DANNY LENNON: Brendan Egan, thank you for joining me on the podcast again.

BRENDAN EGAN Good to be back, yeah. It's hard to believe it's been two years. Time flies.

DANNY LENNON: Time does fly indeed, and you've been up to plenty in the meantime which we will probably get into, and lots of changes going on. And today we are particularly interested in talking about some of the recent research and this whole area of exogenous ketone supplementation and as we were just talking off air, how there's maybe a lot of misconceptions and a lot of fanfare around this. But you being one of the people that's been looking at this, particularly in the area of sport science and how this might relate to athletic performance, so maybe before we get started on this just to kind of set the scene, I think maybe some definitions are always helpful. So when we are talking about just ketone bodies in general, maybe for people what exactly are the different ketone bodies that there are and then what are we going to be talking about in these differences in what endogenous ketone production versus exogenous ketone production.

BRENDAN EGAN So ketone bodies that we are generally talking about are acetoacetate, beta-hydroxybutyrate and acetone. They are produced in situations in the body where you

have a lack of relative glucose availability. So we are talking about things like starvation, prolonged fasting, ketogenic diets. Anytime where you've got a reduction in glucose intake or levels in the blood you see elevations in free fatty acids and it's the presentation of these free fatty acids at the liver that drives the formation of ketones, the process is called ketogenesis.

So the primary endpoint for ketogenesis is acetoacetate, but most of the circulating form of ketones is in the form of beta-hydroxybutyrate. There's a small amount of acetone that's typically what people describe when they have the smell on their breath in a ketogenic diet stage. But primarily when we are talking about the effects on metabolism and the use of exogenous ketones we are talking about beta-hydroxybutyrate, which is sometimes referred to as BHB and that's that is having the most pronounced effects, when it comes to effects on metabolism.

DANNY LENNON: Perfect. So with that production that we may get, this whole area of exogenous supplementation has come about from essentially trying to get some circulating form of these ketone bodies without having to go through that process, right?

BRENDAN EGAN So the ketogenic diet or prolonged fasting, these are, I would say for most high intensity sports or in practical approaches if we are talking about enhancing performance. So I am sure most of your listeners are where the ketogenic diet is a low carbohydrate diet, it's typically around about 5% of calories coming from carbohydrates, about 15 from protein, the other 80% or so coming from fats. And under those conditions, we get a fairly large increase in the production of ketone bodies but what's quite different – that would be of course called endogenous ketosis. What's different about exogenous ketosis is that you are supplying these ketones in the form of a supplement. And we'll talk about the different forms of those and I am sure in a second, but again the metabolic milieu in the body at the time of endogenous versus exogenous ketosis is quite different. So, for example, in the ketogenic state you are usually talking about high levels of circulating free fatty acids, low levels of insulin, and glucose where contrast to that in the case

of exogenous ketone supplements in fact in the study that's been most widely cited of showing the performance benefit, there was a large amount of carbohydrate provided at the same time.

So there are quite distinct metabolic states and in fact I will go as far as to say that we shouldn't really be conflating the idea of the ketogenic state with the exogenous ketone supplemented state. I think they are really quite different from a metabolic point of view and quite distinct. One of the students whose working on the project has been Mark Evans, he recently remarked that if exogenous ketones, in other words, ketone there, they wouldn't be near as controversial a topic. I think people are conflating the two ideas of whether a ketogenic diet and exogenous ketone are the same thing when they are really quite diverse and we should probably consider exogenous ketones as a separate substrate in isolated experiments and look at it from that point of view.

DANNY LENNON: So going along with that, we have this certain physiology that's associated with being in ketosis via a nutritional ketosis via the diet. Exogenous ketones on the other hand they are these substrates we may use. So if we now look at sporting performance for example and this is where the kind of interest lies. We have this other fuel substrate to come in. What is the proposed reason why they may exert a benefit as opposed to normal fueling are not using this exogenous ketone.

BRENDAN EGAN Yeah, so I think the important thing maybe to say from the start is that ketones are produced during these periods of low glucose availability because they serve as a substrate for the brain in particular. But there are mechanisms of oxidation of ketones in most peripheral tissues, including the heart and the skeletal muscles. So the question obviously, there's a few ways you could probably tackle this. So one is how much do skeletal muscles rely on ketones in any given state. So in the fasting stage, they are probably making somewhere around a 2 to 10% contribution to energy provision during exercise in the fasting stage.

The problem with the research that was done in the 70s and 80s is that most of the way that the ketosis

was achieved was by prolonged fasting, and as I said, that's quite different to what might be achieved by an exogenous ketone supplement. So if you are to look then at the recent Cox et al paper that was published in cell metabolism, they were able to quantify the amount of exogenous ketone – sorry of BHB being oxidized during exercise, and they estimated that it's somewhere between 16 and 18%. So again, the difference between what's been seen in the fasting state versus the supplemented state is quite different. Anyway, the bottom-line from that point of view though is that ketones can be used as a fuel within working skeletal muscles. That's the first point. They also exert fairly obvious metabolic effects. Again, this was shown in the types of fasting studies or the infusion studies that were done in the 70s and 80s. And that's that they are able to cause glycogen sparing. In the case of a couple of papers including the Cox paper they were able to show a reduction in lactate production. They have effects on mobilization of free fatty acid so elevated ketone levels are antilipolytic so it's actually lowering the breakdown of fats.

But conversely, based on the data again from the Cox paper, it looks like they would enhance the oxidation of intramuscular triglyceride or the contribution of intramuscular triglyceride as a fuel source. So we have the direct effects where they've been metabolized to produce ATP and obviously provide energy and then we have the indirect effects where they are all trained to substrate metabolism both in the periphery and in the skeletal muscle itself. So those two things combined would suggest that as again taking it as a supplemental form of substrate that it can have effects within the body. Of course the question remains with any kind of supplement is what is its application in various different sporting contexts, those dependent effects, all these types of things that we will probably discuss or speculate on. But in principle at least, as I said, it can be used as a fuel in skeletal muscle and it has the ability to alter fuel selection in muscle as well.

DANNY LENNON: So going along with this and maybe just to play devil's advocate is if we have this case where someone's on a carbohydrate based diet, they got full glycogen stores, and now they are adding exogenous ketones on top of

this during exercise, that can potentially be useful as you've highlighted because it might be sparing for glycogen, maybe the same goes for muscle protein as well. And so if that's the case, is that different if you were just to simply supplement it with a isochoric amount of glucose during that activity, oxidize that rather than tapping into glycogen stores or just something else to this all kind of glycogen sparing thing with exogenous ketone specifically?

BRENDAN EGAN Yeah, so I suppose the best way to answer that, I mean, the Cox paper was able to show that in situations where carbohydrate provision was optimal, so they had controlled diet, they were elite cyclists, they provided them with high carbohydrate diets in advance, they provided them with a rate of carbohydrate delivery during their exercise test that was consistent with what we recommend as optimal fueling strategy during exercise. And on top of that, then they added the ketones and it was the effect of the addition of the ketones on time tried performance, that was the notable outcome, at least from a performance point of view in that particular study. So, we would say, at the moment, I mean, we are talking about one study where it's been really rigorously interrogated. You would say that there is this benefit of adding this extra substrate.

Of course, the argument then is, well, I mean one of the criticisms of – well, it's true of ketogenic diets and of exogenous ketones, is that the mechanism of action that leads to glycogen sparing is likely through the inhibition of pyruvate dehydrogenase or phosphofructokinase, essentially limiting flocks through the glycolytic pathway. And the extrapolation of that is that when an athlete would be required to do very, very high intensity bursts that they may not then be able to call on the glycolytic pathway to the same extent that they would if the ketones weren't present. That needs again to be rigorously tested. It's a fairly interesting hypothesis. I think it's certainly in the ketogenic diet scenario I would say that there's a good bit of evidence for that, but that remains to be seen in the exogenous ketone stage.

DANNY LENNON: Yeah. That's an interesting one. That was one of the things that I thought that I was going to ask you about

this potential for some degree of metabolic inflexibility where – because I know certainly in like low carb, high fat diets, I think Trent Stellingwerff often talked about this down regulation of pyruvate dehydrogenase. And then I think one of the papers that I'd actually looked at recently, I am sure you saw was, I think it was Omali was the paper they did, and where they kind of saw the same thing in impaired exercise performance with the supplementation. Just so that I have it clearly, when you are talking about this, on other hand we could say with this glycogen sparing effect which could be a positive, on the other side the exact same thing could be a negative because you are affecting carbohydrate utilizations, you are basically not able to use it as effectively.

BRENDAN EGAN That's the bottom line, yeah. So Louisburg I think has put this very well in her review from 2015, I think it was – are we talking about glycogen sparing, are we talking about glycogen impairing and I think that's a good way of thinking about it. And the answer is we don't know right now, it could be either/or and there's some people who think it's impairing and other people think it's pairing. And so I think it's an interesting question that we are going to need to look at.

DANNY LENNON: Sure. One thing we didn't maybe touch on yet was the different forms that these supplements can now come in. So commercially they've been in various forms, there's maybe some talk previously about maybe free acid forms which have a lot of problems. A lot of the commercial ones right now, it seems to be using ketone salts and now we are seeing ketone esters in research. I could maybe touch on some of the difference between those.

BRENDAN EGAN Of course, yeah. The ketone ester is the one that's been used most widely in the literature and that is what was the Cox paper and a couple of recent papers Hole's work and a Vandoran paper as well. And this is – the ketone ester is an esterified form beta-hydroxybutyrate and butanediol. So butanediol is a molecule that's metabolized in the liver and elevates levels of BHB. So effectively, with the ketone ester you can deliver a fairly high amount and induce a very large change in BHB with a relatively small amount of them – that's called a product ingested. These esters

have been developed in the US predominantly and they are not commercially available. At present although, there are moves in the pipeline to get these commercially available, but they have typically been used in research.

The ketone salts then would have been on the market for several years now and these are typically BHB, beta-hydroxybutyrate and combined with the potassium, calcium or magnesium salts. So there are several on the markets, I won't name certain brand names, but there's an interesting thing with them is that the amount of BHB that is delivered per, let's call it per product or per serving, is relatively low compared to an ester and it has the side effect of having a large amount of salt delivered, as I said in the form of potassium, calcium or magnesium, sodium as well.

So in our hands at least with the products that we've tested, generally speaking, we've seen an inability to raise BHB levels to a level that will be considered impactful on performance. So in our general physiology review, well, it was published earlier this year, we speculated that there would be an optimal zone a goldilocks zone as such for BHB levels in the circulation which would be somewhere between 1 and 5 millimolar but certainly I don't think levels below 1 millimolar of BHB are going to have an effect on performance. There may be other effects that they would have, but certainly on performance I don't think they are going to have an effect. And at least as I said, in our hands and looking at the couple of papers that have come out even in the last couple of weeks, as it happens, on ketone salts, they don't seem to have an ability to raise BHB levels above 1. In our hands, we again, try to escalate those type of responses given more and more of the commercially available salts, and ultimately as you can probably guess, they cause diarrhea, vomiting and so on.

So once you have this really strong salt load on the GI tract, more than likely they are going to have a vomiting effect or diarrhea effect. And so at the moment we have a manuscript in review and in the 18 or 19 in the end that we had trained females and males, 13 of those had GI issues when we gave the

ketone salt prior to exercise. So, the salts require a bit more work and I think there are companies who are definitely trying to reduce the salt load delivered in conjunction with the beta-hydroxybutyrate. And as I said, if that was able to be achieved, then they are more likely to have a bit more efficacy. But obviously the gold standard, let's call it at the moment would be the ketone esters, but as they stand, they are not available.

So the ones that have been studied so far have been the so-called Veech or Clarke monoester and then Dom D'Agostino's group in Florida have also got their own diester which is a slightly different makeup and may have slightly different metabolic effects but again all to be tested.

DANNY LENNON: What timeframes are we seeing for how quickly this elevates ketone levels and then how long will that kind of stay elevated?

BRENDAN EGAN That's a great question. So with the ester they are elevated within blood within about 10 minutes. Again, we've tested the ester in recent weeks and with BHB ester it's remarkable how quickly the BHB levels rise after the ingestion of the dose that's been described in the Cox paper. The salt on the other hand, their maximal peak we are seeing generally in our hand somewhere around 0.5 to 0.7 millimolar. And that's occurring about let's say 60 minutes after the ingestion of a serving. And in our hands again, as I said, we were having these problems with gastrointestinal effects, so we actually divided the servings up into two to try and prevent that GI distress but in terms of elevating the BHB levels it still only got it up to the level that I described, and that was as I said, typically in our letter. So the kinetics are completely different in terms of their ability to their ability to raise BHB.

One other point I suppose to make on the salt is that the salt – so you are probably familiar with racemic mixtures and this idea of D and L forms of them, of molecules. So the D form seems to be – the DBHB seems to be the active form. The other form seems to have less of an effect. But many of the ketone salts that are on the market are in the form of D-L, BHB

combined in with the salt. There's one or two exceptions and of those that we've tested in our own hands, it's quite dramatic that they are producing better increases in BHB. And so I think there will be more interesting companies being able to produce these DBHB salts in the future and that would again improve the delivery of BHB or the elevation of BHB that occurs after ingestion.

DANNY LENNON: Yeah, at least from what I've seen, it seems that typically the form that would be circulating in our bloodstream from say a ketogenic diet is going to be deformed nearly exclusively. So we don't really know what's going on with this L form right now or do we – is it kind of just an inert thing or does it have any effects in them?

BRENDAN EGAN I wouldn't say it's inert. Of the literature that's out there, again going back a couple of decades, what it's looking like, that the L form is somehow involved in fatty acid synthesis. So it's not inert but its role in skeletal muscle and performances, it would be completely unknown. There was a paper published back in 2014 looking at longevity in a model of C elegans, the worm model, and they are able to show that say the D-L form compared to the D form, compared to the L form that there was a divergent effects with the different forms in terms of extension of lifespan. So the D form was able to extend lifespan, the L form at the same concentration had no effect versus control, and the D-L at the same concentration had a kind of in-between effect whereas the D-L form at double the concentration which actually was the same as the D form in the first experiment, that was able to have the same effect as the D form. So all that would point to the fact that it's the concentration of the D form specifically that at least in longevity is having its effects. And I think that's a really nice model of trying to isolate the effects of the isoforms.

DANNY LENNON: I think I saw one group that mainly involved a thing in epilepsy research that had been working with an acetoacetate ester instead – but then there's – I know one of the groups maybe even in Oxford I think that worked with a beta-hydroxybutyrate esters would be of the opinion that that's the form for sporting performance at least is the reason is, can you maybe

touch on why that might be the case or do we kind of know what's going on?

BRENDAN EGAN Well, you are right. The acetoacetate diester is the one that I mentioned from Florida and I guess the speculation if we are talking about performance is that as we understand it right now, beta-hydroxybutyrate, BHB would be the primary factor that would influence performance. With the acetoacetate diester you are getting a large elevation – acetoacetate as well as BHB within the blood. And the idea – again, this is all speculation – would be that the levels of BHB aren't reaching the level that's suitable for performance benefit and the change in acetoacetate, that could be beneficial in situations like this, seizures and hypoxia and so on that's been studied, but it may not be advantageous when it comes to performance. But that is pure speculation. I haven't seen any diet on that to date.

DANNY LENNON: Yeah. So already we talked about the effects maybe on sparing glycogen for example and directly oxidizing these ketones for as a fuel source. One of the other areas that you touched on in your review and maybe it links a lot with your kind of research is looking at this as a signaling molecule and some of the effects it has. What are some of the kind of metabolic pathways that might influence and what are the kind of practical implications of these pathways that it affects?

BRENDAN EGAN Well, there are two ways to go with this. One is direct effects on protein synthesis which I will talk about and then of course there's the effects on signaling as you mentioned through HDAC inhibition. So, first of all taking the idea of protein synthesis and this is where we move kind of from performance into the recovery paradigm. So of course everyone who listens to this I am sure is aware of the idea that protein synthesis is measured as the marker of muscle growth and repair. And usually anytime we are talking about things like the ability of losing to stimulate protein synthesis or of whey protein during recovery, all of these are targeting – maximizing protein synthesis as a means to enhance recovery growth repair and so forth.

It turns out that a paper going back into the mid 80s from Srinair's group showed that the infusion of

sodium beta-hydroxybutyrate led to inhibition of losing oxidation and about a 10% elevation in muscle protein synthesis measured as fraction of synthesis measured as fractional synthesis written in that study. And this is analogous to what would be achieved with some of the studies that have used either losing enrichment of protein sources or whey protein and so forth. So if we were to draw parallels then we would say that there's probably some effect of elevating beta-hydroxybutyrate in the post-exercise period on muscle protein synthesis.

So a recently published paper from Peter Espel's group, they were looking at glycogen replenishment but also looked at signaling pathways towards muscle protein synthesis or the classic mTOR pathway and they were able to show that in contrast to a placebo, carbohydrate plus protein ingestion, they had ketones plus carbohydrate plus protein and they are able to show elevations in signaling down the mTOR cascade. So that would be again – that's a surrogate measure. Obviously, a study would need to be done that looks at outcomes in terms of adaptation and muscle size and so forth. But the preliminary evidence would be suggestive anyway that there could be a benefit and recovery from the protein synthesis side of things with beta-hydroxybutyrate.

Again, I would say that it's all going to depend on the levels which you can get the BHB level and concentration in the blood up to as far as recovery. I suppose just to touch on that, just because I mentioned it, there have been that paper and of course another paper from the Oxford group that looked at recovery of muscle glycogen. And although, the hospital group didn't see any difference in muscle glycogen in the presence of the ketone ester, in the recovery formulation, the Oxford group were able to see a difference. There are difference in the models. One was unilateral exercise, one was glycogen depletion and variable intensity cycling, one was Hole's work – the Oxford group, they looked at a two-hour window where there was a Hyperinsulinemic-euglycemic clamp. The Oxford group looked at a more ecologically valid feeding type of paradigm. So there are differences between the studies but I think again that's a very promising scenario is the area around

recovery whether it's glycogen or protein synthesis, something that needs to be examined.

Getting back to the question of signaling, so the major premise behind this was a paper that was published in 2013 in science that showed that beta-hydroxybutyrate is a HDAC inhibitor. And so a HDAC system and deacetylase as they are called, they are negative regulators or transcription. So the idea is that with something like beta-hydroxybutyrate, you are inhibiting HDAC activity therefore you are lifting the brick so to speak on transcription regulation and the interesting thing is that HDAC inhibits the transcription of a variety of what we would call exercise responsive genes, so things like GLUT4, PGC-1 alpha, a variety of factors that we typically measure and exercise studies as outcome measures or measures of adaptation.

So from a mechanistic basis what you might suggest is that if you had a situation where you could inhibit HDAC which occurs anyway with exercise, but if there was a situation where further inhibition will be beneficial, then you could again maybe postulate that there would be a benefit in terms of the adoptive response in the presence of ketone supplement during that recovery period. Again, that remains to be seen. I mean, the major outcome of the paper that was published in 2013 was around oxidative stress, and there was a subsequent paper published that looked at inhibition of the inflammasome. These are things that – for me the jury is really still out, like do we want to be inhibiting oxidative and then inflammation in the post-exercise period. You will get people who will argue that both of those things are good things, that they are part of the adoptive response. I am kind of in that camp. The studies that have used either high levels of antioxidants or even some of the cold water immersion work where you see that there's a blunting of the adaptive response. I think that could be at that level.

So it's one of these things, we need a lot of studies to figure out which is best. Do we try and use ketones from that perspective or do we just let these processes have their natural way. I think that remains to be seen, and as I've discussed many times on your

podcast, I mean, it's all about the context and what we are trying to recover from, are we preparing for the next event, are we trying to enhance adaptation. I mean, these are the types of questions that come up anytime we talk about nutrition or supplements.

DANNY LENNON: Yeah, there's that kind of reoccurring theme that there's still a lot more we need to work out. And obviously it seems that a lot of that work is kind of underway. So at least within the – for athletic performance, what are kind of some of the next areas that need to be kind of teased apart or you think where that research is going in the next few years?

BRENDAN EGAN Well, I think if we take from – we started out reviewing sometime around – we started writing it around the summer of 2016. It was published then in middle of this year. When we were writing that there had been no papers published on exogenous ketones, the Cox paper then came out just as we were submitting that review so there was a quick reedit. But since then, there's probably been another handful of papers in humans probably – off the top of my head I am thinking five, six papers at most, two in performance, two in recovery and couple of others that are in the pipeline, one from ourselves. So it's a very young field, and the work that's been done in other fields whether it's in terms of protein supplementation, recovery, whether it's in terms of carbohydrates, ingestion during exercise, you could argue that a lot of those similar studies need to be done with ketones if we are going to get exogenous ketones, if we are going to get answers to what the benefits are.

So from our perspective, our interest is going to be in running best protocols, everything up-to-date and now it has been around cycling protocols. I think performance definitely has to be measured. We've done some work that as I mentioned on the metabolic response we are trying to get published at the moment. But I think performance is what we need to look at and then obviously teasing out around what's been done so far at short term recovery, looking at how that could affect the adaptive response over time. So we are talking about similar paradigms, short term recovery, adaptive responses and performance. It's an

open book at this stage in terms of finding the answers to those questions.

DANNY LENNON: And that's the thing considering there's so little research on this area right now, but what is there – it seems to be mechanistically a lot of promise there or some sort of potential to explore. But yeah, we are in a situation where maybe it's not been looked at all that much. Does that kind of go back to maybe what we were talking about earlier before we started recording of some areas not taking this as seriously or maybe brushing it aside because of the fanfare and over the top kind of hype that tends to be around anything to do with ketosis and then therefore now there's kind of people talking about using the ketone supplements as part of like their healthy diet or losing weight or something. And therefore a lot of it just becomes, oh, this area is another kind of...

BRENDAN EGAN Another fad or something, yeah. I mean, I think there's definitely an element of that. But what we tried to do in our review was trying to be objective and look at the papers that have been published and sort of point to what needed to be done in the future. And it was funny because the Van Loon group published a review right around the same time, completely independent, we had no discussions, didn't know it was coming out. And we reached more or less the same conclusions. We had a slightly – we believe that there might be more energy than they believed in their review. But by and large we had come to many of the same conclusions.

So there are plenty of groups working independently on the area and there are people taking it seriously. I think one of the issues that's going to be in the research is that the – as I said, I don't believe at the moment what's commercially available in salt form is relevant to what we are trying to do in research. The esters aren't commercially available but these groups are interested in collaboration, so I think there will be more papers coming out again from independent groups. So I think over the next 12 to 24 months we are going to see a lot in this field and it maybe that in 24 months' time to go, well that was very interesting, there was a big hullabaloo for a while and it's gone now. It could be like that. But I think that there's

enough in it. I think there's a – as I said, we wouldn't have written the review and came to conclusion that we did unless we looked objectively at the data and saw that there's some promise within that.

I think one of the things we had mentioned so far is that in terms of the enzymes that are responsible for ketone oxidation in skeletal muscle, those are responsive to exercise and training at least in animal studies. But what's hard to believe is that that's never been looked out as far as we can tell in humans. But we made this speculation in the review that in those individuals who are highly trained, have a high proportion of type 1 muscle fibers and high obviously aerobic fitness, that those are the ones who are most likely to benefit from exogenous ketone and supplementations. So again, that's another caveat and another condition that you are sticking on this area. So it may well end up being that there's a very specific cohort of athletes competing in specific sports or challenges where it is appropriate from performance point of view. What happens from the point of view of recovery and adaptation? Again that's another, as I said, several times it's an open book.

DANNY LENNON: I mean, that throws up the possibility that it could just be something to do with driving these adaptations, similar to the way like the low glycogen availability training is like rather than performance in the session, looking at adaptation, could you potentially see that this could be something similar?

BRENDAN EGAN That's kind of the way I am thinking at the moment. I think the most promise as a general tool is going to be in recovery and adaptation. I think as I just said there, I think in performance it's going to be in very specific context. It's not going to be across the board and there were a couple of caveats that we put into the review in the looking forward kind of section. We were talking about the fact that there are certain situations where the inhibition of lipolysis that seems to occur with them, with high levels of beta-hydroxybutyrate that that maybe detrimental to performance, particularly in long duration type activities. And then equally if we are going with this idea of glycogen impairment, if that is the case, then that would be detrimental in terms of sports where glycogen is a limiting factor or

certainly where high intensity bursts were lying under glycolytic pathway are predominant. So that's one of the things we are hoping to get in our next study is looking at an intermittent running type protocol to look at the performance benefits if any that come from that.

DANNY LENNON: Yeah, maybe we can turn to a couple of questions that tend to pop up anytime exogenous ketone supplements are mentioned, and one relates to what you just mentioned about this antilipolytic effect in that using these ketone supplements are essentially going to suppress availability of pulling fat from fat cells which is very much counter to maybe what a lot of people tend to believe if they are kind of in this gated community of thinking by using these exogenous ketone supplements that's going to help me burn more fat.

BRENDAN EGAN I think what you are talking about there is a conflation of the idea of the ketogenic diet and exogenous ketones. I think it's just an oversimplification that people are – conclusion that people are coming to, that's incorrect. So as you said and we've just briefly discussed, the antilipolytic effects would effectively be reducing the mobilization of fat stores. And one of the benefits of exercise is that you mobilize – if we are talking about fat loss and weight reduction is that you mobilize these fat stores and then you obviously consequently oxidate and burn off some of that fat. It's a very minor part of how we lose fat to exercise. So I think it's a mistake to say that ketone, exogenous ketones are going to help burn fat. I think that's completely erroneous. But I think it's also probably not true to say that if you take them, you won't burn any fat, like I just don't think it works like that.

I mean, in the recent Omali paper that you mentioned, they talked about elevation in fat oxidation during exercise. There may be some issues around the interpretation of the exchange ratio in that, but the Cox paper also suggested that intramuscular triglycerides are being more heavily relied on in the presence of exogenous ketone use as well. So I think again you are talking about different pathways, whether it's in the adipose tissue or whether it's in the skeletal muscle and I don't think –

on the overall picture of things, I don't think the use of ketone, exogenous ketone supplement is going to be positive or negative towards fat loss, considering all these other things that influence that.

I suppose one quick comment is that I see from time to time people are mentioning raspberry ketones as if they are somewhat related, but it is proposed as supplemental fat loss there but again not very much evidence to support them, but again shouldn't be confused with exogenous ketones.

DANNY LENNON: Yeah. It's unfortunate you share that kind of thing. That's an important point because I think when we look at this kind of state of ketosis, and this point you've been hammering along, it's just completely different, you can't even compare the two, the fat burning effects so to speak is because you are using fatty acids to make these ketones not the ketones themselves are causing the fat burn effect.

BRENDAN EGAN Exactly. So the other thing as well I would say is that – I've seen talk of the appetite suppressing effect of exogenous ketones and based on any human diet that I've seen I don't see that in the literature, whether there's anecdotes and so forth that have got that out there. I think again, that could be the confusion of this spontaneous reduction in food intake that occurs on a ketogenic diet. And that being attributed to ketones and therefore the idea that, well, okay if we take exogenous ketones, it will have the same effect. Again, that's just – it's conflation of two different concepts, and I think again that's – I mean, it's something that should be tested again rigorously but at the moment, in humans at least, that doubt isn't there. So I wouldn't be suggesting that they cause appetite suppression either.

DANNY LENNON: Yeah. Just to go back to some of the stuff on exercise performance, obviously we have ketones available, we have the carbohydrate stores in someone with full glycogen stores. There's going to be fat present if they are going to use some of that protein. So we have all these different substrates available for energy provision. Do we know anything about proportionately how that's going to play out in a

situation when we have someone that's on a carb based diet using exogenous ketones?

BRENDAN EGAN

It's kind of tricky to say, so again in the Cox paper, one of their early studies was to look at the response of exercise and its relation to ketone concentration. So they looked at a low intensity exercise, modern intensity exercise and at moderate to higher intensities of exercise the ketone levels were lower compared to the lower intensity exercise. In other words, it seemed that at a higher intensity of exercise more ketones were being oxidized. And then subsequently, as I said, in one of the studies in that paper, at one of the later experiments, they were able to show that the oxidation rate of ketones was contributing around let's call it 15 to 20% of energy provision. But the question you are specifically asking there about whether you provide even more carbohydrate or whether you are on a low carbohydrate diet, if you have these divergent types of fueling strategies, does that influence the amount of ketones that are being oxidized – again the answer is we don't know. That still needs to be done.

One of the things from the early work that was done, again in the 70s and 80s on the prolonged fasting and so forth, there seemed to be an auto-inhibitory effect of elevating ketone bodies to further and further extent. So if we look at say an overnight fast compared to a three-day fast, compared to a week-long fast, the metabolic clearance rate, in other words, the amount of ketones being oxidized in the periphery, that declines with increasing amounts of ketone bodies. That's why we proposed that there was this – you know, an optimal zone for getting to in terms of performance benefits, because once you go above a certain threshold, that's probably somewhere around 3 to 5 millimolars, at least from that old data it was suggested that there's an inhibitory effect. In other words, the ketones won't be oxidized in skeletal muscle. And it makes sense because it's like if you are in this really prolonged fast or starvation mode, and ketone levels are getting higher and higher, it's probably better to keep them for the brain rather than shuttling them to the muscle. And so I think that's probably what's going on in that scenario.

So, again a question I have been asked several times is what do I think if someone was on a ketogenic diet and they take exogenous ketones, is that going to be a performance benefit. And I am just saying at the moment, my interpretation of literature would be that if you are on a ketogenic diet, and ketone levels are elevated to round about 3 millimolar that you might be getting some inhibition of – actually of the oxidation of ketone bodies in the skeletal muscle. And again that's my read of the mobile data but again it's an experiment that needs to be done so my mind may change on this.

DANNY LENNON: Yeah, it's certainly interesting. I think there's maybe that flawed idea that the higher you drive ketones, the better – the deeper stay of ketosis or whatever that's termed to be. But if you are oxidizing, would not stand to reason that you are going to be using them up so they are not going to be appearing as much.

BRENDAN EGAN And I think that's going to be the – that's the kind of question we need to answer is that are you utilizing them to an extent that they are not having any great effect when you add more in there or is there an inhibition that's taking place that's not allowing the exogenous form that you take to be actually utilized by the muscle, I think it's a really good research question if anyone wants to do it.

DANNY LENNON: Nice. Is there anything in this whole kind of conversation that we haven't touched on yet when it comes to exogenous ketones that is important kind of message to get out or is something that you see talked about or thrown out by people...?

BRENDAN EGAN I think we've covered the majority of bases. I mean, as I said, I think the idea that they are only for performance, I think is again is a mistake, I think that they've got at least interior they've got applications beyond performance. And I think that's, as I said earlier, that's to my mind where the most promise is. And so I think that's where there's at least a couple of groups that I know who are working in that space around recovery and adaptation. And I think that's where we are going to see a bit more in the future. The performance side of things, as I said, because it's quite – and I think other people have recognized this that

it's quite specific situations where there might be benefits. I think they are probably going to be less done on that. But I do think that in the next, like I said, year to two years, and hopefully we are contributing to this. There's going to be plenty of work that comes out there, yeah.

DANNY LENNON: Brilliant. We will wrap it up there. Brendan thanks so much for your input, very insightful conversation and like I said a very interesting area of research, so looking forward to what you published and everyone else.

BRENDAN EGAN Great.

DANNY LENNON: Yeah, thanks for that, and we will talk to you soon.

BRENDAN EGAN Thanks very much.

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