DANNY LENNON: Cliff, welcome to the podcast my man.

CLIFF HARVEY: Good to be here Danny.

DANNY LENNON: Yeah, thank you for joining me. I've been trying to plan this and been looking for this for quite a while. Before we get into any of the questions, I'm intrigued about Cliff. From an overview level, how would you explain to people the typical area of research that you've been involved with, and then outside of the research you've been doing more recently, your work as a practitioner?

CLIFF HARVEY: Yeah, good question, I mean, it's really the other way round to some degree. I started as a practitioner around 22 odd years ago, and just by virtue of having an enquiring mind at the time, I sort of started looking into low carb and ketogenic diets, probably at a time when it really wasn't the done thing, particularly in clinical nutrition, we're talking about back in the 1990s. And so, I worked a lot with all sorts of iterations of low carbohydrate or what I sort of call carbohydrate-appropriate diets over the last couple of decades. And then it was when I came back from Canada, in around 2011, that I started thinking about maybe getting back into academia again and wasn't really sure if there'd be much of a way forward with that. But

thankfully the team at AUT was starting to look into low carb and keto, they had previously thought I was kind of crazy but they invited me up to talk about the research that we could do and whether we had a path forward there. And so I ended up doing my masters and doctorate in ketogenesis and keto flu predominantly, but also looking at the individualization of diet for people. So basically looking at that carb spectrum and what's appropriate for the individual so we're not dogmatic about applying low carb or keto.

DANNY LENNON: Right, and I think there's a couple of things that are interesting within that. One is that when you started not only looking into carbohydrate restriction and specifically ketogenic diets, that was way before any of this modern interest, let's say, over the last number of years, where it's kind of exploded, this was quite a while back, not only were you looking into these, you had been applying them with yourself and your clients as a practitioner, right?

CLIFF HARVEY: Yeah, exactly. I mean, they were obviously, you know, we stand on the shoulders of giants, there were a lot of iterations of low carb around; and as we well know, keto, for example, has been studied for over 100 years for epilepsy, and in the 1990s there was sort of a resurgence and interest particularly in bodybuilding led by Mauro Dipasquale; and obviously a little bit further back, Atkins; but guys like Dan Duchaine, they were really into this low carb idea, and so that's really where we picked it up because were interested in bodybuilding, weightlifting, powerlifting. And we sort of saw some of the flaws in the dietary guidelines and saw that there was some utility for these low carb approaches for some people at least; and then for others, there was this carbohydrate spectrum, and some people obviously thrive on higher, some on lower, but there is this sort of spectrum that we can apply based on the individual.

DANNY LENNON: One thing we could look at is outcomes from using different types of dietary interventions. But with something like a ketogenic diet or something that would lead to this physiological state of ketosis, what did you find most intriguing or interesting about that?

CLIFF HARVEY: Going way back, I think, like many people, when we first started using it ourselves and maybe using it with clients, we did look at it quite naively. So this is again going back two decades or so. We kind of thought, well, this could be almost like a flawless approach for fat loss. And obviously, in the intervening time, we've realized that's not the case, it's nothing magical. But obviously, having done a lot of work in that space and worked a lot more and more with it clinically, I think some of the most exciting areas for particularly keto are really in the space of neurodegeneration, recovery from traumatic brain injuries and concussion, possible benefits for cognition and mood, and maybe even for things like depression, bipolar disorder. So I think a lot of the mental health and neurodegeneration aspects are probably the most exciting for me, because I think that's what we could really see some of the utility of these ketone bodies within the body.

DANNY LENNON: And that's certainly a topic I want to circle back to later on, and I remember we had some brief conversation about some of these ideas that I want to get into a bit deeper. I think one of the really important aspects to what you just said is that I think sometimes we can maybe fall into the trap of just having discussions in nutrition in general, but also when it comes to diets of differing amounts of carbohydrate and ketogenic diets and so on. I am looking at this in terms of say ketones are an energy substrate and carbohydrates and energy substrate and just think of it in these terms whereas, as you say, some of these other applications we know that, for example, beta hydroxybutyrate is not just an energetic metabolite, it has, so their signaling functions as well, right, so just trying to think through things a bit deeper allows us

to look at these various different clinical applications I guess.

CLIFF HARVEY: Yeah, exactly. I mean, obviously that's where it's interesting because you take the ketone molecule beta hydroxybutyrate and it's very multimodal in the way it works. It does have those signaling functions that you suggested and it's anti-inflammatory. It provides that fuel source directly for the brain and central nervous system. But it's one that is very appropriate when you have damaged the glucose transporters and neurons or maybe a distortion of the blood-brain barrier but it also helps to increase relative adenosine in the brain, reduces glutamate, and therefore excited toxicity, increases GABA and therefore sort of relaxation. So there's all these various things that are happening that are not just down to its fuel role. But one thing that I think is interesting within that, if we're looking at this as practitioners, is recognizing our own scope is pretty important here as well, because, as we discussed with ERIC and OMAR, a lot of times were very much framed by what our desired outcome is or what the desired outcome of our clients is. And if you're very focused on performance or if you're very focused on strength and power or physique, you're not really going to be that aware or even really care that much about some of these other clinical applications. And so, it's very easy then to write off particular dietary approaches for whatever reason. On the other hand, people who are more clinically focused might write off other dietary approaches because that's not what they are looking for in terms of their error outcomes. So when you mentioned outcomes and nutrition, I think that's a critical thing, and I talked about that a lot with ERIC is this idea of outcomes based nutrition is really the key, because we need to look at what the desired outcome is and just look at the absolute best way to approach that for the individual, and then leave the dogma at home because it's not really, it's completely unimportant.

DANNY LENNON: Maybe just to kind of take a step back that will help us frame some of the ideas we get into throughout this conversation, when we talk about the process of ketogenesis, why is it that we make ketones, I suppose, from a perspective of within the body, what is it that's going on that leads to this production, why is that happening and what are some of the fundamentals we should be aware of?

CLIFF HARVEY: Yeah, that's a really important question, I think that's one of the reasons there's a lot of misunderstanding of keto. I really think it's quite simple. If we restrict carbohydrate past a point, then the body simply cannot produce enough glucose in an ongoing fashion to supply the fuel that's required for the brain and central nervous system. So it starts to convert fats and some amino acids like leucine and lysine in particular, but other amino acids as well, into these ketone bodies that can be fuels for the brain and central nervous system. So because of that, it's sort of been looked at as a survival mechanism that allows us to get through periods of famine which is true. But it's also probably fair to say that in a primal state, the human animal would go in and out of ketosis relatively frequently, because there's not always abundant carbohydrate available. And so it seems to me at least to be a fairly normal and appropriate situation for the body to go in periodically in order to provide their fuel for the brain of central nervous system. And as we sort of mentioned before, there are some particular benefits from that as well.

DANNY LENNON: So one thing that I think is interesting to consider when we look at the application of the ketogenic diet in, well, a whole host of different ways we could look at that in terms of different outcomes is trying to tease apart, and this becomes very difficult I think practically, but trying to differentiate between the say "benefits" we have from increased ketone levels via a ketogenic diet versus the benefits gleaned from carbohydrate restriction per se. So just having that lowered level of carbohydrate

versus actual, the role of something directly being done by ketones. Where do we even start in trying to tease apart this kind of idea?

CLIFF HARVEY: Yeah, that's a big one, and it's a really important question, because I think too many people look at carbohydrate restriction and the resulting ketosis as being the magic bullet, it's the panacea for everything from weight loss through to improved cognition and all these types of things. Basically, people will look at that as being the universal answer to a lot of questions. But I think, when we're trying to pull apart that idea of ketones versus carb restriction, we really need to again look at the utility, you know, what are we trying to achieve here, and I think that's why I think the evidence is pretty clear that if we have problems with blood glucose regulation, in other words, metabolic syndrome, diabetes, then it's pretty clear that low carbohydrate diets are the most effective dietary intervention. And that includes ketogenic diets, and they can be some specific benefits obviously for people with diabetes from ketogenic diets, because it's also providing those ketones that help protect the brain, help protect the brain from glycative damaged, help protect the brain from hypoglycemic episodes and things like that. But when we move out of that spectrum, when we're looking at say weight or fat loss, again, a lot of people would jump into keto as being this magical panacea for weight and fat loss. But really, I'd say, on balance, we could achieve the same weight or fat loss with other dietary strategies done well.

Now, again, on balance, I think low carb is probably more effective for fat loss, even past the short term. I know a lot of people would say that the effect size narrows to nothing, I think the effect size does narrow a lot over time, but there is still probably some residual benefits for fat loss and particularly, again, for those people who have metabolic disorder. But because the effect size narrows so much, I think then the key becomes, for a lot of people, adherence.

What can you psychosocially and behaviorally stick to, what's going to be best within your food environment? Because at the end of the day, you're probably going to see pretty similar outcomes over a longer period of time. So then we moved from that into the clinical setting and that's when the actual utility of the ketone molecule I think becomes key, and that's when we start to see the specific benefits for things like epilepsy, the neurodegenerative disorders like Alzheimer's, Huntington's, Parkinson's, amyotrophic lateral sclerosis; and also possibly some emerging stuff around other aspects of mental health or other conditions.

And so, it's interesting because there is very much the spectrum, and I think within a lot of that spectrum the key really is what can you stick to and also what's the context of the diet, because, if we pull apart everything else, probably 80 or 90% of the effectiveness, I think, comes down to eating natural unprocessed food. But on the fringes there are very specific benefits that either come from carbohydrate restriction on the one end or the utility of the ketone molecule on the other end.

DANNY LENNON: Yes, a couple of really interesting components in that. One, if we talk about adherence first, because, if we look at an overview level of, let's say, a lot of studies, adherence to not only a ketogenic diet but pretty much most diets is pretty poor at scale; and I think you could probably make a case that that might be even more difficult for, let's say, a wide population of people if they were recommended to undergo a ketogenic diet just given the basis of the food restriction, right? But again, that's nothing in apparently specific to a ketogenic diet, we see pretty poor adherence to a lot of diets at scale. But on the other end, we have a large group of people that we see either within studies but also reported anecdotally and just when you look at the online community of not only can they stick long term to something like a ketogenic diet but they wax lyrical about the ease of doing so or how this is the diet that they

most like to stick to or enjoy doing. So again, this is probably an almost impossible question to answer, but to you, what are the factors that might dictate where an individual may be along that spectrum between those two extremes in terms of their ability to adhere to a ketogenic diet, maybe this extrapolates further to any diet in general?

CLIFF HARVEY: Yeah, I think it's an interesting question because the narrative that we often hear is that low-carb and especially keto are very difficult to stick to and that's one of the big criticisms of a ketogenic diet, is it's very hard to stick to. So if for a lot of people the effect is not going to be that much different to following a different dietary strategy in which they are able to autoregulate their energy intake, their calories in, then there's really no benefit. I would dispute that because, from what I've seen, the systematic reviews of the evidence show that adherence is probably marginally better for a low carb or ketogenic diet. So while adherence is relatively poor anyway, if we are seeing some benefit from a ketogenic or low carb diet in terms of adherence rates, then it's certainly no worse than another diet in terms of being hard to stick to. And I think there's an interesting tangent within that; well, there's actually two really, two threads within that. One is that if you start to pull that apart, it's probably fair to say that people with metabolic syndrome or people who are more insulin resistant probably have a harder time sticking to high carb low fat dietary regimens. And so, they typically have better adherence rates from low carb and keto and they're probably going to actually benefit from those most as well. And so that could be skewing the numbers a little bit, so those most at risk and who would most benefit from a low carb diet tend to actually adhere to it that little bit better.

The other interesting thing is we noticed within one of our qualitative studies something that we need to do a bit more research on, but we noticed this sort of behavioral pattern that

seemed to exist between people, and it was the pattern between what we called abstainers and moderators, and the abstainers were those people who behaviorally and psycho emotionally, psychosocially were much more likely to have problems with sugar in particular, but sugar and carbohydrate overall. In other words, they felt that if they resumed eating sugar or resumed eating carbohydrate, then it would be a slippery slope and they simply wouldn't be able to stick to it. And so, for them, the abstention idea was very powerful, and it actually made things quite easy for them because they would basically just look at this compendium of food that they had which was, okay, I can eat this stuff, which was all the low carb foods and I simply don't eat any of those carbs, and they found that quite easy to get through their heads, that was quite easy for them to understand. On the other hand, we had people who we classed as moderators, who, although they enjoyed the process of being in a ketogenic diet study, at the end of it, they were reporting, well, I enjoyed this but I'd like to go back to adding in just a bit of carbohydrate, maybe some whole grains, some legumes, some yams, whatever it happens to be; and I feel like that would actually help me to stick to this for the long term.

So two quite clear behavioral patterns. So I think there's a couple of things going on, we basically got the physiological drivers that maybe we benefit from particular diets and we actually stick to them better anyway, but also the behavioral side of things in which we just have a compendium or an idea of food that we can understand better and we can stick to better and that doesn't have a lot of those habitual drivers that are really compulsive or obsessive for us.

DANNY LENNON: I think even beyond that, with any conversation around adherence to dietary interventions, I think trying to narrow that down to say what macronutrient breakdown is best for adherence is kind of missing the bigger picture that the

things that really determine that are probably going to be outside of specifically the nutrition I think in a lot of cases. So when you compare diet studies that have say a behavioral component, a social support component, checkins with practitioners versus just recommendations for people to go and do themselves, you just see completely different outcomes in terms of adherence to the diet regardless of the diet strategy itself; and so that's why I think maybe if people look at the Virta Health trial that they did, one of the big successes of that is – again, we can largely look at the kind of nutritional component but also you have a program where people have opted in themselves, have this massive amount of support, have accountability or are paying for a program, and so all these things make up factors that relate to the adherence and probably success of a dietary intervention, right?

CLIFF HARVEY: Absolutely. I think that holistic view that the client, let's say, in a clinical setting or even more appropriately that the holistic view of just us as people, is critically important; and unfortunately, people sort of turn away as soon as you start to say holism because they think you're talking about kaftans and [inaudible 00:25:29] and things like that. But really, what we're looking at there is the whole person and what helps them to achieve the human potential. But yeah, it's a very interesting thing, because we obviously need to have those other aspects that are part of our food and overall lifestyle environment. But I think that also marries up with the physiological drivers as well, and one thing that certainly should be mentioned is that even with adherence, as it relates to outcomes, I think we're often missing a lot of the important stuff there as well, particularly, people's vegetable intake, nutrients' efficiency and protein intake. Because of course, if we have, you know, we could have a diet trial that's basically designed to fail in which people are simply not eating enough nutrient dense plant matter, let's say,

and also not enough protein, and they're probably not going to adhere all that well because they're simply not satiated. So I think the autoregulation of energy that's provided by nutrients' efficiency and protein is critically important, and that's why, when we start to pull apart particularly the big observational studies that are often very conflicting, take the ERIC Cohort, all the studies that came out of that versus the PURE study, everyone thinks they're showing very conflicting results. One sort of favors low carb, one favors moderate to high carb, but really, they both actually favor a diet that's based on natural unprocessed food and the rest is just noise.

DANNY LENNON: One thing I did actually want to pull back on that you had mentioned previous to that along with the adherence piece was you talked about carbohydrate restriction and impacts on body composition and how you felt there was actually a slight advantage for low carbohydrate diets in that sense. Just to confirm, is that looking at things, kind of pragmatically differences and/or physiologically, so is it down to differences in whether people have more satiety, they stick to it better, etc., or if were to narrow things down to, let's say, an energy intake matched situation, do you still think physiologically potential superiority for carbohydrate restriction at least in some folks?

CLIFF HARVEY: I think it certainly can be, and that is borne out by the research, and particularly when you look at subgroup analysis, we are comparing say higher carb versus lower carb and then the subgroup analysis also includes very low carb. I think we do see greater improvements in for fat loss and more ancillary benefits as well. So a slightly greater effect for fat loss and more ancillary benefits in terms of blood glucose control and reductions and triglycerides and things like that. But the important thing, the important point that needs to be made is that these studies typically look at people with obesity or overweight or who are metabolically

disordered, and so it's likely that there will be a greater benefit from low carb anyway. When we look at gen pop, I think we still see some persistent benefits from low carb for fat loss; but when we're starting to look at athletic populations, I think that effect is probably going to fall to nothingness, and it may even start to go the other way because although the diet fits trial which is probably the biggest of this type didn't really find any difference in outcomes based on insulin homeostasis, the four previous trials had found some difference, and we certainly think that if we look at our data for example that there probably is some difference there as well. So someone's insulin homeostasis or their relative insulin resistance versus sensitivity at baseline is likely to have some effect on that, but obviously it comes down to outcomes based dieting, right, and I think it's important to also mention that while I would say that on balance I think that low carb is probably still going to give superior benefits for fat loss for a lot of people, I would also say, conversely, that a higher carb diet I think is going to give increased benefits for people for muscle gain. So we really need to look at what the desired outcome is when we talk specifically about body composition.

DANNY LENNON: So mechanistically, in that sense, if were to be able to control tightly someone's energy intake, what is it that's leading to maybe an increased energy expenditure or at least less of a drop in energy expenditure in the low carb group that would infer those potential benefits?

CLIFF HARVEY: If we're looking at a completely – if we're looking at complete energy balance and protein matching, there's probably going to be very little difference, but there might still be an increased rate of fat loss in a lot of people, particularly those who are more insulin resistant, and really that just comes down to that there's likely to be some increase in metabolic activity from a low carb diet even when matched for calories. And I know that's contentious but there was the recent study that

sort of showed that, and I thought it showed it quite well. But also I think that people who are more insulin resistant are simply going to have more problems with the whole milieu of biochemical things that are happening in response to insulin. Now, we all know that the insulin hypothesis is very limited and it's very flawed in the way that most people think about it, but there are still going to be effects there particularly with respect to the ability to release adipose tissue – sorry, release stored fat from adipose tissue as compared to the typical approach that most people take when they talk about insulin which is that it's simply a storage hormone. Probably its biggest role is to inhibit a better glucose output but also to help inhibit that release of fatty acids from adipose tissue. So where we have that, we can have more of a resistance to fat loss rather than an increased tendency towards fat gain.

DANNY LENNON: So one thing that I did want to mention before we get into some of the neuroprotection brain trauma area was just to touch on one of the papers that you were actually the lead author on that I think came out earlier this year, fairly recently, looking at the impact of low carbohydrate diets that had different levels of carbohydrate restriction and how that impacted some cardio metabolic markers and I think also body composition as well. Can you just give a kind of brief overview of that study design and what you are aiming to look at?

CLIFF HARVEY: Yeah, so basically we wanted to look at any differences between three different low carbohydrate diets, so we had one sort of non-keto or moderate to low carbohydrate diet was 25% calories from carbs, the low carbohydrate diet was 15% calories from carbs, and the very low carb ketogenic diet was 5% calories from carbs. So they were basically habitual calorie diets, so we measured the – it was from reporting that we calculated the habitual energy intake of the participants over a week and then had them stick to that, so they were basically eating their habitual calories within

protein matched all the group, so they were eating about, I think, 1.4 grams of protein per kilo body weight per day. So if protein sufficient diet and then the rest was basically made up from their carb allocation and the rest from lipids. So we really just wanted to compare those low carb diets because it simply hadn't been done, it was the first study to actually compare different truly low carb diets. And what we found over a 12-week period that there was not a lot of effect between the diets to be honest but the trend was towards greater improvements in the very low carb group, so greater weight loss, we didn't measure anthropometry unfortunately, but we just measured weight, so greater weight loss, greater improvement in various cardiometabolic measures like triglycerides in particular and the highest or greatest increase in HDL and things like that.

DANNY LENNON: With that, what was the calorie intake like across the study, was there differences between the groups in how they were able to stick to what they were assigned essentially?

CLIFF HARVEY: Not with respect to calories, the calorie intake was obviously per individual but there was no real difference between the groups for there. There was, interestingly, the very low carb group, it was reported in the media a little bit that the very low carb group had trouble adhering to the diet, because they were supposed to be at 5% calories from carbs obviously. Now, the main carb intake for that very low carb ketogenic group was actually 8%, so they weren't hitting their targets; but within the 95% confidence intervals, they were still fairly well-distributed, so they had a fairly narrow range there, so we could conclude that although the spread was slightly greater in that very low carb group, it was not significantly different to the other groups. So what I'm getting at there is although they hit that 5% mark, they were fairly consistent around 8%. So we looked at that slightly differently to a lot of people because the 25% calories from carb

group were just under there. So, in other words, they adhered fine. The 15% calories from carb group were just under that as well, so they adhered fine. The 5% group were at 8%, but relatively consistently. So we looked at that as being, well, they aspired to 5%, they couldn't quite hit it because it probably is too restrictive, but in attempting to hit 5%, they had 8%, and if they got better outcomes overall, then maybe the aspiration to that greater carb restriction actually does have some worth. Now, because the effect size between the groups was relatively small, I'm not going to hang my head on that, but if someone did want to get the absolute best benefit and I knew nothing else about them, particularly with respect to weight or those key markers like triglycerides in particular, then we might go lower up than more moderate.

DANNY LENNON: Right. So yeah, that's a good point, because it wasn't like they had got down to 3% and then over the course of study it was getting worse and worse. Like you say, it's consistent across, it shows that it's not really a loss of adherence over time, it's like that was the lowest that was pragmatically achievable I guess.

CLIFF HARVEY: Yeah, and that probably comes from our guidelines as well. We do like to give people good healthy nutrition plans irrespective of the sort of carb content. So although we're circumspect about the vegetable intake and things like that, we want people to try and eat the recommended amount of vegetables, for example, for health, because we want to compare three different healthy diets, because otherwise we're sort of designing to succeed sort of thing. And that probably made it more difficult for people as well, because there's obviously less leeway at that very low in there at 5%; and we would know pragmatically, like, you and I, as practitioners, would know pragmatically that achieving 5% or even achieving certain gram quantities of carbohydrate is completely unimportant

anyway, the context of the diet is so much more important.

DANNY LENNON: What was the deal with people's typical habitual diet before getting into the study where they are all on a more moderate to higher carbohydrate intake, was there people that had done low carb diets before, what do we know about their habitual diet?

CLIFF HARVEY: So we excluded – there was no, from what I remember at least, there was no significant difference between the diets beforehand. The participants were excluded if they had been on a low carb or keto diet previously. But having said that, most of the participants were not on what we call high carb diets anyway. Again, I think from memory, that the habitual diet was typically around sort of 40 odd% calories from carbohydrate so that would be considered by some people to be low carb. I wouldn't consider it low carb, but that's a pretty common thing I think we're seeing now is that people's carb intake has drifted back a little bit anyway, and I think without the demographic that we had access to, you know, we're based on the North Shore of Auckland, it's a relatively affluent area, we had a population that was skewed a little bit more towards females, I think there is attention paid to carbohydrate even if people aren't on low carb diets per se, and there's also I think with the more affluent populations and particularly those who weren't overweight. So this wasn't a weight-loss study obviously, because it was a habitual calories, but we also excluded people who were obese and overweight actually. So we were basically looking at healthy normal populations who are probably more likely to be in that more moderate range anyway, and a lot of them nowadays are starting to restrict carbohydrate without really realizing it. So it was a fairly modest restriction of carb for that, let's say, 40 to 25% group.

DANNY LENNON: With those people that you feel would get a benefit from carbohydrate restriction, do you

see that as a linear scaling relationship of, as you restrict the carbohydrate, as you do that, you are getting more and more benefit, as you go along, or is there kind of a certain threshold point that some people would need to pass that they need to get under in order to get some of those benefits – and again, I'm sure that's context dependent on the person, but how would you kind of think about, is it kind of a linear or a threshold kind of concept.

CLIFF HARVEY: It's a really good question because I think it really does depend on the individual, because we will see people who get anomalous results, we will see people who will maybe get worse results going on a lower carb diet and that goes the other way. So they basically, the more they restrict carbohydrate, the worse their results get. Now, why is that? Is that because of the other stuff that's happening? Is that because it's not good for them behaviorally, and they are actually not being adherent? We don't always know exactly. But I would say, overall, if I could point to a trend, it would probably be that there is a linear – I'm going to get hammered for this I know – but there probably is on balance, across everybody, a linear trend towards improved results. But it's so small as to I think being consequential. Now, again I'm talking about particular results, fat loss and improvements in triglycerides and other key markers like blood glucose and HDL and things like that.

DANNY LENNON: When we, or, at least I think in a fair chunk of trials, looking at low carbohydrate, high fat diets, where we do see improvements in many cases and things like blood glucose, insulin, triglycerides, like you say, the one that tends to go in the opposite direction tends to be LDL cholesterol. What did you see in your particular study, was there any significant change or differences between those groups in terms of LDL cholesterol?

CLIFF HARVEY: Yes, so the LDL and total cholesterol did go up. So they basically went up and they went up at

least in the moderate low carb group, but interestingly they went up most in the low carb group, and there was a smaller increase in the very low carb group. So in this, you know, it's obviously just one trial, but in this one trial, we didn't see a linear effect there. So I'm not sure why that is, that could just be an anomaly again, but there certainly wasn't a consistency via the other way in the same way that we might have seen somewhat of a linear trend for, I guess, the positive trends.

DANNY LENNON: We could get more into the whole LDL thing, but I think that would be probably another hour in itself. So for the sake of time, something that we chatted over briefly, given our mutual interest in combat sports, was nutritional interventions and how they may relate to traumatic brain injury; and here is one of the areas that, as you mentioned before, ketosis and even the use of exogenous ketones are discussions that are starting to be had by people. So when it comes to a traumatic brain injury, at least from my understanding, one of the reasons why we might look to something like a ketogenic diet or supply of exogenous tones is that in the aftermath of a traumatic brain injury we see that that neurological tissue can become quite insulin resistant, is that accurate?

CLIFF HARVEY: Yeah, certainly, it can become insulin resistant and the glucose transporters themselves can become damaged, the blood-brain barrier can become distorted – it often is in the case of a concussion or traumatic brain injury and that allows long-chain fats that wouldn't typically get into the brain to get in, and that can create additional hypoxic damage. So basically by having ketones available, we allow a non-glucose feel, so it's not dependent on those glucose transporters, they can help to displace long-chain fats if they have gotten and therefore it helps to reduce that hypoxic damage, and we also then see the other ancillary benefits. So again, it's the other stuff that we would think is important in preventing

your neurodegenerative disorders. We see things like reductions and oxidation in the brains for increase glutathione; we see reductions and inflammation which is obviously part of the secondary damage that occurs with concussion, and reductions in that, particularly glutamate driven excited toxicity, which can really ramp away in the sort of secondary phase of concussion as well. So there's a lot of different things going on and it all sort of points towards their being utility from these ketone bodies plus of course there's evidence to suggest that the ketones will help directly with neurogenesis anyway.

DANNY LENNON: So one area we could look at would be that impact on say neuroprotection or kind of use of a ketogenic diet kind of prophylactically in terms of some of those things like neurodegenerative diseases, prevention, and so on. On the other side what I'm going to try and get to here is on a more acute setting, trying to look at the impact immediately either in and around a period when there's likely going to be a concussion or traumatic brain injury or a period directly after; and I think, one of the examples I'd given to you is if we have an athlete who competes in combat sports, in most cases, we could say they're going to probably benefit from a decently high degree of carbohydrate, particularly when they're trying to aim for high-end performance at certain times, and so, maybe a continued ketogenic diet is kind of off the table; but if they've just had a fight, for example, and now they enter a period where they've maybe taken a significant degree of head trauma, and again, we probably have to speculate on some of this, but what would you think is a fairly useful intervention that mechanistically would make sense for someone in that position?

CLIFF HARVEY: I think we take a step back and again unpack the utility of ketones from the ketogenic diet a little bit. The reason I say that is, back in the early days, we're talking 20 to 25 years ago here, we kind of used to think that ketosis was

this on/off switch, you know, you restrict carbs enough and suddenly the body starts to produce ketones. And of course, we know, that's not the case. The body is always producing and using ketones. And so, for your typical person who is eating a high carb, maybe ultra-refined type diet, you'll still measure their blood and see maybe 0.1-0.2 millimoles. What we often see with people who are eating a diet that is more based around natural unprocessed foods is typically they're a little bit higher anyway, so let's say, 0.3-0.4 millimoles beta hydroxybutyrate. So the interesting thing there is there's still going to be increased beta hydroxybutyrate which is giving some protection, some sort of prophylaxis. Now, I think we can also, even within the context of maybe a moderate or higher carb diet, still have slightly higher ketones than that if we use, for example, MCTs. And that provides, for a combat sport athlete, just that little bit of extra ketone based protection, because, I think, rather than just looking at it as a reaction to concussion, we do want to look at the prophylaxis to the concussive damage as well.

One thing that a lot of people are also doing now is to take exogenous ketones, both before or during the event, and I don't think there's any contraindication to that even if you are on a higher carbohydrate diet, because ketones plus carbs actually provide for a pretty interesting mixed fueling strategy, and it can improve glycogen repletion post workout or it can help to spare glycogen and all sorts of things. So a lot of the research where people actually see benefits for performance from ketones, it's not because of the ketones per se, it's ketones plus carbs. But certainly, if someone does get a knock to the head, then I think immediately, I mean, with my athletes, I certainly apply ketones immediately, and we continue to do that for several weeks. So we'll look in the post concussive period at probably a diet that is slightly lower in carbohydrate than what they're habitually on, we would definitely apply MCTs as a foundation for ketogenesis,

we'd apply exogenous ketones as well on top of that. And obviously, given my naturopathic background, again, I'm going to get lampooned for that, but, because of my naturopathic background, I'm pretty into medicinal mushrooms as well. So we use lion's mane a lot because of its fairly well-proven effects on neurogenesis now.

DANNY LENNON: Yeah, lion's mane was one that you had mentioned to me when we talked, and indeed after kind of looking at it, we do actually see some pretty good evidence around its efficacy, right?

CLIFF HARVEY: Yeah, and, I mean, it's across the board, it started off being very promising, and now we've got functional human trials and things that show some pretty extraordinary benefits for cognition and for, like, say, neurogenesis and things like that. Of course, it's not proven beyond a doubt, but we certainly see enough levels of evidence that it's very promising. And given that there are other ancillary benefits from not just lion's mane, but lion's mane and the other medicinal mushrooms as well, and they've got such a long history of use without any significant contraindications that I can really find, it kind of makes sense, you know, if you've got an athlete that's at risk, you basically might as well. And we've seen pretty profound effects in post TBI using that combination therapy, MCTs, exogenous ketones and lion's mane, and we've even been trialing some interesting combination therapies for other conditions as well, utilizing lion's mane. So I'm a big fan.

DANNY LENNON: Yeah, and I think that's the thing, when you're working in practice with a combat sport athlete and there's as much on the line as brain health, then, to a certain degree, there's certain tradeoffs you have to accept, maybe it's probably not a good idea just to wait around for more definitive evidence if we have something that has a pretty low risk profile, like there is going to be no inherent harm that I'm aware of

that's going to likely come from having some lion's mane mushrooms or other mushrooms. With that presumably at that acute phase, if that's done supplementally, do you include many of that within the diet in the long term for certain types of athletes or how do you incorporate that?

CLIFF HARVEY: I certainly, I mean, I'll definitely use those things in the post-concussion period, but habitually, yes, I quite often have people taking MCTs, just because I think if, for example, we're going to be adding oils to a diet, let's say, in a smoothie or something like that, I figure why not because it does have additional functional benefits; you know, while I don't think that MCTs are magical either, I think when you compare them to other roles that you could be adding to provide for their lipid based fuel, there are some benefits there; they're basically displacing other fats that don't have the same effect on fatty acid oxidation and they certainly don't have the same effect on ketogenesis and things like that. Exogenous ketones, I typically don't apply across the board because some people, if they're on a higher carb diet, they simply may not benefit from them as much. However, if people are on a lower carb diet or they've had significant brain injuries in the past, then they often can benefit from exogenous ketones habitually as well, but only as a tool, not taking them every day necessarily, it's more when they feel they have brain fog coming on or we've been trialing it with migraines as well, so when they feel the sort of the pre-effects of a migraine to try some exogenous ketones in that state as well. And the mushrooms, I don't necessarily prescribe them across the board habitually for people, but I certainly talk to my clients about them because I just think they're fascinating; and I think the range of mushrooms that people can take that have a large number of health benefits, it's pretty interesting stuff. So we'll look at all sorts of things from quarter sips through the lion's mane, shiitake, reishi, chaga, Turkey tail.

And I'm actually about to publish a medical case. I had a young client with autoimmune hepatitis and there's basically no research on it, particularly, with respect to nutrition and supplementation. But there is some fairly interesting emerging research on liver disease and certain mushrooms like chaga and reishi, and we couldn't really get any movement forward with this case; and obviously, the docs were wanting to put him on some pretty serious immune suppressants; and so, we basically asked for some time and they were happy to give us that to try some other things. And so, I put together a combination treatment which involved nutrition and things like that, we weren't really getting enough movement forward still. And so, I applied relatively high dose mushrooms, particularly, chaga and reishi, about 3 grams plus per day of mushroom powders, and his liver enzymes started to fall immediately, and now he's just about to get off all of the last residual meds and his liver enzymes and all his immune markers are within range. So it's pretty interesting stuff. Now, it could just be placebo, it could have been what was going to happen anyway, I'm not sort of going to, you know, again, pin my head to this, but it was certainly a very interesting turnaround. So I think we need to do a lot more research in that area.

And some of these things that are done in clinical practice, I think, that one of the reasons I really want to start publishing a lot of these medical cases, obviously, it doesn't provide for any sort of unequivocal proving, it's certainly not there, but it generates hypotheses so that then we or others can go on and do the proper clinical trials to demonstrate whether this is actually in effect. I think that's important, because otherwise we're losing so much data there, and we're losing so much that could drive really interesting research.

DANNY LENNON: And with something like a concussion or head trauma after a sporting event, if someone did

want to try to implement some of these potential strategies, supplementation wise, is there any general dosage and frequency recommendations you would give for either the exogenous ketones or, let's say, they go to the lion's mane supplement or so on, is there any kind of things they should be, as a starting point?

CLIFF HARVEY: Yeah, I would typically give people as the foundation, MCTs, and I typically would titrate the dose up from one teaspoon three times a day, and then add one teaspoon at each of those servings until the person was up to about two tablespoons. But in the case of post-concussion, you do want to jump in a little bit deeper straight away, so it's that's with the tablespoon three times a day and then try and get that up to two tablespoons three times a day, just to provide for baseline ketone production. On top of that, I'd be looking at 3 grams per day of lion's mane or equivalent, so that might be 3 grams equivalent of mushroom powder with a liquid tincture for example. You can get liquid tinctures that have 1 gram equivalent per 2 milliliter serves, so basically that have about 3 grams per day. And in terms of exogenous ketones in the immediate post-concussion setting, assuming the client can afford it because they can be quite expensive, I'd be looking at around a 5 to 10 gram serve of beta hydroxybutyrate three times a day and then tapering that back to say two times a day after the first couple of weeks. And after about four to six weeks, I'd probably drop that back to just when that the client felt they needed it most, so if they are experiencing brain fog or brain fade or anything like that.

DANNY LENNON: One thing to kind of round us out with this kind of discussion that we've got into some of these different areas of research, and you've mentioned some that you're particularly interested in, going forward, over the next number of years, what do you think are some of the most interesting research questions related to ketogenic diets, ketosis, carbohydrate

restriction, whatever you feel that are most intriguing to you, what are those kind of big research questions?

CLIFF HARVEY: I think, specifically related to low carb and keto, I think it's going to be the continued exploration of neurodegeneration, and then it's starting to progress very rapidly now into depression and bipolar disorder and those other mental health challenges. So I think in terms of that area, that's going to be most exciting and I find that most exciting. But overall, I hope that people are excited about the more boring stuff actually, because, one thing that I'm a real fan of is getting into these studies, particularly, the observational studies and trying to pull them apart and see what the real commonalities in good diets are. And it's getting back to those basics of natural whole unprocessed foods; and when we're eating those as the basis of our diet, the foundation of our diet, the rest, with the people, for most people most of the time, whether they're eating slightly higher carbs, slightly lower carbs, whatever, it doesn't really matter too much. Now, I'm getting to my big point here because I think that we need to start moving beyond health and beyond nutrition. We are so focused in this modern world on food, on nutrition, and on health, whether we're achieving it or not, that's seen as being the goal. But to my mind, health is not the goal. If you suddenly achieve health overnight, you're not necessarily going to be happy.

So I think if we can start to look at research, and at narrative, at media that helps people to look beyond these things, while we still want to achieve health, health is the foundation of us being able to achieve our human potential, and that's so much more than health, that's about pursuing things that we love and being creative and pursuing them with passion and being purposeful, all these cool things that basically might make life worth living. And so, that's why I think if we start to move more into that and experiment and research that a bit more, we're

really going to start to open the doors to just greater human potential overall. And so, I want to really become more involved again as I was in my early post-grad journey actually in the mind-body healthcare research, particularly looking at mindfulness and things like that; but also getting on board with a lot of the research that's happening now into psychedelics and other things that can really help to improve human potential, and, in the same breath, sort of counter a lot of our mental health challenges. So hopefully that wasn't too much of a tirade, but I got there in the end.

DANNY LENNON: No, I'm so glad you mentioned it, because, when some of these things aren't considered, trying to talk about eating more vegetables, it's kind of a pointless kind of thing or just from a diet, and they're really important, and they can play a role here for sure, but there's these big fundamental pieces that are going to take a lot more than understanding what good nutrition is and are going to be far more profound I think on long-term health. And so, yeah, I'm super excited, you said that. Cliff, for people who are no doubt going to want to follow up on more of the work you're doing, check out what you've got going on, follow you on social media, all that type of stuff, where is the best places on the internet for them to go and find you?

CLIFF HARVEY: The best place which is the hub for all my stuff they can find my social and everything else there, it's my website cliffharvey.com.

DANNY LENNON: Awesome. With that, Cliff, we come to the very final question I always end the show on. If you could advise people to do one thing each day that would have a positive impact on any area of their life, what would that one thing be?

CLIFF HARVEY: That's a great question Danny, because my answer to that has changed in the last couple of weeks. If you would have asked me that two weeks ago, I would have said, meditation. But right now, I think I'd say go for a walk in nature every day, because I think by virtue of the

activity that's bringing mindfulness into your life anyway, and I think we're beginning to see now the extraordinary benefits of being out in nature and being mobile in nature, because we're getting a combination of things from movement through to the direct effects of being in a natural environment, through to the sort of transition into mindfulness that walking in nature often propels anyway. So, I would say, if people did one thing or added one thing to their daily regimen, it would be going for a walk in nature every day.

DANNY LENNON: Cliff, let me say, just thank you so much for giving your time today for the amazing conversation and then just the continued work you do, it's been a pleasure chatting with you my man.

CLIFF HARVEY: Thank You Danny, I've just knocked off one of my other life goals being on the podcast with you.

DANNY LENNON: Glad we can make it happen, my man.

CLIFF HARVEY: Awesome. Thanks buddy.

Support Sigma Nutrition on Patreon!