. And immediately, the fat cells begin to undergo dramatic lipolysis and you also get acidosis in the cells and the pH of the blood changes, becomes very acidotic. And this is life threatening and in its most severe form, 1 in 300 people will end up dead or permanently maimed from cerebral edema or other things. So we as physicians live in terror about this and we teach our families to measure ketones, either in the urine or the blood as a biomarker, as a tool to test for this life threatening insulin deficiency. Our only other tool to look for that is while we have glucose, in most cases the glucose is elevated, but people can also have elevated glucose if they just ate a bunch of carbs and they didn't cover for them or if their coverage was inadequate. Or also clinical symptoms, so people who are really sick with DKA, they become comatose, they have no energy, they're

super thirsty, they're breathing fast all the time, they're very weak.

Okay, so endocrinologists are terrified about diabetic ketoacidosis or DKA and we're hyper-vigilant and we're always looking out for – and again, our major biomarker is ketones measured in the urine or the blood and beta-hydroxybutyrate is something that can be easily measured in the blood and we use these ketone strips that measure both acetoacetate and beta-hydroxybutyrate. Okay, now let's talk about low-carb high fat approaches. So if you switch to eating fat as your primary macronutrient, what happens is you get some ketones that build up in your blood and presumably the reason is, those fatty acids become the primary substrate energy homeostasis and some of that floats out and is detectable in either blood or urine. Also it's possible to reduce the amount of circulating insulin that's present in your body to very low levels because most of the energy requirement is in the form of fats, not carbohydrates. So you're insulin goes to less and less and less and some people on these on these low-carb high fat approaches have bona-fide what we call nutritional ketosis.

Their ketones are present in very high quantities and they are maybe 0.5mM per liter, 1 or 2, they can get pretty high. Okay, so the problem with that if you have type 1 diabetes is if you're actively eating a low-carb diet and you know that your ketones can be at 0.4 or 1 or 1.2 depending upon how much fat you ate over the past 24hrs and whether or not you've recently exercised, and by the way, exercise can drive up ketones. And then you go and you measure your ketones and then by the way, you maybe don't feel so well, now you can't tell the difference between diabetic ketoacidosis and simple nutritional ketosis. And that inability to differentiate in between those two things represents a potential danger. So I think that this concern has led a lot of endocrinologists to say, "Well, you can't do low-carb because your ketones are going to be so high that we won't be able to tell if you have DKA versus or simple ketotic." There are also a few people in the field who are totally confused and who think that ketones themselves cause DKA. They're wrong! They don't and we know this because there are children and adults who

have been treated with low-carb approaches who have normal pHs, they're not acidotic. So it's a little bit silly, it's like I smell smoke, but the smoke could be from a fireplace or could be from house fire and there is a real difference.

DANNY LENNON: Yeah, for sure. I'm really glad you mentioned that because that was actually going to be something I was going to ask about that again, we have these two very distinct, completely different things of diabetic ketoacidosis versus just a state of being in ketosis via a ketogenic diet or very carbohydrate diet. And these two states are obviously not related, they're very different. But again, that's the potential downside that maybe gets promoted that because we can use ketone levels in the blood and measuring them as a way to detect for ketoacidosis by now embarking on a ketogenic diet and having elevated ketones that maybe muddies to water and makes early detection that state of ketoacidosis more difficult. Does that actually play out in theory? What way around that would there be for someone if they did want to embark on a low carbohydrate diet for example?

JAKE KUSHNER: Yeah. This is a good question. So I will say that many people outside of the low-carb community view ketogenic diet as synonymous with any low-carb approach and that is not true. And you ask anybody who is trying to follow a diet with nutritional ketosis, they can tell you it's actually very hard to get into ketosis. You have to really restrict your protein because protein can impart turned to carbohydrate. So what we often hear from people who are trying a low-carb approach is actually is that they can't get into ketosis. So I actually think that the concern around ketones is somewhat, it's wrong. It's all about putting ketone levels in context. For anybody who eats a fairly medium protein diet, I think it's going to be pretty difficult to get your carbs up, sorry your ketones up in the danger range, i.e. the level of 4 or 6 or 8mM.

And I'm not saying that those levels are dangerous for someone who is eating a low-carb diet, I'm saying those levels are dangerous for somebody who has type 1 diabetes in is on a high carb diet and how might be going into DKA. So because they indicate this acidosis, so again, I would imagine

that a lower carb approach was still eating some carbs or eating some protein would make it very difficult to have high ketone levels and would simply all this. But the other way to do it is to simply be more circumspective about your body and say, "Okay, I do have this vulnerability to DKA because I have type 1 diabetes. The pumps don't work, it's possible that I could slide into DKA and not realize it. I'm going to have to be extra careful. What are the measures that I'm using to prevent diabetic ketoacidosis?"f By the way, it's also possible that we as a field would come up with better strategies to prevent DKA in people like for instance, administering these ultra long acting forms of insulin. And there are new insulins in the market that actually last for more than 48hrs, so if you take them every 24hrs it's very, very difficult to go into DKA and maybe these forms of insulin would be far better for somebody who is taking a nutritional ketosis approach. So if you asked me, what would be a great randomized control trial, I would have nutritional ketosis on one arm with maybe ultra long acting insulin versus regular insulin because I would love to know how do we prevent DKA in a large population. There's a lot we don't know.

DANNY LENNON: Yeah, for sure. Thanks for that answer. And, so maybe to start rounding this up and get us some kind of take away points here, when it comes to your best understanding both from what you've seen in the research and obviously the work you've done as a practitioner, when it comes down to lifestyle advice, nutritional treatment, how to best manage someone with type 1 diabetes because I'm sure there are people with type 1 that are listening to it, there are also physicians and doctors and dieticians listening as well. From what we currently know and what we've talked about here in the context of carbohydrate restriction in type 1 diabetes, where do we go back to when we're trying to think of a standard default care? Is it to the point now where you think that for you at least, that's the place to go, that's carbohydrate restricted or low carbohydrate diet should be a default model to start a patient with? Or is it more so just one potential tool that maybe used with certain types of individuals and might not suitable to others for example? Or

how should people think about, I suppose, the default best standard of care to work with a type 1 diabetic?

JAKE KUSHNER: Well, we're still in the early days of understanding the potential impact and benefit of low-carb nutrition for people with type 1 diabetes. And I would say, at best it should be an option and, so we're attempting to develop at pathway, a low-carb pathway here in our Diabetes Center and we want to essentially begin to define the elements and then study its impact. But I don't think we're at the point where it's appropriate for everyone. But I have seen some families who have done it and they've had really amazing results, some of these anecdotes are just wonderful. I saw somebody just a couple of weekends ago, who had type 1 diabetes, who had been on a low-carb approach for eight months and her blood glucose is nearly normal and her mom said to me, "You know what, we switched as a family and I've lost over 30 pounds myself." And she goes, "My daughter is just thriving." Her daughter is going off to college and is just really doing well. So that says to me that there is a lot of potential, but I think what Diabetes Centers need to do is begin to sort of understand this and codify it and build systems around it and measure it. And that's true of much of what we do. We tend to be mired in anecdotes and we don't embrace Systems of Care.

And I think the obvious thing to do for anybody who is interested in this is to, if for instance your provider says, "Hey maybe we should develop a pilot study around low-carb and try to figure out what's the potential benefit. What are the potential dangers, what are the opportunities for us to study, what could we learn by this, who would we offer this pilot to, how will we study the impact of the pilot, who do we offer it to?" And I think for patients or for families, one option is to simply go to the head of your department or to your provider and say, "Look, we'd really like to do this, but we want to partner with you" And we're not saying this is the only way to go, but we want this as an option and we want to partner with you so that you can help us understand it's potential benefit for people like us and also the potential downsides too. So I think that patients and advocates can engage in the healthcare system and if they do so in

constructive ways, they can win people over to at least consider it. And again, we're going to need lots and lots of anecdotes from the field in order to really understand it, both its benefits as well as its potential dangers.

DANNY LENNON: Yeah, for sure. I think that sums up quite nicely that there is like you say, a bit of a way to go and there is an awful of more research needed, but it's certainly a tool that has shown some promise. And I agree with you, hopefully we can get some really good quality trials over the next number of years that elucidate more of the answers to some of the questions we've explored. Dr. Kushner, we're just coming up in time here, so before I get to the very final question, where can people get in contact with you or find more of your work online or find you on social media, any of that type of thing? Where is the best place for them to find you online?

JAKE KUSHNER: Sure. So I'm on Twitter and I am frequently tweeting on things related to low-carb or also to insulin access. It's Jake Kushner, J_A_K_E_K_U_S_H_N_E_R_M_D, all one word. That's probably the best approach and all of my contact info is linked there as well. But for low carb, for people who want to get introduced to low-carb and type 1 diabetes, there are many, many resources including a wonderful Facebook group called 'Typeonegrit, T_Y_P_E_O_N_E_G_R_I_T', which is run by R D Dikeman. I mentioned Dr. Bernstein's book, which is a great place to start. I would also, for anybody who's interested in a low-carb read, Dr. Stephen Phinney's 'The Art and The Science of Low-carb Living', which is just wonderful, absolutely for checking out. And also Adam Brown, who works in San Francisco has written a book called 'Diabetes Landmines' and that's a really great book and Adam Brown has down quite a bit of advocacy for people with type 1 diabetes and low-carb approaches. He's done many experiments on his own and recently he's published a book talking about the impact of low carb.

DANNY LENNON: Perfect. And for everyone listening, I'm going to link up to all of that in the show notes so you can go and click through and check everything that Dr. Kushner just mentioned. And, so with that we come to the final question that we always in

this show and this could be to do with pretty much anything completely outside of today's topic. And it's simply, if you could advice people to do one thing each day that would have a positive impact on any area of their life, what would that one thing be?

JAKE KUSHNER: You have to love life. You have to enjoy what you do and pursue passion and I think that's what I tell all these kids who live with type 1 diabetes; relentlessly pursue the things you enjoy and don't give up.

DANNY LENNON: Wonderful. A great way to round off this episode and with that Dr. Kushner, I want to say thank you so much, number one for the information that you've given and the time you've given up today to put that across and for the continued work you do. Thank you so much for being part of the podcast.

JAKE KUSHNER: Honored to be a part of this. Thank you so much. Great questions!