

# **Brianna Stubbs, PhD**

## **Ketogenesis, Metabolism and Ketone Ester Supplementation**



==== Episode 211 =====



DANNY LENNON:

Brianna, welcome to the podcast. How are you doing?

BRIANNA STUBBS:

I'm great. Thanks for having me Danny.

DANNY LENNON:

My absolute pleasure. I've been reading a number of pieces of work that you have published long with your colleagues over the past couple of years. And I've been able to hear some of your insights outside of that the main as well through various interviews and so on. and it's really pick my interest to get you on to try and give people I supposed a clear understanding of a lot of terms that are becoming more and more familiar to them, where they're hearing from different places. And stuff where there's obviously a lot of hype and interest and fascination.

But sometimes, they kind of – waters got muddied and when we're trying to interpret, some of these works. So before we get into the main topic of the show, I wanted to start with more of selfless question just about your athletic background which I know you were a high level rower. But all those saying high level rower is probably a pretty large under statement based on what you're up to do. Can you maybe just give people idea of your career in sport?

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BRIANNA STUBBS:

Yeah. So as a kid growing up, I did a ton of in sport. I did cycling and triathlon and I row and did horse riding until the age of about 10 or 11. And I decided I sort of starting to specialize a little bit more and focusing in on rowing.

And so as a little kid, I competed in a lot of different races eventually, represented Great Britain for the first time age 16 and under 16 match against funds. It was really lucky enough from there to get a scholarship to a school where I could row more easily and then in around my studies and that allowed me to get represent – gaining representation for GD again age 18 and I won a silver medal at the world genie at rowing championships. But at that point, you know, it's like pretty invested and the growing and went to Oxford and obviously growing in some really big sport there. I road in the Oxy Cambridge both raise twice and won it twice represented Great Britain in the under 23 woman's 8.

From there, decided that when you are under 23, you can compete in open weight or light weight categories, that's the first age where there's weight cap degree. And so I decided to make the change from being an open weight athletes of being a light weight athlete and so I was able to make a change into that weight category. I won the under 23 world championships as a light weight and then that start was the start of a four stint on the senior national team training, I mean a stint is a really full time. This is a long side my PhD. So it was training two or three sessions a day, six days a week with the precision national growing team in the U.K. and run a silver medal, I won the gold medal up the world champion deeps in the light weight women's club.

DANNY LENNON:

Yes. Super impressive and I think definitely for the athletes and people coming from a sports background that are listening, give some good context on some of the topics will probably discuss later on in the show. But if we turn over to the area of research that you'd

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be involved with within at academia and probably what we're going to spend the bulk of the bulk of today's conversation on.

Your research was primarily around ketone metabolism, correct?

BRIANNA STUBBS:

Yes.

DANNY LENNON:

Can you maybe explain that research a bit more specifically than that what kind of your doctoral work led you to be examining?

BRIANNA STUBBS:

So, I was part of the team based at the University of Oxford headed by Professor Karen Crock and the researcher doing who is a PR own the human studies was Dr. Peacocks and the first ortho and so metabolism paper which I know you discussed at length with Brent and Nigan, a few opts back. And so, I was part of that team.

We were looking at the effects of ketone metabolism on exercise performance and also just general metabolic state during exercise. And then sort of my own work that I was PI on was looking at the difference between different exogenous ketone supplements. So, differences between ketone salts and ketone ester and also, I sort of specialized a little bit in on the effects of exogenous ketone of appetite as well. So my own, my personal research, it was quite varied and I was definite, I was part of the athlete team as well as – of having my own work running parallel to that.

DANNY LENNON:

Yes. Super cool and we're –we'll definitely talk about exogenous ketones because they are quite the hot topic right now. But before that, maybe just to if we talk about ketone genesis and maybe turned out for the moment and just kind of set the scene for people. A question that maybe people don't often ask is, why do we make ketones in the first place and maybe for more of the kind of neuro perspective, how does the body go about doing that?

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BRIANNA STUBBS:

I love this. I love to be able to tell the story. So I mean, I'll come back to thousands of years ago when weren't surrounded by carbohydrate rich food and we have sort of hunt and gather for our -I mean it's the ancestral argument. And basically, if we our brains are very, very metabolically demanding and our brains can only really run glucose normally because fats, we have a lot of energy stored as fat inside our body. The fats are unable to, in a large way cross the blood brain barrier and fill the brain.

And so, this is a bit of a problem because it has big periods of time in between opportunities to consume carbohydrate then our blood glucose will drop and that will threatened brain function. But we have all of these energy sort of fats and what is a way that we can make this fat available for the brain. What is the way that we can get our brains be able to top into all of these energy store and that – the ounce to that is ketone genesis.

And so, this kind of boost some – onto the second part of your question. If you either first for prolonged period of time or follow a very, very low carbohydrate diet for a long period of time, you liver glycogen and your muscle glycogen source become depleted and the level of free fatty acids in your blood begin to rise. And so free fatty acids from your fats tissue or adipose tissue travels in the blood and the liver is able to then convert that free fatty acids into ketones. Then overtime again, you know, maybe like three to five days, ketone levels start to run perfect. It takes a really long time to ketone levels to reach high levels. You know, up to 40 days really before you'll be saying levels, six, you know, six and uploads. But maybe after two to three days, your blood ketone levels might be somewhere between one to two millimeters maybe. And so, as that ketone production rounds up, the ketone can act as a fuel for the brain and replace glucose.

And so one of the classical experiments that was done back in the mid 1900s, back then it was ethical to starve people for science and it wouldn't get by obese approval nowadays. But they have some obese people. Some people who needed to lose the weight anyway and they gave them a bit – a mineral pill and some water and that was it for about 50 days and measured how long it took for the ketone levels to rise and how much of their brains energy, the ketones were kind of accounting for. And so, after that really long period of fasting, ketone said, really almost you know, we're replacing quite a large amount of the glucose needs of the brain. So ketones were accounting for about 60 percent of the brains energy requirements in the ketone genic state.

So that means that the body didn't need to break down proteins stools for gluco to be a gluconeogenics substrate and so that means that you protect your lean mass and you delay the time in which you're going to kill over and die because you're just wasting away.

DANNY LENNON:

For sure. And so, with – when we build typically first here about some of these ideas, it's probably easy to see why some arguments can be made or some claims that people tend to make around ketogenic diets of why getting into ketosis might be useful metabolic state and so on. And as supposed, at this point, the amount of, I would say inaccurate ideas that can pop up when the topic of ketones or keytosis arises is quite alarming. And probably this is just a function just maybe how main stream if we can call that ketogenic diets have become over the past year or two.

With that, what are the primary misconceptions that you see coming up quite regularly within say that general population when ideas around ketones or ketosis. Or any of the related ideas are brought up. Is there any ones that are most common?

BRIANNA STUBBS:

So I think the one that stands out the most is that ketosis equal falls fat burning. And so I think it's kind

of a language, a language problem. Because I worked in the field of exogenous ketones and so, I would give people the ketone drink and be able to read elevated levels of BHP in their blood and say ah, you've had my drink. You are in ketosis. But that's very different to someone who has fasted off related diet and is measuring BHP in their blood.

Now both – in both of these settings, I would say that the person is in ketosis, because I'm describing ketosis as measuring elevated levels of BHP in the blood. But you've got there in very different ways. And so, people equate ketosis with fat burning and I would say endogenous ketosis, yes you are burning fat to do that. But exogenous ketosis definitely not. So, I think a lot of the conversations I've had with other people in the field highlights the need for clearer language going forwards whether we talk about being in a ketogenic state because you can be in a ketogenic state and that leads to ketosis. But you can't be in ketosis having not being ketogenics.

So when I say, ketogenics, I mean that you are producing your own ketone bodies. I would say that's probably the biggest misconception. It's very difficult because the languages also similar and there's a lot conflation around those ten. So I think the biggest – the biggest misconceptions is that ketosis equals fat burning and in reality for me anyway, ketosis is having elevated levels of ketones in their blood and it doesn't tell you about how the ketones got in there.

DANNY LENNON:

For sure. And I think one maybe related concept that tends to pop up when we talking about ketone levels is particularly going with the idea if someone is starting into this idea of using a ketogenic diet or even using exogenous ketones to increase the levels of ketones in our blood with the idea that they're doing it to improve their health or maybe even improve body composition say if they're overweight or obese. And the idea being if they feel that this is A, being told as something healthy, then the – maybe assumption that

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they make that might be a logical is then going and thinking, well the higher these level of ketones that I just ramp them up more and more, that's better.

And beyond circumstances. What we're talking about a therapeutic effect maybe in like some sort of clinical case where we do want to look at that. Do you think there is one, any kind of merit to people aiming for specific concentration of ketones in the blood. And two, even knowing what that level is like is that specific number even got a car like to something related to health or likelihood of losing body fat for example.

BRIANNA STUBBS:

I mean that is a good question. It's quite complicated. I'm going to take a little bit of times unpacket. I think and to answer the first part, I think that depending on what effect you are interested in, the threshold of ketone levels will be slightly different. And so I know that – so I've done work with ketone salts and ketone ester and the levels of ketones that you get with the two are quite different. So be ketone salts can't raise blood ketone levels as much as ketone esters. But when method things like blood glucose and blood fatty acids, the level that the ketones, both ketone drinks effects those two metrics is kind of similar.

And personally, I think that because and there is a physiological minimum of blood glucose. You're not going to continue pushing blood glucose down to zero and a healthy person anyway with an entire insulin access. And similarly with that, you're always going to have, you know, a very small amount of like policies going on even if you got ketones there acting to inhibit like policies. So I think if you're interested in using ketone drinks to modulate your glucose or liquid levels, then the threshold for that will be relatively kind of lower. And there different, there's a method analysis which I've read about the effects of ketones on appetite and it seems to suggest that the level were quite there. The ketosis is again quite low. So it maybe that you reach a maximum, a fact of lower level. But

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things like exercise performance certainly, I know that people have coded like a goldilocks spots. So in the middle where you know, you don't want too much but you don't want too little, you need – you need enough of it there to have an effect. Does that completely answer the question? Did I cover all the points there?

DANNY LENNON:

Yeah, for sure. I think that gives us some good contacts and we'll probably dig a bit deeper into some of those as well. Probably maybe to again from a kind of outset for people trying to wrap their head around this, if they haven't like going to this before. At least from a rather maybe from a mechanistic perspective or really just why someone might consider trying to elevate ketones in the blood. And particularly when we're talking about exogenous ketones supplements, what tends to be the advantage that is promoted through or promoted by maybe proponents of using the exogenous ketones.

As in what – what is the goal of elevating ketones through exogenous ketones as opposed to someone using a ketogenic diet let's say.

BRIANNA STUBBS:

Yeah. Sorry, I realized that that was kind of like second part of your question. I didn't really answer it. So yeah, if you're following a ketogenic diet then the aim is to elevate ketones and use that as kind of a mark up of carbohydrate restriction. So if you – and in order – the reason that you would be trying to restrict your carbohydrate is to improve your metabolic health whether that's by increasingly using your body fat as a fuel and when you see ketone production increasing and also showing that you'd managed to maintain low levels of insulin, so probably driving down your blood glucose levels as a secondary effect of having low carbohydrate in the diet.

So what you're looking for and the ketogenic diet or fasting is lower levels of low glucose, lower levels of insulin and increase mobilization of body fats. So

those, the people tend to follow the ketogenic diet mainly for weight loss metabolic health kind of goals.

I mean there's a certain interesting subset of benefits that you get from following all that – it's thought that you get from following a ketogenic diet or from doing intermittent fasting that's more around longevity and information. And it's ketones themselves that implicated in several of those processes. So, I've had that you guys speak before about the NLLP3 and farmazom and how ketones can inhibit deformation of this inflammatory, mark up the infarct, I mean the system inflammatory process. And ketones also effecting gene expression through histone, the acetylate and ambition as well. So you've got like your weight level and metabolic health kind of subset or benefits and then you've got your inflammatory and genic expression subsets of benefits. And I think that if you're interested in weight loss and metabolic health, then that's never going to be re – pitch later by just taking exogenous ketones. You would have to change your diet as well.

Because a big part of that is maintaining lower levels of glucose and insulin through the diet. And so, you know, and also taking exogenous ketones as I mentioned a second ago, it actually slows down the release of fat from your adipose tissue because this is a natural negative feedback loop. So if you were producing ketones yourself, as your ketone levels reach a certain point, you're going to want to slow tat process down so that the ketone levels don't continue to rise. And so, ketones themselves act on the receptive that slows down really piece of free fatty acids – free fatty acids being substrate for ketone production. And so, you limit the substrate. That's less ketones and that kind of keep set a stable level.

However, if you take exogenous ketones, then they act on the same respect in the fat and they stop fat release or slow down fat release. And that's happening on the background of fats already been kind of a normal

level. So you see, people's fatty acid levels going down. So it's, you know, taking exogenous ketone doesn't melt battle a few infarct. Actually, it does the exact opposite who are interested in fat burning and losing weight, taking exogenous ketones as actually flowing down fat break – and it's interesting question though because in – if you take exogenous ketones, your levels are high for maybe three, five hours depending on what the – how higher levels are and if you exercise. But then going of course from that, what is the effect on body composition if ketones and modulating your appetite and modeling the use of intramuscular fat. That's kind of complicated story to unpredict there I think going forward, how exogenous ketones effect body composition.

DANNY LENNON:

Yes. So, I mean and you're first getting into some of that. Because like you said, I think that's a super important point that you bring up and it's actually one that maybe clarifies the position where definitely people that have shown the past had a couple of points of confusion that say, when on one hand, they're hearing about ketones and producing ketones by the body is supposedly good for fat lost because we're using up these free fatty acids. And then they hear something on previous episodes.

So for example, the one with Brent and Nigan when we're talking about this anti life politic fix of ketones that you just mentioned Brianna and trying to consolidate that idea into that last sentence you gave is brilliant because it able people to see where that differential is.

So if we talk about body fat loss and changing body composition, obviously it's being, as probably well discussed on this show before as well that the ketogenic diet into itself isn't something magical like bends around the rules of energy balance so much as to perhaps more from a practical sense is able to allow some people to easier get into negative energy balance whether that through a number of different things

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that we can talk about. Maybe one of those from a practical sent is what you just mentioned a moment ago around, it's effect on appetite. And I know that you actually published some work and I think was just out last month if I'm correct.

So for those listening in the future, we're talking about November 2017, and it was looking at the effect of a ketone ester supplement on gralin levels or how ghrelin was effected, which for those things that we can think of as an appetite hormone. Can you tell me a bit about the set up of that study, how – what you were setting out to examine how you put that together and then some of the kind of key points from it.

BRIANNA STUBBS:

Yeah, and I was really, really – please, when I was listening back to your conversation with Brendon, because he said that he had a lot of anecdotes and a lot of stories about ketones and appetite and not yet seen any data. So I think this is the first kind of contribution to that field. And the reason that we did – we set out to run that study was because of all of these stories and our own experience in the lab and giving to athletes was that people often reported feeling a lot less hungry afterwards. And so, you know, my task from professor clock was about, you know, that is there any way that we can try and get it quantified measure on this and try to get an handle on it.

And so, the set up of the study was people were having ketone drinks or taste match, volume match, color match, amount, isochloric as well, so same amount of calories as dextrose. So glucose drinks. And so, they would come in and they'd have baseline bloods done and have their study drink.

They didn't you know, blinded to their allocation and they would sit and we were come in blood samples and also people were filling in visual analog scale. So it was a three point visual analog scale asking people how hungry they were, how full they were and what

desire, what they desire to eat was. And I mean, I remember running a study and having that run measure. I had, I mean each person had to the seven rate time points per experiment and I was running through, I think it was 15 people through these two arms and so spent a lot of time with the rule of measuring out these scales and I didn't – personally, I didn't really think we were going to see anything before, people just didn't really see where they were paying attention, when they fill in these studies, it was just something they just found look, and put some marks in the line. I was like this is going to be such noisy day to this. No way that we're going to see anything in this. And then after the study finished and I did the analysis and put out all the numbers in, the statistics on it that were real clear, divergences between how hungry and how full people felt on the ketone drink compared with the same amount of calories as glucose. And I supposed I'd like to at this point caveat the whole thing when saying obviously, glucose is probably not. Their the best control. It be interesting to do it with maybe like a protein load and also compared fat load as well. But this was, you know, preliminary kind of study.

And so that was what we run with at the time. So – but what was nice was not only did we have these kind of subjective feelings of you know, a suppressed appetite and reduce desire to eat but we also, we are able to measuring the blood differences and ghrelin. And so, as you said, ghrelin is classically associated as being the hunger hormone. And so if you have the same amount of calories as ketone compared with glucose, your hunger hormone, ghrelin was significantly lower in this sort of, I think it was between two to four hours afterwards.

So immediately, you have a calorie bonus ghrelin goes down to the same amount with glucose and with ketones but then it stays lower for longer when you're in ketosis. And this actually merry up really, really nicely with some stuff that have been done in humans

in the ketogenic diet. There was a big study published in 2013 by Semetra which I can link to you, the link to you for you show next. And they showed a decrease in ghrelin and those people are following a ketogenic diet as well. So, it was an interesting – interesting parallel that we could mimic – mimic that with ketone drink and then interesting possible mechanism for the decrease in appetite we saw. Although that said, I'd be interested in the future to look and do some brain metabolism imaging as well, because I think just, you know, appetite is a balance between peripheral mediators of such as whole ends in the actual level of substrates in the blood but then also the brain – effects in the brain as well. You know, and all that you have as hormones and substrates and itself are affecting the brain.

So it's a really complicated picture that we need to unpick. But if you know, if we go back to these whole confusions about whether drinking ketones could help with weight loss, my answer so that would be there's definitely not a fat burning effect. But if it is kind of a calorie control there, and maybe you know, a rigid carbohydrate diet, you also and you raise your ketone levels a little bit further with the exogenous ketones then that may provide a further benefit with appetite control that helps you meet your body composition and weight loss goals. And another little tidbit on top of that is that we've seen exogenous ketones help to preserve muscle protein mass and trigger muscle proteins since so if you're really interested in body composition as, it's an interesting thing like avenue for future investigation there. And whether supplementing with exogenous ketones could be helpful there.

DANNY LENNON:

Yeah, for sure and there's a number of things there. First I think it was excellent to see not in the study that you're looking at the subjective mark because there are, I think just as important as lucky as something objective like ghrelin levels, having the actual subjective feelings of hunger differ between

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those two groups as super important to see. And the fact that well sure, you can make the point. Dextrose isn't maybe the best. It's giving us something that we're showing you. This is not just down to the calories that's in the exogenous ketone, right? There's something else going on and like you say, the fact that so many people tend to anecdotally report that, gives us a good idea of at least mechanistically, it makes sense at right now. So I – go ahead.

BRIANNA STUBBS:

Yeah, I mean – I'm just going to say quickly, quickly that and I think yeah, it's really important to get preliminary data like this out so there is not just like anecdote so that you can – we can discuss it like this now and other people can discuss it. And also an interesting point that the result showed was that obviously, with the dextrose insulin was higher and it was higher for you know, a little bit of time. And insulin is constantly but it's associated with decrease appetite. So despite this increase in insulin with dextrose the key to – the effect of ketone on appetite was still greater and then similarly with blood sugar after the dextrose drink, blood glucose levels were higher having had the glucose drink. And again, that's something that is associated with greatest society, having higher blood glucose. So the – what was interesting was despite these other two observations which would normally make you think their appetite would be greater if you had more incident, higher blood glucose. With the ketone, we still had low ghrelin and lower appetite. So it's interesting and it was good to be able to get a combination of the subjective and the physiological kind of markers destiny.

DANNY LENNON:

Sure. And if I can ask about some of the individual data points. If anything strikes you off hand, was there – how much of a variance where we're seeing in people's responses to this. Was it fairly tight in that – in most people are seeing a similar response with the ketone drink or do we see – tend to see this inter

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individual variation and how people are actually going to respond to this at least in terms of appetite.

BRIANNA STUBBS:

So I mean, a couple of things. First of, I correlated people's blood ketone levels with the change in their appetite and that was quite. We had you know 20 year blokes coming in and the idea of fasting until lunch time for them was just something that they hated. And they always, always starving, hungry when they came, you know, hungry when they came out. You know it's sort of – it was like difficult to get them through the morning as well as other people less so.

So I think there's a huge amount of variation in how experience hunger. And a lot of that is due to our social norms around when we eat and how much we normally eat. And so I think it's – I think it would be difficult to make a sweeping statement about ketones and appetite and how much you would expect people to – you know I think then really the data was tighter what I had expect. I think like there was a consistent effect. But there's a certain amount of individual variability according your normal eating – you're normal eating patterns.

DANNY LENNON:

Sure. So at this point with all the different potential areas where were looking at Exogenous Ketones or just the ketones in general of how they influence metabolism and then secondary knock on effects there are still so many open questions and avenues for research to look at. From either your own perspective or even that of your colleagues when you're in that group in Oxford.

Is there any particular area that you're either most bullish about or most confident in that this is the likely area where we may see a real valuable application for Exogenous Ketones because obviously at this point there's a lot of people speculating on different areas and maybe some more promise than others. Is there any of that you particularly think

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could be something is at least right now the most promising area.

BRIANNA STUBBS:

Yeah. I mean if takes us a little well away from where like my own research background is. But I'm actually most bullish about some of the clinical applications for Exogenous Ketones. And I think that most of them I've discussed. I think it's interesting to you know for us as to me as -- and as always, you know, dealing with clients who are interested in like body composition to speculate around the applications for performance and for just general like metabolic health. But I think that those are very promising and definitely should be research further. But I'm very, very excited to see what comes in the next, you know, generation of research around things like traumatic brain injury because that's interesting to me because it quite covers the what. But also it's a massive problem in pediatrics and you know just general – the general population of going forward.

And so my rationale there is that there's a lot of animal work that been done using either injections of ketones or the ketogenic showing that ketones can have a protected effect if the brain is subjected to impact. So what happens if you hit your head is that you get injury, like release of neurotransmitters. And then when the brain is trying to like compensate for that there's a period of maybe up to four to five days. And it can vary according to how severe that injury is. But there's a period of time where the brain is less able to use glucose.

And as we kind of talk of that very stuff it's real problem for the brain because the brain can't use that. If the brain can't use glucose it becomes a – like an energy deficit. And that's when damage start to occur to the brain and that if you have repeated concussions or, you know, or really bad concussions that can be what leads to long term brain damage. And so the theory is then and the work seems to suggest that supplemental with ketones in that period of

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compromised glucose metabolism could rescue the brain from long term – help the brain recover quicker and rescue and potentially some of the long term damage that's caused by impact.

And so for me – you know I'm a big fan and obviously out here in the U.S. the NFL is a big sport as well. So it's got immediate sporting applications but then also big applications for the head trauma and people going forward. So I'm excited to see that be investigated further. But it's difficult to do unfortunately. So I think were just – I'm interested to see how that happens. But then also we've got some interesting case studies published using the ketone as different Oxford where it was given someone who had Alzheimer's disease and again some people refer to some type of neurodegenerative diseases as the type three diabetes.

So compromised glucose metabolism in the brain is being like a very big contributor to the disease progress. So in that case study we say that his symptoms – the symptoms were much improved by taking ketone. So that's something I'm interested in. Another – there's a friend of mine called Elena Gross whose looking at Exogenous ketones for migraine again like ketones in the brain. Like how can we – how can we help people with – with actually were actually struggling with real diseases. That's something that I'm interested to see going forward. So I hope to be part of that kind of research part time.

DANNY LENNON:

Sure. And I agree. That's such a fascinating area because to some degree like if we talk about body composition or so on like we have at least decent chunk of answers in that area outside of even looking at ketones that people can improve body composition without this method if it's available, right? But if we have something where were talking about traumatic brain injury and we still need a lot of help in that area. Anything that's going to play a beneficial role is going to be huge.

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And I think it's probably worth mentioning as well of when you mention that ketone that you guys were using in Oxford. That was – that'd be quite different to what we see in other studies. That was acid acetate ester, correct?

BRIANNA STUBBS:

Actually in the University of Oxford were using the beta-hydroxybutyrate monoester. And yeah, I think you said when you introduced Brendon. So there is the -- and that's placed – come from the University of Florida and his group. To date they've done most of their work in animals. Although very recently there was a study – one study in humans and that was run by the Australian Institute of Sport. But that's the only study of that in humans. As well as our beta-hydroxybutyrate monoester that was developed by Dr. Richard Ditch and then all the human studies were done in Oxford.

We have I think it might be 8 or 9 or 10 publications in humans now. Don't quote me on the exact number. But it's been much more widely studied in humans as is still a little earlier on.

DANNY LENNON:

Okay, perfect. Yeah – no, thanks for clarifying that. And that kind of leads on to something I was going to ask you. I think I might have touched on it briefly with Brendon. But I think given your background and where you're kind of working now might be able to be better informed on giving us a kind of more up to date picture of where we are with consumer versions of Exogenous ketones. So compared to what we're seeing in a lot of these trials that are being shown most promise. Where are we in terms of being able to see that form of Exogenous ketone within consumer products. And or are we going to get anytime soon or are we seeing right now?

BRIANNA STUBBS:

No, I mean yeah. I'm really excited to be able to tell you it's now available to buy on the internet. The ketone that was developed in Oxford, the beta-hydroxybutyrate monoester. Karen Clarke at the

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University of Oxford made a partnership with the company that I now work for called Human. That's spelled H-V-M-N. Kind of a bit quirky just to confused people. It's a U.S. based company. And we've launched it as – their product is called human ketone.

And so you get one bag and it contains 25 mills of the ketone, the BHB Ketone Ester that was studied in the which I'm going that to our paper. And so people can pre-order it now and they will be shipping in January. People can try it for themselves.

DANNY LENNON:

And a very cool and for maybe who hadn't heard our previous episode on Exogenous ketones if you listen to that you'll see and a bit more in depth to why that's kind of important and maybe some of the limitations of some of the at least that the previously produced ketones salts or even free acid form but mainly ketones salts were used consumer wide. So that's interesting that that's now available. One thing before we start wrapping up Brianna that I wanted to really get to was a small bit around the athletic performance piece particularly given your interest in that area.

And perhaps I think a good place start is actually with one of the studies that you were involved with publishing I think last year which we looked at ketone, esters and the effect on fuel preference in endurance athletes I believe. Can you maybe again give some cliff notes on how that study is conducted and some of the primary findings that are of most relevant to people listening?

BRIANNA STUBBS:

Yeah, I mean so the paper that you're talking about there it was actually made up of five different studies. And so we went from the very basic level of – the first study with the question that was asked was if you give ketones before exercise and then exercise do you use more ketones than if you just stayed at rest. And so we did two different exercise intensity and we saw that rest levels get up to say six. And then if you exercise at 17 percent that increased and then at 45 percent

ketones levels, it was kind of intermediate. So it's showing that there was a kind of intensity dependent effect on ketone usage. Exercise intensity dependent effect.

So then we set about looking out at the different metabolism and the series of studies that followed looking at muscle metabolism and doing Metabolomics as well as some sustaining. And we showed so the headlines are that in the blood anyway you have lower levels lactic acid after a ketone drink. Lower levels of blood glucose and lower levels of pre-fatty acids. So the other thing – the other fuels that normally supply exercise are lower after you've had a ketone drink. And this is ketone by themselves. We – we were – because we were fixing the work loads then. So people would able to equivalent work with very different metabolism.

And we say that taking ketones with carbohydrates meant that there was a glycogen sparing effect. And I know there's some debate around whether this is glycogen sparing with glycogen in pairing. But we saw that taking ketones before exercise led to a very, very big reduction in the amount of muscle glycogen that was used as well as an increase in their intramuscular fat that was used during exercise. And it was interesting so we use as a controller in some of these studies Vitamin B3 so nicotinic acid. And the reason that we did that was because nicotinic acid also inhibits like in the same way ketones do.

And so we were interested to see whether if we stopped but didn't provide another fuel less ketones what happened to metabolism and what happened to performance. And so we -- if you stop and Vitamin B3 and nicotinic acid I don't have ketones there then people really, really struggled really tanked. But if you have a low level three fatty acids but you also have elevated ketones it showing that ketones were able to provide energy for the body to exercise. And it still complete the work load. And so the final study that we

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ran was kind of more focused in performance. And so we had athletes come in. And these were very, very highly trained elite athletes.

And they did two time trials. One with ketones and gold standard carbohydrates and one with just gold standard carbohydrates topped up with ketones. And we say that these athletes pretty much across the board all did better with a little bit of ketones. And the big improvement was 2.3 percent. So about 400 meters over the 30 minute time travel we run. So before they -- time travel they did an hour of fixed intensity, 75 percent in order to kind of deplete them. And then the 30 minute time travel at the end.

And that was where we saw the performance improvement. So it's, you know, you hear people discussing whether or not the study is real world. But it's certainly an interesting primer going forward. And I – I am pretty bullet about the fact that Exogenous ketones in the right context will be a really useful tool for athletes trying to get – unlock their like the upper limits of their physiological performance.

DANNY LENNON:

Yeah, sure and so maybe to touch on some implications that we maybe seeing from that or at least what you and the group would interpret from that. First to maybe ask you about that point you brought up around glycogen sparing versus glycogen in pairing. And obviously I think the group down Australia Louise Bark and colleagues have talked about that in the context of low carb, low high fat diets in general and with athletes whether this decrease glycogen breakdown that we see in athletes is actually beneficial what you would assume on the front end or is it just decreasing their ability to actually use carbohydrate.

And so if we kind of put that in place for Exogenous ketones where do you right now stand on that? Which side of that would you be leaning towards? And kind of a base around what you've seen.

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BRIANNA STUBBS:

Well, in it by saying I'm certainly more research needs to be done. And I'm like perfectly open to changing my view as more research comes out. But I kind of – I feel like a lot of the work that has been done in fact adopted athletes in any case there's long – there's you know long term changes enzyme activity and enzyme expression that would limit the ability to breakdown glycogen.

And also I'd like to the patient is still pretty unclear. And I mean know that Jeff published a study in 2015. They said it was called the Faster Study. And then he looked at glycogen usage and the fact that athletes compared with athletes on a conventional diet. And they were really surprised because they found that not only did fat adopted athletes have similar starting levels of glycogen. They also depleted glycogen just similar level during exercise despite oxidizing a lot less carbohydrate.

And then also in the recovery from exercise they depleted glycogen just as well. So we didn't think, you know, I don't think were quite you know definitive answer yet as to how longer because a lot of the studies that have been done in Australia you know people would argue perhaps that the adaptation period isn't long enough. And also in Jeff study the athletes that they enrolled were following the low carbohydrate diet because it worked for them. So I know it's not, you know, ideally you'd kind of design a study and you'd apply the same intervention to every one and hope to see the same effect.

But I think with diet anyway there's a certain amount of self selection as to what works for you. And so maybe Jeff population of athletes that were training and doing really well on the low carbohydrate diet are actually more interesting to study because there are athletes and it worked you know performing and it still works to them. So rather than just broad brush, putting every one in a low carb diet and expecting it

work the same for every one for a, you know, short period of time.

So I think you know first off more research might come out. Second off, the research that those at the moment is not quite clear. And then with Exogenous ketones I think there's not going to be any long term changes in the amount of enzymes that you have because you're following a normal diet. Then you're still able to train high intensity system. So you'll have the capability, the enzymatic machinery that you need to be able to do high intensity exercise.

And I sit a little bit on the fence as to because I kind of feel like with metabolism there's never an on and an off switch. If you increase the demand on a pathway to a certain point you're going to get flat through that pathway if it's needed. And so I think that ties in nicely with the classic paper. I think it was in 2002. And he was – he plotted out really beautifully the bell curve of carbohydrate and fat oxidation exercise intensity showing that pass a certain point fat oxidation decreases and carbohydrate oxidation increases in terms of intensity.

And so I think there – and my personal feeling is that if you take Exogenous ketones and then try and exercise the demand on the pathway is going to outweigh the inhibition – I mean inhibition that there might be of ketones. You know it's never on or off. I think that if you – if you pull through that pathway my personal feeling is that you'll still going be able to do that. It's just what is the strongest stimulus at the time?

And I'm interested to see – so we've done some preliminary stuff in Oxford. And I actually was a participant in one of those more recent studies. We did VO<sub>2</sub> maps testing. And it doesn't look like there's a decrement in peak paroxy or too max test. But I know we've also done some stuff looking at wind gate testing like 10 second testing on bicycles. And there

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maybe a small decrease. So there's a lot of the research still to be done. You know 10 seconds is short. The VO<sub>2</sub> max test is slightly longer whereas the most relevant, you know, point to look at for athletes and especially athletes doing an intermittent kind of sport maybe more like soccer, football, rugby in a way are sprinting and then resting.

It's very difficult to extrapolate from these individual results because yes, okay taking Exogenous ketones may scrub out a little bit off of your top end power for a 10 second bike test. But if you're a soccer player and you're game, your ultimate performance is the net of the 80 minutes where you sprint and then you have to recover and be ready to go again and ready to go again. And also then make cognitive decisions for me it's kind of interesting to speculate that adding Exogenous ketones and on top of that you know potentially glycogen, potentially lowering lactate, providing a fuel and maybe also providing fuel for the brain in helping with the cognitive process is involved in that. It's kind of interesting to me to speculate on what the performance might be and whether that would be positive.

DANNY LENNON:

Sure. And so if we have – if we go with a hypothetical that we can see a benefit for performance which we still need to determine. If we go with that based on what we know about ketone metabolism. What do you think would be the likely timing of the supplement or the dosage or what are even seeing current studies looking at performance in terms of timing and dosage?

BRIANNA STUBBS:

Yeah, so I mean the way that we're recommending that people take human ketone is take it between 60 to 30 minutes before you start your activity. If you're on a normal diet we recommend you taking it along side carbohydrate. You know if you're following a low carbohydrate diet then ketones can still act as an energy source. You don't need to take carbohydrate to get an effect of having ketones as a fuel in the blood.

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And so the general guidance would be yeah, 30 minute before with carbohydrate. If you're using it – I know you talked with Brendon at length about using it for recovery and that's something I'm really interested in as well. A positive feedback from the cycling teams and things that worked with using this. And so I think in that case you would take it following exercise as soon as you can along with your normal protein carbohydrates.

I think the interesting thing about ketones is that they can just work alongside whatever you're taking normally. You know there's no reason to modulate your carbohydrate intake. You can still take caffeine along with it. You can still take nitrates along with it. And the recovery it's going to work best if you take it with protein and carbohydrates as well. I think that the type of activity that is best suited for at the moment that we have the most evidence for would be someone's whose looking to run maybe a marathon or someone whose doing a road race and cycling. Something that's really for me I feel like you're going to start seeing benefit if you're exercising over 45 minutes, over an hour like the longer the better. The longer and the more near your critical lactate threshold the better I think.

DANNY LENNON:

Yeah, awesome. Brianna we could stay and take about this for a long time. But I'm going to start and try to wrap things up here. Before I do one kind of final question just to end on that note, when it comes either the athletic performance side or if we're looking some of these clinical applications what do you hope or do you think might next in terms of their – what the research is going to evaluate. What's the kind of next key question and any of those areas pick your preference that will be the next one to try and get at least some preliminary idea about.

BRIANNA STUBBS:

I think it's in like two buckets. I think in terms of sport I'm really interested to see recovery and training studies done like what's the effect of having these

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training. I know you talked with Brendon about whether or not that would blunt or help with adaptation to training. I'm interested to find out more about that because my personal view is that you need periodize diet and training and periodize all these to get maximum effect. So I would say periods of Exogenous ketones feeding with periods of not feeding it. I would be optimal for training. And then also looking at recovery [00:52:02] are all very interesting. And then in terms of clinical stuff I'd love to see TVI happening. But I know that already people are using -- this is a completely different note, Exogenous ketones in for cancer models and so I know that both Florida around Oxford. We've got collaborations going on looking at that. And so really, really excited to see those results being published in the next year or so because running in right now.

DANNY LENNON:

Yeah, sure. And like you said there's so many different areas where it's been looked at and time will tell where some of these lies. But definitely looking at the mechanistic stuff it's clear that there's at least some promise in some areas for different application. It's just trying from now tease apart where exactly that is and where the best as well as put the real practical stuff in place so --

BRIANNA STUBBS:

Yeah.

DANNY LENNON:

It's going to be super interesting to see.

BRIANNA STUBBS:

I think what I'd like to say like as we're kind of closing out is that I completely understand the natural tendency of people to be like well you're kind of saying this is good for sport. And you say you can take it before and you take it afterwards. And you can take it for TBI. You can take outside. You can take it for cancer. You know but the laundry list of things that we kind of even talked about in this short podcast it is --you know it's a lot of things. And I can understand why people might be skeptical about that.

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And my answer to that would be that metabolism is like such a central process. And understanding the differences, not only the differences between Endogenous and Exogenous Ketones here is really important. But what having the ketone ester available means is this really powerful way to study the effects of BHB in isolation. And it – it's perfectly likely that it's not going to be good for half of the things that we talked about.

But I think that people should resist from touching it for not being good for something. It's really like focusing on the thing that is going to be good for because I'm sure that in one of the areas we've talked about today or one of the areas that we haven't had time to talk about today ketones, ketogenic diets and or Exogenous Ketones are going to be really transformative. And so I really – I just really don't want that this massive bubble of excitement around them that gets burst as soon as the first thing is found not to be effective.

And you know I don't want to hold up investigation into all of these other really, really worthwhile areas that definitely super deserving of more research. So I think people just need to keep in mind and we need to address these questions as soon as we can. And keep an open mind as to how these things might have worked in other settings. And I'm trying to see how it goes.

DANNY LENNON:

Yeah, I agree. I think that's such an important point because certainly when you see a lot of the hysteria about diets and ketones and just people making all sorts of different claims it – obviously that does raise someone's like skeptical eye as it should go. But I think it's important like you say that we don't go to the complete opposite end and say okay, this is a reason just to dismiss this out of hand because I've seen it happen as well.

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Any time someone mentions a diet people just switch off and don't even listen even though it could be very – very worthwhile application and there certainly applications for that. And like you say it's with all the stuff that's been investigated it's highly likely we're going to see at least one where there's going to be some clear benefit and application of using even Exogenous Ketones supplementation. So yes, say skeptical. But also be open minded because don't dismissive of something. And I think maybe that's a final note to you I'm sure as someone's whose been involved with like high end research in this area.

That can be something that can be quite I supposed annoying as well where because of all – at least in some kind of online community that say kind of the craziness around ketogenic diets and ketosis. That's one way – in some way takes away from the valuable research that's been done because people get drawn and conflict the two things, right? The crazy side and any one making that discussion at all.

BRIANNA STUBBS:

Yeah, I think – I hope that the field of ketosis doesn't become associated quackery and yeah, I'd just – I'd hope that people who can use the energy to kind of push forward the research. And I think I mean another important thing to note is that the research just takes a long time. So the research that we discussed that we published in cell metabolism there's five studies.

That was going from just before I started my PhD. So you know this going maybe like six or seven years before it was published all of these five studies. It's very rare that you get things that turn around in six months or a year from conception through to running, through to publication and then acceptance. I mean in terms of even just getting something published in a journal it can take six months.

So you know popular media is much, much more fickle than that. And people can communicate on

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Facebook and on the internet much, much quicker than that. And so whereas you know it's going to take a little bit of time for all these question to be unpicked. And it's quite possible you've been looking at objectively that it's going to go out of fashion or, you know, be kind of consigned to the crazy bin before all these even questions get answered. And so that's why I wish people to be patient with it and keep asking the right questions.

And support research where they can. And briefings critically and properly because you know this is not going to be answered in the next two years or maybe even the next five years. This is – I've heard, I think it was Brendon who say people say that when we needed – when we discovered the addition of carbohydrate and how that affects exercise performance were still working on that now how best to give it and what affects it has and how it's having those effects.

And this Exogenous Ketones in sport and all of the field is going to be an endeavor like that. And we need to, you know, if we get something that doesn't work OK, maybe the dosing isn't quite right. It actually wasn't quite right. Let's reevaluate and go again because it's because it's something that could work we think – I think it deserve really thorough inquiry. And I think it's going to be a whole new field for the next you know 20 years, 20, 30 years. And so I think that's the better comparison rather than say oh well you know Exogenous Ketones they come along.

There's all this hype. Well we've got one study and they never do this or they never do that and then therefore scrape them. No this is like – this is hopefully I hope going to be the birth of the new field looking at ketogenic diets and Exogenous Ketones worry about the whole range of different things. So be patient with it and watch as the story unfolds.

DANNY LENNON:

Sure. I think it's just one of those classic cases of as in most things in nutrition that it's somewhere in that

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safe middle range of neither extreme. It's not the answer to every single potential ailment. But it's at the same time doesn't mean there's going to be zero application ever in any possible way. So I think yeah, somewhere in the middle is usually a good place to orient ourselves. Brianna, a perfect way to round out the episode.

With that Brianna I want to say thank you so much for taking the time out today to come and talk about some of the work that you've done. And obviously get us clear on a few ideas that are out there. So I really appreciate your time and your information. And it's been great having you.