Diet Doctor Podcast
with Brianna Stubbs, PhD
Episode 45

Dr. Bret Scher: Welcome back to the Diet Doctor podcast with Dr. Bret Scher. Today I'm joined by Dr. Brianna Stubbs who is the chief translational scientist at the Buck Institute. And they are focusing a lot on longevity and prolonging health span. And she transitioned to this from an athletic background and an athletic research background studying ketogenic diet and exogenous ketones, how they affect athletic performance.

And now she's transitioning both to athletic performance and health span. So it's really interesting to sort of get her perspective on where ketones fit into the whole picture of performance for an elite athlete and for an everyday athlete and then how that also may translate to health and longevity.

Now in the beginning part, probably the first half of this interview, we spent a lot of time talking about sports and athletics and athletic performance. So if that doesn't apply to you, if you're not interested, fast-forward halfway through and you'll pick up on some of more of the health aspects. But it's great to get a perspective. She thinks from a scientific mind of evaluating the evidence before making big claims and I think that's a good take-home message for all of us.

But I think you will get some takeaways here about where ketones fit into this picture and whether they're right for you. So enjoy this interview with Dr. Brianna Stubbs and make sure you go to DietDoctor.com; you can see the full episode and a transcript of it if you are a Diet Doctor member and also subscribe to our YouTube channel so get all our regular updates. All right, thanks, here's our interview with Dr. Brianna Stubbs.

Dr. Brianna Stubbs, thank you so much for joining me on the Diet Doctor podcast.

Dr. Brianna Stubbs: What a pleasure to be here today. And I hope you're enjoying the fantastic Metabolic Health Summit as much as I am.

Bret: Oh, it's wonderful... and you gave your talk earlier.

Brianna: Very relieved to have that out of the way.

Bret: Nice to have it done, now you can relax and enjoy the rest of the conference.

Brianna: After this I'm off to the bar.

Bret: Good, very good. Now I want to talk a little bit so viewers get to know sort of where you came from and how you started with this because you started from a pure athletic background as

a world champion rower and actually rowing across the English Channel at age 12.

Brianna: Well, that's not the peak of athletic performance, but I guess it says a little bit about my personality. That was something that I asked my dad if he would help me do when I was 12.

Bret: So you certainly started at a young age and then worked your way up to being a world champion rower. And how did you find your way into sort of the scientific world and the ketone world?

Brianna: Sure, I mean I was always really interested in biology and how the human body worked, so much so that actually when I went to university or school in America, when I went off to university I was studying medicine. So my plan correct choice was to be an M.D., a medical doctor.

And so I was studying all the basic systems of the human biology in my undergraduate course and also at the University I was starting to take rowing more and more seriously and I'd been on the junior international team and the under 23 international team, so that was getting more and more serious as well.

And it was almost like this very random perfect storm of random events. So I was rowing on the team and all of a sudden I see this advert for a study looking at ketone esters in rowers and they were offering to pay people come into row machine test which I was doing for free otherwise. And I was in my freshman year, I was like this sounds like a great way to make a little bit of beer money, you know, go and do that.

Bret: The irony... beer money for doing ketone research.

Brianna: I didn't actually and still don't really drink beer. I can't really remember what I spent that on-- probably on traveling to rowing races and things like that, because a lot of it was self-funded at that stage. And it wasn't like tons and tons of money. It was nice pocket money.

But yes, I went and took part in this study and it was so relevant to my personal interest, but also was really building on what I was studying in the classroom; all of this biochemistry which kind of seemed bit dry to me quite frankly, as you study all this big metabolic pathway, the Krebs Cycle and study all the different pathways of fat burning and carbohydrate burning. We didn't really go into that much detail about ketosis.

I do remember we were taught about it, but it wasn't something that stuck in my mind. So doing this study and meeting the research team really started to trigger a lot of questions in me about how metabolism and sport interacted and also how ketones and supplementing with ketones could fit into this.

And so on as part of my medical training I was able to do a summer research project which I did in a lab group and I got more and more involved with the research there and so when it came time, my rowing was actually really taking off and I needed to step back a little bit from my studies to focus on that. The research lab offered me a position as an assistant, helping to run a number of these studies.

So it was good because it was flexible work and they were really understanding of the fact that my training was really demanding. And that assistant position kind of somehow converted into a PhD position that you know I was interested in doing good work. And so they brought me on. And really the good thing is while I was at the medical school were happy that I was doing a PhD and they could turn a blind eye to the fact that I was rowing all the time.

And they actually held the place open for me in medical school that I could have come back to at any point, which was a really nice safety net. So I was just really free to go after the research and pursue my own athletic ambitions as well. The two fitted alongside one another really nicely, because actually, especially as I progressed into the senior team, I moved into the lightweight category, so I had to think I spent a lot of time in caloric restriction and in more of a ketogenic state.

So actually understanding starvation metabolism and ketone metabolism, especially as it pertained to exercise, it was not hard work at all for me to really get into the literature and understand the implications of the physiological effects were having on my performance and therefore the implications for other athletes as well.

Bret: Yeah, so first of all, I just have to comment that I think it says a lot about your abilities and your intellect that you can use an M.D. degree as sort of like a safety net. That's pretty impressive, first of all. But I really liked what you said about learning the Krebs cycle, but knowing the practical implications of what it can do and then also you personally sort of experiencing it to see how the ketones work for you in your athletic training.

I think it's that personal experience that makes us driven even more and that much more interested in studying it and subsequently you've turned into an amazing researcher doing all the studies and sort of being on the forefront of ketones and ketogenic diets for athletic performance. Now, as we get into this, I think we need to differentiate a couple of different things.

I mean there's a ketogenic diet and then there's exogenous ketones and then for athletic performance, there's elite athletic performance, there's sort of everyday athlete performance and then there are the different sports with different demands. So there is really a lot of specifics. You can't just say it's good for sports, it's not good for sports. you sort of have to get into the specifics. So walk us through a little bit, you know, how do ketones in general help with sports and then kind of help us differentiate the specifics.

Brianna: Gosh, you want me to start with exogenous, endogenous ketosis?

Bret: We'll start with endogenous, because the most people-- the low barrier of entry for a lot of people is probably they're already on ketogenic diet and they want to know how it's going to affect their athletic performance and then we can go into exogenous from there.

Brianna: Okay, so the rationale behind going on a ketogenic diet for athletic performance is that when you become keto adapted, you get really, really good at burning fat for energy. And so Dr. Volek over a high state University, he's one of the world leaders in this field and he actually showed that if you get adapted to a ketogenic diet the rate of fat oxidation can be two or maybe even three times higher than an regular athlete who is not fat-adapted.

So, some of the values that he published in his study was showing that it was-- I think it was 50% higher fat oxidation than it had ever been published before, like 1.5 g per minute plays a normal sort of 0.6 to 0.8 g per minute. So when you become keto adapted, you're really, really good at burning fat. Now, if we take a step back and look at it from a theory based perspective, we have a lot more energy on board our body stored as fat compared with glycogen.

So glycogen is the storage form of carbohydrate and we have it in our liver, and we also have it in our muscles and then the energy in glycogen represents about 2000 cal. So, it's quite a lot more than most people would burn on an average 30 minute jog around the park, but for elite athletes with very high-energy rates and especially as the event starts to get longer, that might start to

become a limiting factor for their ability to continue that exercise.

And so the theory behind the ketogenic diet therefore is that you... be able to up-regulate your body's ability to burn this fat stores where we have I think about 150,000 cal worth of fat store, many, many more times energy stored as fat. And so we can tap into that and in theory should push out the time in which you would get exhausted.

Now, I think this now brings us on to a point that you mentioned which is the difference between elite athletes and more recreational athletes. So, for early athletes actually there is very few events and the marathon is the longest event that is in the Olympics. And then now we're seeing marathons being completed in near two hours.

So, I mean it's not what I would class as an extreme endurance-- obviously it's an endurance event, but it's maybe not something where the glycogen availability plus the ability to take on exogenous carbohydrate is really the limiting factor and what the limiting factor for performance for these athletes is the ability to produce energy as fast as possible.

Now fat has a more complex metabolic breakdown pathway, beta oxidation has many steps and glycolysis by comparison is quick and fast and in terms of oxygen efficiency also glucose is an efficient fuel source for exercising muscle. So at the moment the school of thought is that for elite athletes exercising at a very high intensity in order to complete their competition they probably still want to be able to burn carbohydrates.

But then if we look at the other part of people here and that's the people who are trying to run a marathon, maybe they're running three hours if they are quite good, but maybe more people completing marathons in more like five hours long and so actually people then on-- so interested in that very, very high intensity performance is a completely different event.

And so for those people they actually might benefit from oxidizing more fat and also for those people things like body composition are going to also be more of an issue and being on a ketogenic diet might help them with that as well. So when people ask me, "Is the ketogenic diet good for sport?", you have to very clearly defined the type of sport you're interested in and also the level of the athlete you're talking about, because there have been some studies and it's not that well studied to date.

I would say that, well, a lot of people who hate the ketogenic diet saying that it doesn't work... but we haven't seen definitive performance decrements of the ketogenic diet--

Bret: Right, and that's an important part. So, can we say the ketogenic diet is--

Brianna: As good.

Bret: --is better then? Or as good as carbohydrates?

Brianna: So I think that where we are with the research right now is that is definitely at least equivalent in many settings for some individuals, because none of the studies report individuals who may have been really, really good responders and so you lose a lot of the detail, the fine resolution of these pictures, right? So there's no reason to doubt that some athletes again are going to perform better on the ketogenic diet, but if we look at all the means, it's kind of nang...

Which is good, because I think some people are like, "You shouldn't do this. It's going to kill your performance." Well, no I think that some studies where it helps a little bit, some studies where it

takes it a little bit off, and in some studies there is no effect. So when we look at the whole body of data I wouldn't feel I would say to an athlete, do what you feel makes you the best.

Bret: Right. And if you're going to get all these other health benefits from it anyway, why not give it a try if it's not going to hurt your athletic performance?

Brianna: But that is more important for those recreational athletes who exercise as part of their lifestyle rather than exercising as their career.

Bret: Right, that's a good point. So you talked about a marathon. So what about the guy who plays pick-up basketball on a regular basis or the woman who likes to swim in the pool and do interval training in the pool? I mean all of a sudden you're talking about a different type of exercise that is generally referred to as more glycolytic, meaning you need some of that quicker energy for intervals sprints and things. Is then maybe the ketogenic diet not the best choice or can it still be helpful in those circumstances?

Brianna: I think, again, it's helpful to segment elite athletes versus non-elite, because if you're an elite athlete and you are-- you know, you're on the US women's soccer team or you're Usain Bolt, all that matters is your ability to produce energy by glycolysis so that if you do anything to blunt that is going to have a big impact on your performance.

But in those two scenarios even if you are playing pick-up basketball casually or you are swimming a 50 m race in a master swim meet, a 0.5 of a percent less efficiencies through glycolysis is likely not to be a major limiting factor to your performance. And, you know, interestingly I've done a lot of work in with the military and this kind of gets a bit emotive, because people like-- well, if the soldiers lost their ability to maximally sprint, what if they couldn't run away from an ambush or something like that.

And I actually had a number of conversations with some veterans who had done years of service and they were like, "We never sprint at 100%. "Because we are carrying ammunition, we are carrying our packs, "we are also trying to navigate where is the best way out of the situation. So there is never an occasion where I am running at 100%."

And so unless you need that 100% then actually maybe their potential for the ketogenic diet to take off that top-end glycolytic maybe it's less important for all but the very most elite people who sprint performance matters the most. So I mean, I would agree with something you said, which is that the other benefits in most cases could be said to outweigh the possible biochemical downsides.

The only thing, as well, to say in the spirit of fairness is that not everyone finds the ketogenic diet easy to adhere to. So I think, you know, as a community we can't say, "Thou shalt be on keto! And this is the only way."

I guess if you're enjoying it, if it's sustainable with your lifestyle, you are finding good health benefits, you are still able to go out and play your pick-up basketball and all of that and you feel better and you are losing weight and all of this, then of course this is like obviously what you should be doing, but if you're the type of person and it's just a struggle every time you walk past the bakery, then you know, probably don't go in the bakery. But still... right?

Bret: Right.

Brianna: Works better for some people than others.

Bret: Yeah, that's a really good perspective. Now I want to go back to what you said about the keto adaptation process. So we talk a lot about sort of the keto flu and becoming fat adapted and usually that takes anywhere from 1 to 2 weeks, depending on your hydration and your electrolytes, but that's a very different scenario than athletic keto adaptation or fat adaptation for athletics. So can you help differentiate between those two?

Brianna: There's an awful lot to unpack there and an awful lot that we don't really know. So for example Dr. Volek talks about glycogen levels in athletes who are on the ketogenic diet. And at the moment we only have three data points. We have Dr. Phinney study, which was a few weeks long I think and the athletes on a ketogenic diet had much level lower levels of muscle glycogen.

And then Dr. Volek has a more recent study with military cadets and that was a more intermediate duration and those athletes had I think it was maybe like 10% decrease in muscle glycogen, and then his study, the FASTER study, which is quite well known with athletes that have been on a ketogenic diet for a couple of years even, those athletes had no difference in resting muscle glycogen.

And muscle glycogen is a really important determinant of athletic performance. So we actually don't know how long it takes the body to adapt to be able to keep muscle glycogen stores optimal when you're on the ketogenic diet. But Dr. Volek's long-term data from those athletes who were on the diet for a long time suggest that you can--

Bret: So using muscle glycogen as the indicator of you have adapted basically.

Brianna: So this is one marker. The flipside of that is the group that's notoriously anti-keto over in Australia; they've shown that some of the chained enzymatic changes inside the muscle cells can occur in as little as four days. So that's why they argue that there is no point in adapting for longer than four days to the ketogenic diet because you've actually got-- and that the change is even reversed that quickly.

So there's big things like muscle glycogen storage, smaller things like on a cellular level about levels of enzyme expression that may even be remodeling of adipose tissue, switching from white fat to brown fat, for example, changes in the amount of lipids in the muscles, so keto adaptation is a hugely dynamic process and there are so many different things that are changing.

Yeah, I think it's very hard to say that we have a good handle on exactly what the timeline of that processes is and maybe to fully keto-adapt is as Dr. Volek suggests a couple of years even--

Bret: Wow!

Brianna: I mean, we can't say for sure; it depends what change you're looking at.

Bret: And that's important because the advice we give as clinicians to our patients when we put them on a ketogenic diet or carbohydrate restricted diet for their health, for diabetes, for weight loss, but if they also are interested in their own athletic performance, you know, just how they do in the gym, how they do on their 5K runs, whatever the case may be, generally we have to advise them that their performance is going to go down for some period of time before it comes back up, but that some period of time is the hard thing--

Brianna: It's very individual as well and it depends how successfully they can implement the diet

and all kinds of things; so there's an awful lot to unpack there. I think it's hard to give a one-size-fits-all recommendation as to how long we should expect that period of time to be.

I would say that I think it's kind of interesting to me how exogenous ketones might help with bridging that adaptation gap, whether it's in terms of the keto flu or whether it's in terms of athletic performance, so, you know, you want to fuel your workout but not completely-- with a rapid energy source but not completely derail your progress with the ketogenic diet.

Bret: Yes, so perfect transition. So let's transition to what we know about using exogenous ketones, ketones that we can just drink to boost our ketone levels and how that affects athletic performance for the elite athlete, but also bringing it back to sort of the everyday person.

Brianna: Yeah, I mean it makes more sense to start with like fairly well trained athletes because they are the group that we've studied today and I think there's an awful lot of work that still needs to be done looking at less trained people and also athletes who were on a ketogenic diet, because a lot of the athlete studies have been done to date use athletes who were on a mixed diet.

So the first thing that I always find really interesting is that athletes themselves, regardless of diet, are quite well poised to metabolize ketones because ketones get taken up into the muscle through the monocarboxylate transporters as we all know, but that transport is also used for lactate.

And so if you're athletically trained, you've already up-regulated that through exposure to lactate. So athletes can get ketones into the muscles quite efficiently compared with someone who is sedentary. So when we are thinking about how ketones might be useful for athletic performance, it's kind of interesting to think about why ketones even evolve for starvation.

They evolved as a fuel and they evolved to alter our carbohydrates burning and turn that down, stop us from breaking down our protein into glucose to complement lipid metabolism and preserve cognitive function. And all those things could be useful for an athlete.

Bret: Right.

Brianna: Athletes can use BHB as a fuel, it can mean that you don't have to take on as much exogenous carbohydrate and like protect our carbohydrate stores. And then in terms of recovery setting, that protein effect could kind of be interesting as well.

So at Oxford we were trying to unpack this state of being in like fed state but also having ketones present as well, because before the discovery and availability of exogenous ketones, you either were in ketosis and you had low carbohydrate availability or you were-- I wanted to say you were either in ketosis and had low carbohydrate availability or you carbohydrates, but no ketones. It was one or the other, it was pretty binary.

Bret: So now you're talking about a physiological state that has really never existed in the history of humankind where you could have high insulin, fed state or at least not low insulin. So carbohydrate availability, insulin not being low and ketones being available... sort of never existed before.

Brianna: No, and from an athletic perspective this is really interesting, because it's like all of a sudden you can get fuel coming in from different pathways that never would've been able to be simultaneously topped at any one time. So it has certainly made sense to us as we started studying this that the reasons why this might end up to be a good thing for athletes. But you never know, so you have to run the studies.

So first we had to see whether the athletes on a non-ketogenic diet could even burn ketones during exercise and so we ran some studies looking at levels of ketones after identical ketone drinks taking a rest or during exercise and we could see the exercise brought down the levels of ketones when you were even taking the same drinks.

So it was like, huh, ketones going down... that probably means they're being burned. I mean there are other possibilities there as well, but we strongly suspected that this decrease in levels of BHB represented ketones oxidation. And then we were looking at other-- so ketones are burned. What's happening to the metabolism of other fuels?

So we did some muscle biopsy work and looked at muscle glycogen before and after exercise as normally at an intensity that's very glycolytic, so 75%, which is normally the most non-fat-adapted athletes that are pretty much completely relying on carbs for that.

And we could see that when we gave the athletes ketones and carbs rather than just carbs, they were hardly touching their muscle glycogen stores at all, which was kind of bizarre and very useful when you stop thinking about wanting to push out and extend the ability to keep exercising because we know that when your glycogen stores run out, that's kind of when you have to stop or take on extra fuel.

Another sign that carb metabolism was being modulated was blood levels of lactic acid. So lactate is produced as a byproduct from glycolysis, carb burning again and we could see the steady-state lactate levels were around about 2 mmol low and you took ketones prior to exercise-- when you took ketones with-- lactate levels were around about 2 mmol low when you took ketones and carbs before exercise rather than just carbs alone.

So that's like-- and lactate is very easy to measure with just a fingerprint test when you're testing athletes as well, so is quite an easy test that people could see that their metabolism was shifting.

Bret: So, it can be used then to prolong the exercise by prolonging the glycogen availability and maybe to increase the intensity or duration by not having as high of a lactate level--

Brianna: Actually shifts the lactate threshold, so that would be shifting your training zones.

Bret: Interesting, and then can that also play into recovery as well?

Brianna: Mm-hmm.

Bret: So it can have multiple different effects from that standpoint.

Brianna: Exactly, it's really interesting. And then the final thing that was kind of neat that we saw was an increase in oxidation intramuscular lipid. So athletes have quite a lot of intramuscular lipid and it's like an adaptation to help athletes with endurance as like put the fat near the mitochondria where it needs to be.

But typically again, as I said, when you get overset in intensity you don't burn that intramuscular lipid because you are reliant on carbohydrates and we saw that at this quite high intensity ketones turn the muscle back on to using fat even more. Which was... it was it was very stuck how different the metabolism was in the presence of ketones versus conventional carb fuel metabolism in these non-keto-adapted athletes.

And so what we saw in those athletes and this is, you know, heavily caveat where there's a small

study and you know, a high-level athletes. But we did see a pretty consistent improvement in performance that was on average at about 400 m over 30 minutes which is about 2%. And to put in perspective 2% would be like separating the first and fourth place at the Olympic marathon. So for high-level athletes an improvement like that is meaningful.

Bret: Right.

Brianna: Then if we try and extrapolate that back to the less trained athletes, this is where I start to get into more like speculation. There's reasons to believe that it would work better and reasons to believe that it would work less well. So for example if you are less well-trained then your performance is probably intrinsically a bit more variable. You know, the better you get at something the more consistently you're going to hit certain performances.

So there's just more room for error in your performance. And then also as I was saying the training of the muscle actually better equips it to take up and metabolize ketones, so maybe there's less benefit when you're less well-trained. But that's a state we don't know, we still need to run the research study.

Bret: Would you say is potentially more beneficial for someone who is a carb burner as opposed to somebody who is already on a ketogenic diet that has--?

Brianna: Yeah, that's a great question then and we can definitely argue this either way. And I've worked with athletes at my previous company HVMN, you know, we had low-carb athletes using this who had really great experiences and others who didn't like it as much. So the way I would argue it both ways is if you are low-carb and ketogenic you are even better tooled up to oxidize ketones and so when you're presented with this big bolus of ketones your body is really great at metabolizing it and it fits right in with your preferred metabolism.

And so that's for the people who I feel like would respond and then on the other hand you could argue that actually when you take a ketones drink one of the key things that happens is ketones dampen lipolysis, which is the process of fat release from our adipose tissue. And so if you take a ketone drink and you dampen lipolysis and then you decrease your plasma free fatty acids, in a fat-adapted athletes... those people are really quite heavily reliant on those plasma free fatty acids.

Bret: Right.

Brianna: It's almost like turning off the tap on their main energy source and actually making it more difficult for them to perform. So I mean we haven't run the science study and I definitely had both reports come back to me. So I can tell you what the real truth is there yet.

Bret: So, it's fascinating, you put you in a position of would you recommend it to sort of the everyday athlete who's already in ketosis. It sounds like it might be hard to recommend that as a performance enhancer. Or you just have to try it and see if it works for you.

Brianna: I would say definitely don't discount it until you've tried it. Because I couldn't tell you what the predictive factor is as to whether it's working or not. You know, whether I think some people really like fasted workouts and other people just feel like really bad and they have to have something, whether it's MCT coffee or whether it's slow release carbs. So we definitely had a lot of positive feedback from low-carb athletes building this into like very long for example mountain bike races and especially athletes like Zac Bitter-- I think he holds the world record for 100 miles.

Bret: 100 miles!

Brianna: He run like a 6:40 a mile.

Bret: 6:40 miles for 100 miles! Unbelievable.

Brianna: But he strategically includes carbohydrates in as well, even though he trains low-carb. So I think as you know your body better, figuring out what you strategically need to include different fuels, you become better at it.

So for anyone who's on a ketogenic diet and would like energy for their workout, so maybe they are training for some kind of race or event, I'd encourage you to try it because at the moment there's very little like risk cost-- You know, the cost benefit analysis is try and see how it works for you. And I know is a way for us to do the science session to be able to give you the definitive recommendation.

Brianna: Right, now briefly, let's get into the difference between salts and esters. And for those who are not athletes, hang with us, we're going to get to some of the longevity and health stuff in a little bit, but just to finish up on the sports part of it which is interesting to me, especially because I do a lot of mountain biking and I don't compete, but it sure is fun to sort of leave your friends in the dust as you're going up that last hill, so every little bit I guess helps.

But let's talk about the salts versus esters in terms of tolerability, efficacy and sort of what you would recommend to people if they just wanted to see if they had a little boost in their athletic performance.

Brianna: This point is actually relevant to people using ketones for every single use case, like all of those things, you know, BHB delivery, tolerability, accessibility of the compounds, all of that would play into your-- you are choosing to use it, whether you're an athlete or whether you are someone looking to like protect your brain health over the long time or maybe experimenting with some of the clinical conditions where ketones are thought to be useful. So this is like copying a question that's relevant to everyone.

So, I mean, let's maybe start with ketones salts. They are the most widely available in consumer products right now so is the easiest to find ketone salt and they tend to be the most price economical.

These molecules consist of typically the ketone beta hydroxybutyrate and that's because acetoacetate and acetone are not very stable and it's difficult to formulate them into a product. So take beta hydroxybutyrate and you bind it with an ionic bond to a mineral, that's typically something like sodium or calcium or potassium. Interestingly enough, but it's also possible to bind ketones to charge amino acids, but the amino acids have quite a big molecular weight, so you end up having to take like mountains and mountains of powder to get a decent amount of a ketones if you do that.

So mostly these minerals like we'd think of like table salt kind of thing, but it's ketones instead. One consideration that people should look out for and it's not always obvious, is that typically the salts mixtures of two optical isoforms of beta hydroxybutyrate-- so when you do chemical synthesis outside the body, you end up with-- well, I should have explained optical isomerism. Optical isomerism kind of refers to this property of molecules where it's always like handedness.

So if we think about our left and right hands, we have four fingers and a thumb and they are mir-

ror images of one another, but they don't overlay on one another. And beta hydroxybutyrate has this property and the enzymes in our body that make ketones and also that break ketones down, specific to one-handed form-- so if we give this other handed form that our body isn't really used to seeing, it certainly won't be making it, but it also is very slow to be breaking it down or using it for anything.

Bret: So people may hear those reference as an L and a D form of the ketone bodies. **Brianna:** Yeah, it's kind of confusing because people either call them R and S, or D and L. And I couldn't tell you exactly in which setting you should be using either one of them, but you use them in pairs, RS or DL.

Bret: Got it.

Brianna: But unless on the product it specifies that it's the D form, then is likely some mixture of the two and this S or L form is like the non-natural form. So we don't really know how that behaves inside the body. We don't think it's useful as an energy form but a lot of my work now at Buck actually focuses on understanding the signaling implications of S - beta hydroxybutyrate which are fascinating.

And I am looking forward to finding out more about that. So especially for athletic performance but also in conditions, for example, Alzheimer's disease, where energy provision is like one of the really key things that the ketones are doing in this kind of situation, you'd always want to be prioritizing D or R beta hydroxybutyrate over the S or L form of beta hydroxybutyrate. So that's just something to be aware of with the salts.

Bret: And what about the esters? How do they differ?

Brianna: So the esters again I think it helps to take a step back and we have this bucket of ketone esters and we assume that all of things in it are kind of similar, but actually a ketone ester is quite a broad term and it refers to a molecule where you have BHB or acetoacetate joined by a special type of bond called and ester bond to a ketone precursor. Those precursors can vary, so it can either be 1-3-butanediol or glycerol or a medium chain fatty acid.

And also you could have monoesters, so one ester bond, diesters, two ester bonds, triesters, three ester bonds. So actually there are tens maybe even hundreds of different possible ketone esters and the chemical structures of those molecules where they did a level of BHB versus acetoacetate, for example, those are all going to impact on what they are useful for, there is going to be big difference in like physical properties of those molecules, like how they taste, which is a really important one, how easy they are--

Bret: Right.

Brianna: And we can get to that later. How easy they are to make and therefore how cheap or expensive they'll be. So this is really like a law of differences within that class. So I think I want to highlight to everyone that if you hear something being like ketone esters do this, you actually have to look and see which ketone ester has been used.

And I think a really neat example actually is... there is the acetoacetate diester that Dr. D'Agostino has been working on and they've actually seen that giving acetoacetate in certain use cases like the CNS oxygen toxicity and in some of the cancer models, actually it's better to give acetoacetate than beta hydroxybutyrate.

Bret: It's interesting that we talk so much about beta hydroxybutyrate, but there are some circumstances where acetoacetate may be better for neurological function.

Brianna: Exactly, it is very interesting and we are already just starting to scratch the surface of understanding the differences, because they are so closely related that one wouldn't necessarily just expect that there would be a difference.

But when you start to look at the biochemistry-- so for example beta hydroxybutyrate may just be better for athletic performance, because if you give BHB then it's going to be converted into acetoacetate and that conversion generates one molecule in part of NADH, which is used for energy production, so you get this extra energy production step in the conversion of BHB to acetoacetate that you wouldn't get if you just gave acetoacetate, for example.

Bret: I knew all that chemistry I learned would come in handy someday.

Brianna: Yes, there you go. Yeah, so ketone esters are a very diverse class of molecules, but generally speaking, firstly they avoid the mineral load that you get with salt and that often means that they are more tolerable; because of that mineral load, there seems to be like a bit of a threshold to how many salts you can consume without G.I. upset. And also just sort of around health concerns, around big boluses of mineral consumption, you know, the effects on your kidneys and your heart and all of that as well.

Then you have the esters, there's none of this mineral load, so they are kind of a little bit more potent in terms of BHB delivery or at least the BHB monoester is very potent in that you could take maybe like a 30 g or a 40 g dose and be at like 6 or 7 or 8 mmol of ketones within 30 minutes.

Bret: So a much higher level and a much lower volume of liquid that you have to consume.

Brianna: Yeah, I mean it doesn't taste great and consuming 30 g of it is a little bit of a--

Bret: Like a tequila shot or something.

Brianna: Yeah, exactly. So yeah, that's the key difference... you know, with the esters depending on the compound again the BHB monoester is quite well-tolerated and we haven't seen high incidences of G.I. effects, whereas the acetoacetate ester in its current form was quite poorly tolerated by athletes.

So, you know, people like... oh, esters make you sick... Well, it's like no, that one ester made people sick... It's going to be different for different compounds and it is now something that we're exploring at Buck, like how can we change up how ketone esters work and stick them together to get different clinical end points.

Bret: Yeah, so it's a great transition. So you are sort of embarking on a new part of your career at the Buck Institute. And I wanted to read... so it's the Buck Institute for Research in Aging and Age-related Diseases and their mission statement is to extend the healthy years of life. That sounds like a great mission statement.

Brianna: I'll tell you what. It's an awesome place to work. You know, we have the ketone biology lab where we have people researching brain health and Alzheimer's, ovarian health, we have people who are specialists in C elegans, which is a little worm, and they give the worms all kinds of different things and see how long they live. What else? I mean sleep experts, exercise experts and it's just so exciting and refreshing to be in a place where there's just so much innovation and

creative thinking around science.

And the institute is set up in a very collaborative way. So everyone comes together very often and there's a lot of sharing of knowledge and expertise between labs. So I think it's a great way to accelerate knowledge and discoveries here. For example we are collaborating with the bioinformatics and AI core to do a very broad look at how different biomarkers are changed during ketogenic diets and compare that to exogenous ketones.

And they have this fantastic way of looking at all of the different markers and showing us like what are the most important differences. And then we also have a fantastic proteomics and mass spectrometry core and we are going to be looking at how beta hydroxybutyrate itself is added to proteins as a post-translational modification. And again if that's different between the diet and exogenous ketones as well.

So what I-- bringing into the team a little bit is this knowledge about exogenous ketones so we're using it as a tool and alongside the ketogenic diet now we will always be comparing diet to esters or diet to exogenous ketones of any kind. And we also are interested in running alongside that arms where we give just targeted S or L beta hydroxybutyrate by itself so that we can isolate any energy effects of the ketones from any potential signaling effects of the ketones as well.

So the experimental designs that are being set up will hopefully allow us to start to tease apart things that are down to carbohydrate restriction, things that are down to BHB, potentially as an energy and then things that are down to BHB as a signal as well. And we can really tap into all of our colleagues and PIs over at Buck to be able to do that - so it's a fantastic environment.

Bret: Yeah and I can tell your enthusiasm for it. Just the way you speak about it and you sort of light up when you talk about it. That's really interesting; it shows that you love what you do. And you can really see the impact is going to have.

When we talk to people about starting a ketogenic diet for their health, whether it's reversing type 2 diabetes, whether it's for weight loss, whether it's for treating insulin resistance or metabolic syndrome, lowering the blood pressure, all these different effects, generally it's the effect of lowering insulin and glucose that is the most important.

That's only going to happen with the nutritional carbohydrate restriction. Adding the ketones probably aren't going to help with that, but can the ketones have an additive effect or different effect? Sounds like that's what you're starting to research. Do we have any data, one way or the other now? Or is it something that we're going to have to wait and hold on for future studies?

Brianna: Well, we know that giving the C elegans worms beta hydroxybutyrate by itself can extend their lifespan. So I suspect that there are isolated effects of the BHB molecule and maybe the acetoacetate molecule as well on gene expression pathways that are associated with aging and aging well and maybe having better health span and lifespan. So I wouldn't completely rule out that ketone esters or ketone supplements would completely not have the same effect as being on the ketogenic diet.

Bret: If you put a C elegans on a ketogenic diet?

Brianna: I don't know if you can. You can definitely put mice on a ketogenic diet but I don't know about the worms. But I would actually recommend it's kind of a little bit deep, but it's a nice place to start. Dr. Richard Veach at the NIH has written a really interesting review talking about caloric

restriction and ketone esters and how all of the different pathways of longevity that they interplay on.

Because this is actually more complicated than just insulin. There's so many different pathways that feed into longevity. And I think that some of these are going to be hit by just consuming ketones by themselves, obviously not all of it. And we say, when we have visitors up at Buck and they are like, "What do I need to do to live longer?" And we are like sleep enough, do some exercise and look at your diet.

And if you're not going to go full ketogenic diet, then do periods of fasting, or time restricted eating. You're always going to meet people where they're at and, you know, I think that we need to be reinstalling periods off ketosis back into our everyday life, because it's something that we've evolved with as a species; periods of plenty and periods of less.

So weather that's just getting up to 16 hours of fasting, 16/8 kind of eating window, whether it's doing one 36-hour fast a week or whether it's going on a ketogenic diet, all of these are going to be small changes that people can make that's going to promote health span and lifespan.

And I think it's always important to meet people where they are at, you know-- It would be hard for me to sit down and tell people, "You need to do what I'm doing and train like 18 hours a week like part of my Ironman training."

Most people will never going to be able to, or want to do that. So it's just like anything that you're doing now, maybe add 5% more and that's always going to be a positive step in the right direction. And another study that I think exemplifies this really nice is John Little at the University of British Columbia looked at the difference that a low carbohydrate breakfast could make to total glucose exposure during the day.

And he found that even just taking out the carbohydrate as a breakfast had an impact on overall exposure during the day that could likely be clinically meaningful. So it's even if you change out like one of your meals a day and make it very, very low carbohydrate, this is going to start to help you metabolic health and then also help how you age as well, so I think it can be kind of extreme for people, some people, to contemplate making that big shift to the ketogenic diet.

But it's like take the first step, start somewhere, whether it's with a little bit of fasting, whether it's with one low carbohydrate meal a day. I know that once you start really committing to that lifestyle, you actually have to really commit to end up with that keto adaptation. But there are sort of like intermediate steps that you can do just to get your body ready for it and understand the process a little better.

Bret: And I think that's a good perspective too about all the other factors for health and longevity. So if you're sleeping three hours a night and you are eating your Doritos and your donuts all day long, taking a ketone ester is probably not where you want to start. You want to start looking at your lifestyle.

Brianna: No, I mean like none of these things are band-aids for actually making proper lifestyle changes that are going to support health into aging. And, you know, we haven't even touched on being part of community and all of those other things as well which we are understanding now are increasingly important for being healthy as we age.

Bret: Yeah, I think that's really interesting, because there are observational studies, so it doesn't

sort of prove that the community is what does it, but you can certainly hypothesize that, you know, having more meaning, being beholden to others, you know, having that love in the relationship makes you want to take better care of yourself. I mean, you can certainly see sort of like the downstream effects, so just being part of the community can have its impact.

Brianna: Yeah, I mean one could notice that actually when people will start doing the ketogenic diet often they'll plug into some kind of an online community, maybe like Diet Doctor, or there's a lot Facebook groups where people are sharing success stories and you know like encouraging one another and sharing recipe ideas.

And actually for some of these people feeling like that they are making progress and they are not alone that's really, really powerful. And helps them to reach their goals.

Bret: Yeah, that makes a lot of sense. So I want to also talk a little bit more about when you talk about health and longevity, another topic that comes up frequently is metformin, the drug metformin. Is that something you have any involvement in at Buck? Are you looking at metformin at all?

Brianna: We are not... the most related thing to that that we are looking at Dr. Eric Verdin's lab is looking a lot at NAD metabolism and NAD supplementation and the roots of NAD synthesis and breakdown. So that's sort of the least ketone thing that I'm kind of tangentially related to right now, but I mean all of the evidence coming out right now around metformin is very interesting and certainly something that I'm following, but not something we're actively researching in our group.

Bret: So people are studying metformin for maybe cancer prevention and for longevity, but now we are learning that there's also maybe some mitochondrial dysfunction and some exercise inhibition from metformin, so it's not all rosy.

Brianna: Well, I would say that with pretty much any intervention there's a rosy side and a less rosy side. I mean, even with ketone esters as an example, you could use it to help you with your performance in recovery, but are you blunting the other adaptations that you need-- we don't know at this stage... There's an argument that you would be blunting the adaptations that you need to like get fitter and stronger and better and the argument was actually made with antioxidants.

So the way that I like to frame up these whole things is like you're either at a point in your life where you are prioritizing performance and in that case you're often trading off the factors that would help you with longevity. I think it's like you kind of have to prioritize one or the other. And when I was an elite athlete, it was performance.

But for many people and especially as you age you need to-- You aren't going to be pounding like goo shots and all of that. You're going to be taking metformin and it doesn't matter so much how much you lift in the gym, but maybe the metformin and the health span that you'll get from taking that, then that's more worthwhile.

So yeah, it seems to me that when you look at the metabolic pathways, like I'm told, for example, athletes are always wanting to boost that for muscle growth and then when we think about longevity-- oh no, turn it down. You've got to pick one of the two things that you're going after there.

Bret: Yeah, so let's talk about mTOR for a little, because it's such a hot topic. It seems that a lot

of people are talking about it. And you want it for growth but too much growth can mean cancer growth or, you know, promoting that if it's already begun. But even if we are not bodybuilders or elite athletes we still want to maintain lean muscle mass and build lean muscle mass so we're not at risk for sarcopenia and follows as we age.

So, we still don't want to completely turn off mTOR. So how do you balance, how you see mTOR in terms of having adequate protein intake for lean muscle mass, or in the setting of a low-carb ketogenic diet? How do you balance that?

Brianna: It's a big meaty science question! One thing that I think it's like not that well understood or not that well-articulated in any case is that there are tissue specific effects, so say the ketogenic diet on mTOR activity and mTOR expression.

For example if you look at John Newman study on mice on the ketogenic diet and at the study that came out of UC Davis at the same time, mice on a ketogenic diet, they were actually seeing different levels of gene expression related to mTOR in the liver place in the muscle place, in other tissues - the brain for example. And so I think we're really only just starting to unpack the tissue specific effects of ketogenic dieting or protein ingestion. Just because we say, protein does this to mTOR, we don't actually know whether this is the same in all of the tissues.

Bret: Right.

Brianna: So I think it's a more complicated story than just a simple headline. Personally I eat protein and I wouldn't be restricting my protein intake out of fear that it would lead to cancer or anything like that.

Bret: And a good perspective that the headlines don't reflect the quality or the level of science frequently.

Brianna: No, I mean unfortunately... everything is going to be distilled down into a headline these days. Not very many people are going to put in the effort to read the academic papers. You know, I read a lot of academic papers and even then it can be hard to distill out the nuances of what's going on. It's easy to miss things that could be important confounders.

And so there's really probably very few people that actually get what an academic paper actually means when it comes out. So, nowadays we take our interpretations from the popular media or from we read on social media or other people's takes as well. And it sometimes misses some important nuances, but I do think that there's a desire to oversimplify everything.

So like protein restriction does this to mTOR, which does this to lifespan or, you know, ketone esters do this to performance. And as we've already discussed, there's a lot of nuance in terms of the ester in terms of the performance, in terms of the athletes level. So you just can't capture all of the necessary nuance in a headline that's click bait.

Bret: Right, so quickly here you mentioned Ironman triathlon training. So you are working with longevity research and training for an Ironman.

Brianna: Mm-hmm. I will live until I am 120.

Bret: But I would argue that they're not related. Because with Ironman triathletes, they have a higher incidence of atrial fibrillation. Studies show that high level endurance athletes will have higher coronary calcification, so more exercise is not necessarily better for health. I mean, do you

have like a little concern?

Brianna: I've never heard of those statistics before.

Bret: So I've just ruined it for you.

Brianna: No, so I've been doing triathlon since I finished rowing. I mean I guess it's probably not that different in terms of the training volume that I was doing while I was on the British international rowing team, it was like 20 hours a week and now maybe more like 16 to 18. I would say from personal experience, I definitely feel like that's some level of addiction and that is not something that I think will be sustainable forever.

I'm enjoying the change of sport and so there's a certain amount of that in there as well, but yeah I mean I don't think-- and you know, even on joints and bone health and all that, I don't think that it's necessary going to be the ideal thing for me to do forever.

I mean, I have some like short-term goals that I want to hit and then after that I think I probably would like readdress my-- I don't know that I'll be an Ironman triathlete forever or doing it at the level which I'm currently trying to push for forever and ever. No and I totally agree that there's probably like a bell curve in terms of health benefits to especially endurance exercise, -because it's hard on your body.

Bret: It is.

Brianna: And for women especially when I was on the rowing team I ended up with RED-- it used to be called female athlete triad, but now it's called RED, which is Relative Energy Deficiency. You know, I was very, very lean and doing all this volume and it really affected my hormones. And, you know, people are concerned about bone health as well and mental health as well, you're just exhausted.

And so yeah, I mean more exercise is certainly not always better. You have to be able to support it with sleep and nutrition and recovery, which is hard when you got a full-time job. I think the people who coach triathletes the best are the people who are like-- There's no point in getting up at 3 AM just so that you can hit the hours of training that you want to hit to try and do Ironman... like that's not productive for health.

And so it comes back to kind of why are you competing in sports... is it your life, is it going to be a professional for most people? The answer is no. And even for me now, I want to compete at a high level, but I don't think I want to be a professional triathlete. That's a small amount of people and most people do it for a relatively short amount of time. So, you know, the average person who is competing in Ironman, you know, it shouldn't be coming at the expense of your health...

Bret: Right.

Brianna: ...or your family and social life and everything like that. So you have to find a balance to make it work. So it is certainly not a sport for everyone and I kind of try and resist a little bit the idea of doing it just because it's this kind of physically quite impressive feat and like long and hard to complete.

But it's been fun to turn my endurance background into this new sport and I've enjoyed traveling and the community there is really great as well. And so as long as you practice it in a healthy way and make sure it complements your lifestyle, then I think it's certainly better than being a couch

potato.

Bret: That's for sure. I've had to make the transition from a triathlete now to trying to be more efficient and trying to hit more of what I think is important for longevity, whether it's resistance training or short interval training and no longer the big long interval trainings. But I know that sometimes is an itch you just have to scratch and I still love my long bike rides and it doesn't necessarily have to do with longevity, it has to do with more sort of almost like psychological therapy and the enjoyment of it and I know it's not for everybody. And it seems like you've got a big dose of that as well.

Brianna: Yeah, I'm working on like turning that down in my life a little bit, but I love being out there on my bike and recently I took part in a three day ride from San Francisco to Santa Barbara...

Bret: Oh, great!

Brianna: ...along Highway 1, it's just beautiful being out on the coast road and there's nothing quite like the feeling of getting back after a really long hard session and just lying on the couch and everything kind of like throbbing, but you're like, "I'm so alive right now."

Bret: Did you take any ketones while you were doing it?

Brianna: So, not on that ride but when I'm doing the Ironman training when my performance really, really matters on those key-like race prep sessions, yeah I used it and it makes a very big difference.

Bret: Great, this has been a wonderful window into sort of who you are and all the amazing work you're doing and I can't wait to see more of your work coming from the Buck Institute.

Brianna: Thanks, it's been a pleasure to chat.

Bret: If people want to learn more about you and read about you, where can you direct them to go?

Brianna: Probably best to find me on Twitter, I'm @BriannaStubbs on Twitter and you'll know it's me because the cover picture is me doing some rowing. I don't know that I am actually up on the Buck website right now, but you can find out more about the research that's going on in the Newman lab which I'm a part on the Buck website and that's probably the best two places to look.

Bret: Fantastic, thank you for taking the time today.

Brianna: Thanks Bret.