DANNY LENNON: Hello, and welcome to another episode of Sigma Nutrition Radio. This is Episode 385 of the podcasts. My name is Danny Lennon, I'm here with Alan Flanagan. Alan, how are you today, sir?

ALAN FLANAGAN: I'm great, I'm good, I'm slowly getting back to normal. What is it? Day eight, day nine now of into this study that I'm running at the minute. So, so far so good, great compliance from participants, which is wonderful.

DANNY LENNON: Excellent. And yeah, you're still recruiting people for this study. So maybe, for people listening, because I'm sure there's a significant number who are based in the UK from which you are going to be recruiting from, can you maybe, first maybe mention what the study is, but then, for anyone who might be interested in becoming a participant, give too many details there too.

ALAN FLANAGAN: Yeah. So the study is looking at the relationship between meal timing and someone's time of day preference. So people tend to either have a preference for kind of being what's colloquially known as a morning type or a night owl, and there is also a relationship between that, your time of day preference, and what's known as

social jetlag, which is, maybe the discrepancy between how much you get to sleep when you're free to choose your sleep-wake cycle, versus how much you actually sleep when you have to get up for work, and all this kind of stuff. So we're looking at the relationship between those factors and meal timing. It's all observational, so there's no lab visits or anything, people complete it at home using an app where it's very easy to use. You take a photograph of the meal that you're eating and it will timestamp that meal, and then you export it in a PDF, and we get the PDF, and we can know that breakfast was at 8:36 a.m. or dinner was at 7:45. And then the app allows you to add some detail in terms of the composition of the meal or what foods you had. So it's going well so far. We are keeping recruitment open until, well, later in the fall. So if anyone is interested, then, yeah, get in touch with me, my university email, which I guess you could put in the show notes maybe. And yeah, just send me an email, and we can take it from there. There's a baseline screening health questionnaire, which I imagine, pretty much every Sigma listener will pass, and then we've got some baseline questionnaires, and then we do the two weeks of tracking diet. So yeah, for anyone interested, get in touch, and we would be happy to have you on board.

DANNY LENNON: Excellent, yeah. So contribute to some science and get in touch if you are based in the UK. So today's topic, we're going to tackle insulin resistance, and then we'll also look at the role of diet not only in driving or progressing that forward, but also then for someone with established insulin resistance, what dietary modifications may be helpful. And so, we're going to try and walk through some of that stuff. This is, of course, an area where there is much misinformation or at least very reductionist simplistic advice, and often when one hears the term insulin resistance, we've kind of been conditioned to think of, oh, that's a blood sugar problem, so therefore it's just all about carbohydrates and sugar, and that's the

cause. So hopefully, we'll try and walk through some of this. I suppose from a starting point, it might be worth mentioning why we think of insulin and blood glucose in the same conversation, or essentially, when there's insulin resistance, why is blood glucose regulation going to be problematic. And, of course, I think maybe the notable thing to know here is that insulin has many roles, in many ways, it acts to reduce blood glucose. So primarily, we can look at, it will inhibit blood glucose secretion at the liver, for example. But also that has other mechanisms, for example, increased glucose disposal into a muscle or fat cell, all connecting together to lower blood glucose as needed. So if there is dysfunction there, and there is a resistance from cells to the action of insulin, we're going to have problems regulating blood glucose.

ALAN FLANAGAN: Yeah, and I think it's that idea that we do, obviously, think of glucose and insulin together, and we should in many respects, but the actual factors that lead to insulin resistance are more complex than just the role of blood glucose specifically and of carbohydrate in the diet. And insulin is quite interesting in terms of our kind of evolutionary mechanisms that we've evolved to maintain homeostasis in different physiological parameters, blood glucose being one of them, that there's a number of mechanisms, whether that's glucagon, or catecholamines like adrenaline, or cortisol, that can all raise blood glucose levels when they go low. And the evolutionary speculation here is that the danger of hypoglycemia would have been more of a persistent threat than hyperglycemia, during periods of evolution and scarcity of nutrient availability, and potentially carbohydrate. But when we fast forward to today's environment, that shifts the landscape a little bit. So we have a number of these processes by which we can raise blood glucose levels, but insulin is the only mechanism by which we lower blood glucose levels. And so, it takes on quite an important role in that capacity in the context of

factors like over nutrition, energy excess, and yes, other related dietary components, whether that's sugar or fat, and we'll get into some of these other macronutrient considerations later, because it goes beyond a purely glucose centric approach.

DANNY LENNON: Yeah, and I think that's going to be crucial to essentially understand that insulin resistance, is this complex metabolic disorder that goes beyond any single pathway. It's not just this one thing, there are many things involved. So if we start working through these, probably one that I think is at the center of many of the things that we'll probably discuss later is the accumulation of ectopic fat that occurs and how that leads to then more downstream problems. For example, that's also going to relate to those changes that we see in fatty acid uptake, lipogenesis, potentially change in energy expenditure, and all those things then in turn can also impact ectopic fat deposition. So from that perspective, this is where I think the important idea that lipids are clearly associated with insulin resistance starts to emerge, and moving away from that glucose centric idea.

ALAN FLANAGAN: I think a good point of departure is probably the liver, because of our understanding of the metabolic complications that result from a state of fatty liver. And once fatty – by fatty, we mean excess or accumulation of triglycerides in liver cells that corresponds to around over 5% of liver cells with an accumulation of intracellular triglyceride, intracellular fat. But a fatty liver is resistant to the action of insulin in suppressing glucose production in the liver. So you mentioned one of these important roles of insulin, well, although we tend to, and I think when most people hear insulin resistance, particularly those that are interested in kind of sport and exercise nutrition, they'll think of peripheral insulin sensitivity, insulin sensitivity and muscle cells and glucose uptake therein. But insulin resistance in the liver is a particularly problematic metabolic

complication of fatty liver, because there's a number of consequences, one is this inability to suppress hepatic glucose production. So in a normal postprandial response with healthy functioning insulin, insulin is acting to dispose of nutrients from the meal, but it's also suppressing the capacity of the body to produce further insulin. Whereas with the state of fatty liver at the end, the liver is continuing to produce glucose even though there's glucose exogenously coming in through diet, and so you end up with an exacerbation of elevated blood glucose levels, hyperglycemia, you end up with elevated insulin levels as well, particularly in the fasting station, fasting insulin correlates very closely with liver fat content.

So as the liver becomes increasingly full of fat, you get higher baseline fasting insulin levels. But what's the consequence from postprandial metabolism is that this state of an insulin resistant fatty liver also impacts on postprandial fat metabolism, and you get an overproduction of very low density lipoproteins in the liver as a result, to deal with an increase in triglycerides. And one of the reasons why there's this upregulation in triglyceride synthesis and VLDL triglyceride synthesis is because of elevated circulating non-esterified fatty acids or free fatty acids. And this is a consequence of hepatic insulin resistance, so you got this insulin resistant liver, and as a result, fatty acids can't be disposed of, and there's this elevation in circulating free fatty acids that, in and of itself, exacerbates things like peripheral insulin sensitivity. But you get this knock-on effect of increased triglycerides and very low density lipoprotein synthesis, and that VLDL is then exported from the liver, laden with these triglyceride, and there are knock-on effects of that even in terms of creating, for example, downstream small dense LDL particles and all of these kind of metabolic consequences that come from an increase in deposition of fat in the liver and the

consequent insulin resistance in the liver that results from that.

DANNY LENNON: Yeah, there's a number of really important points there, and I think just to clarify for people earlier, when we mentioned this phrase ectopic fat accumulation, ectopic fat here, we're referring to essentially the storage of those triglycerides in tissues other than adipose tissue, and these tissues that normally would only contain a small amount of fat. So Alan here has mentioned the liver. We could be talking about heart, pancreas, skeletal muscle, etc., where we get excess accumulation in those places. And just also as a point of reference for more on fatty liver, specifically, Alan authored a Sigma statement that's available on the website that goes in depth on that. But as you just noted, we have several studies that all kind of corroborate this strong association between non-alcoholic fatty liver disease and hepatic insulin resistance. And some of what you were saying there also ties into the kind of twin cycle hypothesis that Roy Taylor talks about – again, that was referenced on the podcast before that people may remember, but I think we'll probably mention that at some stage as well, where we have that kind of feedback you just mentioned that relates to the liver and also ends up tying in the pancreas as well. And in those cases, then we see the kind of ultimate downstream effects of development of type 2 diabetes, and that getting worse and worse.

ALAN FLANAGAN: Yeah, the twin cycle hypothesis, you have the previous episodes, I can't remember the number, with Roy Taylor, which was fantastic, where he goes into the development of this hypothesis, where what we've been discussing so far is the accumulation of fat in the liver. But there comes a point when there is spillover from – and the liver tends to be the first visceral organ that starts to fill with fat, just because it’s a primary site through which nutrients, fat and carbohydrate are metabolized postprandially, but you have to spill over then into other organs and the

pancreas and you have an accumulation of intracellular fat in the pancreas that also then impairs and exacerbates the decline of the capacity of beta cells to produce and secrete insulin in response to rising blood glucose levels. And then, there's also, and you mentioned, skeletal muscle as well – there's a relationship again between the increasing fat depose within skeletal muscle which there is an extent of and that can relate as well to impaired insulin signaling and resistance. So across the board really, in terms of these various metabolic organs and tissues that we would associate with proper postprandial metabolism, and I say postprandial specifically because it's removing this conversation away from just a purely glucose carbohydrate centric view, is, it's a complex interplay between particularly carbohydrate and fat in the diet and the capacity of dietary fat to influence some of these processes. And some of the tightly controlled feeding studies that we looked at in that statement on nonalcoholic fatty liver disease, for example, have clearly showed that in conditions of energy balance, then dietary fat, saturated fat, in particular, will increase liver fat to a much more pronounced level than even simple sugars. So there is relevance for nutrient balance and subtype in this conversation as well.

DANNY LENNON: And that's actually crucial, because we're obviously going to talk about the importance of a calorie surplus and excess fat accumulation in general, which also is going to increase risk of some of these things. But as you know, some of those other factors outside of energy balance can be problematic. And actually, one of the extreme examples I remember reading about was in cases of people with severe congenital lipodystrophy, where these are individuals that have little to no adipose tissue really, and they store lipids ectopically, so in all these other places that we've just referenced. And, as a consequence, they end up developing hepatic steatosis, hepatic insulin resistance, and you end up having this hepatic or liver insulin

resistance, and therefore development of all those kind of comorbidities that we just mentioned as well, which is kind of just an interesting kind of side note. But in relation to the twin cycle hypothesis, and as a kind of summary, I think we can think of that chain of events being at the start, typically, it's going to be positive energy balance, there's going to be some degree of liver fat accumulation that leads to this liver insulin resistance. We get an increased baseline instance secretion because of that. That further increases liver fat. And we have insulin stimulating the conversion of glucose to fat in that case. That leads to increased blood glucose. The higher blood glucose has further insulin secretion, and more liver fat accumulation, again, this idea of it being a cycle, because we're causing this more and more. And with the increased liver fat, then we get that increased VLDL triglyceride production that Alan mentioned, that in turn can lead to this increased fat accumulation on the pancreas, that causes decreased beta cell function, that increases blood glucose, and then you have all these cycles continuing to turn, and things just getting worse and worse, essentially.

So with that, maybe let’s look at some of these potential drivers, from a nutritional standpoint. If we maybe talk first an energy surplus and then fat mass gain, clearly being a driver, if we have excess fat accumulation, because a certain degree of that is likely to appear in some of these ectopic regions. And then maybe afterwards, we can talk about the development of insulin resistance potentially without excess weight gain, or at least that is noticeable in a lot of cases.

ALAN FLANAGAN: Energy balance, it is arguably the primary driver. The macronutrient composition of the diet is relevant, but because this isn't purely a glucose centric issue, because it's certainly not a sugar only issue as you would hear from some diet circles, this capacity for the ability to regulate blood glucose levels and these

underlying processes that relate to metabolic health and metabolic function primarily come back to a situation of energy excess, and not to any individual macronutrient per se. And so, I think that's always really the most logical point of departure. I mean, in this context, we know that with overfeeding studies, sure, in very tightly controlled circumstances, the extent to which ectopic fat will increase can be somewhat modified or attenuated by certain dietary manipulations, but there the context of very tightly controlled deliberate feeding studies, that's not the context of the habitual diet across the population.

So I think primarily we have this situation of an energy imbalance, and by imbalance, we mean, tipped to chronic energy excess. That chronic energy excess coming in the context of essentially mixed diets, which typify the macronutrient composition of the typical Western diet with anything from 35 to 45% dietary fat and anything from maybe 45 to 60% carbohydrate, the composition of that is relevant, but in the context of chronic energy surplus, it's less relevant than the over-nutrition and continual and constant supply of energy and nutrients over time, that continued elevation and blood glucose itself as a result of this diet, the interaction between fat and carbohydrate that we've kind of briefly described so far in terms of exacerbations, postprandial ability to clear blood glucose and clear fat from the circulation, the accumulation of fat over time in the liver and the spillover of that into other visceral organs and tissues, and the impact of all of these processes on the capacity of cells, both in skeletal muscle and in the liver to uptake glucose; and, of course, then over time, the capacity of the beta cells to match the rate of glucose production in the body, and their progressive over time inability to do so resulting ultimately in beta cell death in terms of long term type 2 diabetes.

DANNY LENNON: Yes, with this chronic energy surplus, and cases where we have excess fat mass accumulation,

that is going to increase the likelihood of this ectopic fat storage and development of insulin resistance from other pathways as well, which we'll probably get onto. But then it's noteworthy, like you say, that depending on what makes up that caloric intake, it can either maybe make that problem even worse, or maybe slightly attenuated, at least, relative to the other type of dietary paradigm. So that throws up the questions of, okay, based on a situation, there's going to be a positive energy balance or calorie surplus. In what cases, would we make things worse? So in other words, if we were trying to make someone insulin resistant, what type of diet would you put them on?

ALAN FLANAGAN: So in addition to the chronic over-nutrition in terms of the evidence that we have, yes, the composition of that diet would primarily be particularly low in unsaturated fats and polyunsaturated fats, in particular. It would be high in saturated fat, which can increase liver fat, even independent of energy balance. And so, in conditions of energy surplus, we tend to see quite a pronounced increase in hepatic fat, and it would be high in refined simple sugars. In conditions of overfeeding and energy excess, you would tend to see a relatively similar contributions to liver fat. The actual impact on insulin sensitivity, in terms of peripheral insulin sensitivity, could be related more to increasing overall adiposity as a result of energy excess. The links between obesity, adiposity, and insulin resistance and diabetes are not necessarily linear, and an explanation for that may in part be some of the genetic components. But it does appear that obesity primarily exerts its effect on insulin resistance, potentially, rather than beta cell function. So it's influencing the overall picture of insulin resistance as a result simply of the increase in adiposity from chronic energy excess. What it may be, certainly over time, and in that context is, rather than obesity causing beta cell failure, it's an inability of the beta cell functions to adapt to obesity fails in some individuals, and obviously results in type 2 diabetes, and then

we have the genetic component as well. But overall that gray area of nonlinear risk tends to be in this region of BMI that we discussed, I think with Spencer, between, say, 27-35. Beyond that the risk of a diagnosis of type 2 diabetes, as a result of higher levels of adiposity, significantly increases. So I think in terms of energy excess, that's obviously our kind of primary focus, but to exacerbate the effects of energy excess in this context, a diet high in both saturated fat and simple sugars would likely be the most deleterious, and obviously, concomitantly low in fiber potentially, and low and unsaturated fats would be the dietary pattern that would probably exacerbate insulin resistance.

DANNY LENNON: Not surprising, probably to many listeners of this podcast, as we've talked about those dietary factors in relation to other cardio metabolic risks, and we're kind of seeing, again, the same actors play out on both the, quote-unquote, good and bad side. Regardless, we have this situation where you have positive energy balance over a long period of time, whether it's excess fat accumulation, particularly at very high levels, like we're saying, once it goes beyond that kind of 35 BMI, that kind of risk becomes more closely tied. And then those things made worse when we have very high intakes of saturated fat and added sugars. So what then about the question that people may have then, well, if I don't eat in a calorie surplus, and I'm not gaining body fat, but my diet maybe isn't, quote-unquote, most nutritionally sound, in other words, I do have a lot of saturated fat and sugar in my diet based on my food choices, but I just managed to regulate my caloric intake, what does that risk profile look like, relative, in terms of if we're specifically focused in on insulin resistance?

ALAN FLANAGAN: This has been something that, again, more some controlled feeding studies have been able to elucidate is that even without conditions of enormous energy excess, there can still be impaired measured insulin sensitivity, in

response to diets that are rich in saturated fat versus a diet that is, for example, rich in unsaturated fat. But what tends to be interesting from the more glucose centric point of view, is that some of those relationships with simple sugars are very much less evident in eucaloric or energy balance conditions. So this comes back to something that I've seen Krista Stanhope publish on this idea of direct and indirect effects when it comes to free sugars. And that really, although free sugars can have their own deleterious effects at certain higher levels, their primary contribution to adverse metabolic health appears to be it through driving energy excess and consequence adiposity, and that is a more indirect relationship with insulin resistance, peripheral insulin resistance as a result of increasing adiposity. Whereas with fat composition, it appears that actually fat composition can modify resistance to insulin in conditions of energy balance, comparing a saturated fat versus unsaturated fat enriched diet. So it may be that you've got these kinds of direct and indirect effects, and obviously, that would be relevant for a total diet pattern, like we've just discussed; and it could be that, for example, someone in a condition of energy balance, if they have the dietary characteristics that we just described in energy excess, well then, we could still see deleterious effects of high simple sugars, for example, through increased triglyceride upregulation, and potentially some of these knock-on effects in terms of atherogenic lipoproteins and otherwise. So there's no free lunch there necessarily. It just may be that the effects on some of these underlying metabolic parameters and hepatic insulin resistance in particular, are more influenced by fat composition in conditions of energy balance, than they would be by simple sugars specifically.

DANNY LENNON: And that's also notable that when you were discussing that it's not this linear association with say, obesity, or a classification for that is that we can clearly have cases where someone

might not appear to have excess fat accumulation because of what they saw more, let's say, internally or viscerally, and then maybe seem like they are someone who is relatively fit /healthy, but can still have the development of insulin resistance. And so, it's worth noting that, I think to this point, we've obviously covered some of those things that are going to drive insulin resistance and lead to progression of insulin resistance. If we then look at some of the dietary modifications that have been used, let's say, in cases where there's already established insulin resistance, some of this literature relates to people with prediabetes or someone with type 2 diabetes, but doesn't necessarily have to be so. But essentially, if we try and look at the question of, for someone with established insulin resistance, what dietary modifications may be good for them in order to control blood glucose and maybe even to regain some instance sensitivity. So there's many areas for us to cover here. From an overview dietary type or pattern or macronutrient composition, maybe two of the big ones that are in opposition that both have proponents saying that they have the answer, on one end of the spectrum, we may have a low carbohydrate, high fat diet, based on this idea of, well, if you're insulin resistant, you don't want carbohydrates in the diet, because you're not set to be able to handle them; on the very other end of the spectrum that we have, basically the complete opposite of a very high carbohydrate, high fiber, whole food plant based diet, and those proponents will say, well, that's what's going to do it because actually, dietary fat is the problem when it comes to insulin resistance. So we're going to have a very low dietary fat intake. Now, there's obviously some nuance with each of those.

ALAN FLANAGAN: I mean, it’s the two monotheisms facing off against each other, as they tend to do, and true to form for both dietary paradigms, the enthusiasm for their intervention outweighs the evidence in both cases, before even any of these dietary interventions in terms of

modifications, we know that the most pronounced effect on improving insulin sensitivity is going to come from achieving moderate weight loss of a kind of five, certainly, it seems more like 7% of initial body weight, improving beta cell function probably requires even more, and it might require up to 15% and even 10% might not be sufficient in people who have a longer duration of diabetes. So it's important that that really is the fundamental driver, how someone achieves that, then comes down to some of these other considerations in terms of preference and diet. But the argument from both of these paradigms that you just mentioned is that both of them are capable of and the word remission gets thrown around a lot, probably too gratuitously, by both movements in almost independent of weight loss, that actually it's the diet itself that will lead to these improvements. So I think it's important to take each of them in turn, and with low carbohydrate diets, the primary outcome, an interesting thing about low carbohydrate diets is low in the literature is often, on average, 30% is the average level of carbohydrate intake.

So the Jeff Voleks of this world would say that's not a low carbohydrate diet, a very low carb ketogenic diet should have less than 50 grams a day of total carbohydrate, or, at a minimum, less than 26% total energy, and there are interventions that use that, but it doesn't mean about 30%. And what you tend to see in these interventions is an improvement in glycemic control in the short term with comparing a low carb to a moderate or higher carbohydrate diet, and that tends to average out over about a year. So short of six months, you will tend to see superior improvements in blood glucose parameters are HbA1c, and that tends to average out over the course of about a year on average. And one of the reasons low carbohydrate diets are effective is because they are effective in essentially reducing the burden on postprandial carbohydrate metabolism and, consequently, on insulin. But a salient feature

of the diets in terms of the evidence to date is that they don't, and I think you discussed this at length with Dr. Nicola Guess as well, they don't actually address the underlying pathology, the evidence that a low carbohydrate diet will result in beta cell function improvements is fairly limited to absent. And so, while a low carbohydrate diet may be effective for someone to, and yes, there is evidence that people come off glucose medications and insulin, but that appears to only be for the duration the carbohydrate restriction is sustained. And because it doesn't address the underlying pathology, when carbohydrate is reintroduced, or if it's reintroduced, well, then the same state of impaired glucose tolerance that proceeded the period of carbohydrate restriction is evident.

So it's an effective clinical tool, but it doesn't appear to address the underlying pathology. And this is then, on the flip side, where the kind of whole food plant based people come in waving, saying, we do fix the underlying pathology, here's a couple of studies from the 1970s. Those studies were by quite a kind of prolific prominent researcher known as James Anderson, who published widely in relation to the role of fiber in the diet, diets of varying high carbohydrate, very high fiber diets, and use some of these diets in insulin treated men with diabetes in the late 1970s. And these were diets that had over 60-70 grams of fiber a day in them. And in these studies, some, I think 50% of the participants were either able to dramatically reduce or discontinue their use of insulin. Now, the problem with these studies is that they haven't really been replicated in a modern context. If you look at the characteristics of the participants that were in these studies, they had a BMI of about 22. They were lean individuals with type 2 diabetes, and the reality is that type 2 then is not the type 2 now. It's not a type 2 defined by ectopic fat deposition, hepatic fat, hepatic insulin resistance, all of these complications that we've talked about before that characterize type 2

now; and perhaps, arguably, they had a genetic component to their type 2, if they were that lean, essentially but were insulin treated for type 2 diabetes.

So those studies are very interesting. The hypothesis may be that this very, very high fiber carbohydrate intake has some effect on stimulating the capacity of beta cells to produce insulin, but they haven't been replicated. And so, those studies are over-cited I think, and over enthusiastically, so it's a fascinating, essentially hypothesis, I think; and those studies should still be treated as exploratory, not explanatory or confirmatory, because they have yet to be repeated in a modern context. And one venture is to think, based on the kind of literature that we do have with current diabetes, and again, having regard to Roy Taylor's work, that perhaps the same pronounced effects would not necessarily be observed with that kind of diet. But again, that's speculation in the absence of dramatic weight loss, so to speak. Now, if a diet like that 60-70 grams of fiber a day, very low fat, we know that even with regard to Kevin Hall's recent metabolic ward study, those diets can be highly satiating. If a diet like that facilitated an individual losing 15% of their body weight, well, then perhaps we could be – one of the outcomes maybe a restoration of beta cell functionality. But until that research is done, I think that there's again, like I said, an over enthusiasm for 40-year-old studies that don't really correlate with the kind of comorbidities and the average clinical presentation of type 2 diabetes in the now.

DANNY LENNON: And exactly what those very low energy diets that we've seen that have led to some restoration of beta cell function have been when we get this significant degree of weight loss, makes it up to like 15% of body weight decreasing. I think one of the crucial points is one of the terminology that you touched on when you were discussing the low carb, high fat diets here, and how some proponents will often

at least on the internet, you will see them claiming that this diet reverses type 2 diabetes. Whereas that term reversal would suggest that, like you say, if you were then to consume a certain type of meal high in carbohydrates, your response would be that of someone who does not have diabetes, that would be a reversal or/cure for the condition. And that's different to either seeing a remission in symptoms, an improvement in those or just a better ability to manage blood glucose. And so, we can definitely see it as a very useful tool, because, of course, it makes sense if we have an issue here with insulin resistance, and we introduce less exogamous glucose into our system, you need to produce less insulin to deal with that anyway. So yeah, from a management point of view, it could be very useful for some people, but that's not necessarily the same thing as saying this reverses that condition per se; and it may not get to some of those real true outcomes that we want, unless it's able to induce the degree of weight loss that we've discussed.

ALAN FLANAGAN: Yeah, exactly. The idea that either diet could result in that word again, remission, independent of weight loss is not evident in terms of any robust evidence. The plant based side will cite the Anderson papers as evidence of full remission because certain participants discontinued insulin, but again, having regard to the characteristics of those participants in that group, I don't think, and no one in diabetes research that I've spoken to about this research, thinks that it's necessarily comparable with an average individual with type 2 in the population now, or certainly with prediabetes or anywhere on that spectrum of impaired glucose tolerance.

DANNY LENNON: So if we were to think of some of the other aspects, I suppose the macronutrient we haven't really discussed so far is that of protein, and I think for maybe a long period of time it was not as appreciated as at least it is now in some circles of looking at dietary

modifications, and insulin resistance/prediabetes/type 2 diabetes. But there is at least a number of suggestions of how that can be useful both for, we can talk about high protein diets generally, but also then the timing of protein and probably later, we can discuss some of the protein preloading studies, etc. But from a total diet perspective or just what happens when we consume protein, that's one that I think more people have pointed to as something that should be more of a focus. I don't know, for example, Nikola tends to be quite big on this right now. What is your current sense of where we are with understanding protein's role?

ALAN FLANAGAN: Yeah, I think it's one of those things that comes back to this idea of moving beyond the glucose centric view, and you would tend to get these arguments that, oh well, it's all about insulin, and therefore, it's all about carbohydrate in the diet and glucose. And really, it's only fat that has really no kind of minimal eliciting of any insulin response. Protein does elicit an insulin response. The amino acid composition of those proteins is important in that, and so there is established amino acid mediated insulin secretion; and that may be through impacts on what are known as incretin hormones, so glucagon like peptide 1, or GLP-1 and gastric inhibitory polypeptide GIP. These are incretin hormones that essentially act to support and augment the release of insulin in response to food intake. They follow a circadian rhythm, which is interesting, which I think we'll touch on later in terms of some of the research on distribution and timing as it relates to these factors. So they're amplified in the morning in the early part of the day, but proteins have the capacity to enhance GIP and GLP-1 secretion and then, by doing so, potentiate the insulin response to a meal.

Some of the studies, like you've mentioned, have looked at protein preloads. There's also kind of some evidence that a higher dietary protein content in the context of macronutrient

manipulation could improve beta cell function, that might be modified by the related fat composition of whatever that dietary intervention is, but the potential role for protein is quite interesting. And I think we could kind of boil it down maybe to two summary points, one is that there is an established amino acid stimulated secretion of insulin that appears to be mediated through these incretin hormones like GLP-1 and GIP, and that results in an augmented insulin response as a result of protein intake, and that might mean that either a higher total protein diet, or indeed in clinical management, targeted use of kind of protein preloads before meals, could be beneficial strategies. And potentially even front loading protein intake, having a very high first meal dietary protein could potentially be a strategy that helps to stimulate first phase insulin response, and again, improve these overall glycemic control parameters.

DANNY LENNON: I know you referenced that, later we'll maybe discuss some of the chrononutrition/circadian aspects to maybe meal distribution, and probably some of the studies we'll mention are from Daniela Jakubowicz and Oren Froy, and, in fact, they did a 2014 RCT on protein preloading, that I think kind of speaks to what you've just said that we know, for example, that whey protein is particularly insulinogenic. And so, I think that study was people with type 2 diabetes, and they had them consume either 50 grams of whey or a placebo before a standardized high glycemic breakfast, and then looked at their response in the three hours afterwards. And you saw that, particularly the early insulin response was something like 96% higher after the whey, but also seemed to be a benefit for the kind of second phase response, at least based on some other studies as well. So that kind of protein preload is interesting even just to consider from a mechanistic point of view of what happens when we digest whey protein, for example, its impact on insulin, and then therefore, how that may help. And it's also

probably worth noting, as we mentioned, protein preloads, that there's been other types of preloading studies that not just center around protein. On this podcast, people may remember Alpana Shukla from Cornell was on talking about some of their studies. They did a couple between 2015 and 2018 on, what they call, the carbohydrate last meal pattern using either protein first, and then the carbohydrates later or fiber first and carbohydrates later, or both protein and fiber early. And they did a few different studies that we can maybe discuss. But again, seeing that same benefit of, if early or before the meal or at the start of the meal, if that's the protein and fiber, and then the carbohydrates come later, there tends to be a benefit potentially there.

ALAN FLANAGAN: Right. Within those studies, right, where within the same meal, so it was the sequence of consumption within a meal, which is interesting, because there was a study from a group in Japan that did meal sequence across the day, so that you can see these effects of essentially order of diet across the day in terms of macronutrient sequence, meal sequence, timing of that sequence, the frequency of those meals, and again Oren Froy and Daniela Jakubowicz published a really nice study last year looking at overall hyperglycemia between three meals and six, and then the actual distribution of that energy. And I think all of these factors are interesting in their own right in terms of trying to kind of see what unifying factor maybe tying some of these threads together, it seems to me that the protein first comes back potentially to this augmentation of the insulin response via GLP-1 and the Jakubowicz study that you mentioned on the protein preload, the increase in GLP-1 and GIP in that study was over 200% from the protein preload. So you get that factor, you get the attenuated postprandial glycemic response, and that may also then relate to what they call the second meal phenomenon, which I know Roy Taylor's group and some others have published on as well, where post the insulin

response and the postprandial glucose response to a second meal, when it's preceded by a meal earlier in the day is much lower, the glucose response is much lower. And interestingly, some research suggests that that might relate to the enhanced first phase insulin response early in the day. The other factor it might relate to is the suppression of free fatty acids. And indeed, that's what Roy Taylor's group showed with this was, it didn't relate to insulin, it related to the suppression of free fatty acids, allowing for a greater uptake of glucose into skeletal muscle in the second meal and a lower overall blood glucose response.

So these factors of macronutrient composition and macronutrient sequence within a meal, between meals, and the timing and distribution of those seem to be all factors that kind of come back to potentially improving either first phase insulin response or reducing postprandial glycaemia, therefore reducing the kind of burden on insulin in that postprandial period. And there's a lot of ifs, buts and maybes in this research, but these are all kind of interesting potential avenues. I think the ultimate conclusion is there really isn't enough evidence at this point to make specific nutrient based recommendations as it relates specifically to beta cell function or to improve beta cell function. We have these kinds of strands of information from some of these protein preload studies, or some of the studies focused on the second meal effect, that that might suggest a potential effect, but they're all kinds of studies that need to be replicated in more detail.

DANNY LENNON: Yeah. And let's actually maybe open a tab on that that I want to come back to, because you've raised essentially a good meta level point about nutrition science generally that we really should hammer home, because we're here, we're looking at, say, the blood glucose response to a meal in a certain study. So what does blood glucose do in the three hours after this certain type of intervention or this meal

order, but then thinking about that in the context of, well, what do we know about impacts on long term health outcomes, so the actual endpoints that we care about, and so maybe we can discuss that a bit later, but I do want to talk a bit about the meal timing and meal frequency, because I think you obviously brought that up, and we've discussed Oren Froy and Daniela Jakubowicz who have not only published on the protein preload, but also in this energy distribution and a nutrient distribution across the day. That obviously has a connection with some of the chrononutrition literature, and it's actually an idea that we've probably discussed a number of times on the podcast before, and I know it's an idea that you're particularly interested in, when we think of all the things that would come under the umbrella of chrononutrition, one of those kind of big questions is, well, how we distribute energy and nutrients across the day. And when we've talked about chrononutrition more generally, at least for some of the potential benefits that we've seen from various different interventions, probably ones with the most consistent results tend to be related to some of these glycemic markers, whether that's glucose, insulin, and so on, so very relevant to today's discussion. So what is your sense of how some of that chrono/meal timing/meal frequency stuff plays into some of these markers of insulin resistance?

ALAN FLANAGAN: Yeah, so it’s an interesting one, because I think, and we've talked about this before, from a weight loss perspective, arguably, timing, distribution, frequency, even intermittent fasting, time restricted eating, probably not superior than any other approach, no inherent metabolic advantage or otherwise. However, from the perspective of metabolic health and glycemic control, even in studies that don't necessarily focus on weight loss, there is quite a clear improvement that's evident, and the magnitude of that improvement is greater with increasing levels of impaired glucose tolerance. So in otherwise healthy people, the effect of

fasting to noon versus breakfast or even in kind of metabolically healthy obese, not much difference. As we start to move towards prediabetes, and even to type 2 diabetes, that's completely altered and the magnitudes of improvement in some of these metabolic parameters glycemic control parameters becomes much greater.

What it may come back to is what we discussed there in relation to incretin hormones. So both GLP-1 and GIP have a diurnal variation, which means they vary across the day, and we know that they are amplified in the early part of the day compared to the evening; and in the early part of the day, that results in a more rapid insulin response to nutrient intake in the morning. So, as an example, there was an intervention that compared the exact same meal, same calorie contents and identical macronutrient composition, but the meal was consumed either at 8:00 am or at 5:00 pm. And in response to the morning meal, you got a rapid elevation in GLP-1 and GIP, and that correlated to a rapid insulin response and a faster lowering of postprandial glucose levels. So what this has kind of led to some interest in is something I touched on a couple of minutes ago called the second meal phenomenon. And this actually goes back – there's not a lot of literature on it overall, which is surprising, but it was first described in 1919, known as the Staub-Traugott effect. And what it was first describing was that, in response to sequential oral glucose tolerance test, the blood glucose response to a second, to a subsequent OGTT, in an individual who'd already been given one was much lower, despite the fact that the exact same amount of exogenous glucose had been given.

So begs the question why does there appear to be this more rapid carbohydrate metabolism potentially in response to this second meal effect. And there's been a number of interventions that have looked specifically at this in relation to both healthy individuals and

individuals with type 2 diabetes, and it appears to be mediated primarily by two factors. One is the suppression of circulating free fatty acids, which from an overnight fast where you haven't consumed food, free fatty acids will tend to be quite high in the morning, just as a natural consequence of being in a fasted state. But if you were to skip breakfast, this is what we've seen in the interventions in individuals with type 2 diabetes, if they were to skip breakfast, and fast until lunch and have their first meal then, well, they continually elevate circulating free fatty acids, and that leads to an impaired postprandial glucose response to the lunch meal, because of this relationship that we described at the start of the episode. Conversely, if you have a morning meal, then you get a suppression of free fatty acids in response to that meal, and that creates, shall we say, a more favorable metabolic state for the second meal in individuals with impaired glucose tolerance.

So suppression of free fatty acids is one, and that appears to relate specifically to morning energy intake. It's much more pronounced in the morning. And then the other factor then is enhanced skeletal muscle glycogen uptake, and that was Roy Taylor's group in a paper about 10 years ago now, 2009 paper, and Yovanovitch was the lead author. And they did an investigation in both healthy individuals, and a separate one in participants with type 2 diabetes, and the intervention with healthy individuals, they used stable isotope tracers to look at exactly what was going on in the postprandial period. And what they found was that the skeletal glycogen, skeletal muscle glycogen uptake was enhanced from the suppression of free fatty acids in the first meal. So the enhanced glycogen uptake in skeletal muscle was primarily mediated not by insulin in this study, but by the suppression of free fatty acids. And they repeated that then in participants with type 2 diabetes, where you got this pronounced reduction of postprandial glucose when a breakfast meal preceded a first

meal. And there is a suggestion, a paper, Lee and colleagues, it was 2011, that the second meal effect could be explained in part, although, again, it's fairly weak evidence so far, could be explained by an enhanced first phase insulin response, which they found.

Most of the studies, even if we bring in some of the Daniela Jakubowicz papers, suggest because they've done a number of publications now, where the suppression of free fatty acids mediating a more beneficial postprandial glucose response to subsequent meals has also been evident. So although we're talking about factors that aren't necessarily improvements in insulin sensitivity as primary outcomes, these are factors that we know are related to the overall metabolic picture of insulin resistance, in terms of elevated free fatty acids and skeletal muscle resistance to insulin and impaired capacity for skeletal muscle to uptake glucose as glycogen.

So I think some of these interventions have seen quite pronounced reductions in both postprandial glucose and in postprandial insulin, comparing either the effect of a breakfast meal versus breakfast skipping in participants with type 2 diabetes, or also comparing the effects of energy distribution with high energy, high protein breakfast as the first meal as well. So, the potential for these interventions, I think for utility in the context of diabetes management is emerging. There's a fairly clear and consistent benefit to glycemic responses in participants with impaired glucose tolerance or diabetes, where a proceeding first early meal, i.e., a breakfast, proceeds a subsequent meal. And from a kind of overall insulin glucose regulation perspective, that appears to potentially be mediated by coinciding the timing of that food intake with the period in which incretin hormones augmenting the insulin response is enhanced and amplified compared to other time periods.

DANNY LENNON: I guess, one area that we maybe haven't touched on yet that is maybe worth just at least mentioning could be in relation to thinking about consumption of the diet as complete meals rather than maybe isolated nutrients, as that's something we've talked about before; but particularly when we know there are differences in the response to consuming certain foods that could have negative downstream consequences, some of which we've discussed, that tend to get mediated by other aspects of the diet. So, as an example, if someone consumes a large serving of butter on its own, and the resulting endotoxemia that occurs from that, that is probably going to be different if you consumed a certain amount of saturated fat from butter as part of a larger meal, full of phytonutrients, micronutrients, fiber, etc. And so you don't get that kind of same response afterwards, and then, I suppose, over time, one would hope that would have less of a risk for some of these negative end results. But in terms of maybe if we think specifically then about blood glucose control and glycaemia, we again know that some of the combinations of foods will alter those. And so, this kind of leads us to the idea of glycemic index, glycemic load of certain foods, and where we should view their relevance for those with established insect resistance as a focus or not to place over what foods should be consumed.

ALAN FLANAGAN: Yeah, I mean, there's a couple of years ago, I remember, a kind of everyone got a bit kind of annoyed, well, various responses to a presentation here where every different carbohydrate food was compared to teaspoons of sugar. And I think it was at a medical conference, and pushback that will, you know, it was a banana, next to the banana is five teaspoons of sugar. And well, that's probably not a reflection of other bananas' metabolism, even if it's consumed alone. But glycemic index, I think people say – I don't think it's controversial, I just think it has some limitations that are well established and not

controversial. That is that the index of an individual food is not necessarily reflective of the quantity in which that food would be consumed, because it's always against a reference 100 grams to glucose. And it's not a reflection of the metabolism of a different quantity of that food or a lower quantity of that food in the context of a mixed meal particularly, that can be modified by the amount of protein in that meal and the fat composition and amount of fat in that meal.

So that limitation of GI is well established, which brings the focus onto glycemic load, which considers more the kind of dose and actual amount that will be consumed of any carbohydrate meal. And I do think that there is a utility for – if we're talking about otherwise healthy individuals who exercise and do all this kind of stuff, which tends to be the avatar everyone wants to default to, which we've talked about before, I don't think that's a helpful heuristic at all, because it's just not representative of the general population, nor the habitual diets in the kind of general population. So I think that there is a utility for it. I think that the benefit of whole grains has been shown in some nice studies – John Kirwan's research group have published a number of interventions, looking at whole grain and rich diets on peripheral insulin sensitivity and finding an improvement in insulin sensitivity in both healthy individuals and in people with impaired glucose tolerance. The capacity to modify the rate at which glucose presents in the bloodstream is an important factor in terms of being able to somewhat match the insulin response to the rate of glucose production. All of these abilities to, by reference now we're talking about carbohydrate type, to modify the postprandial metabolism picture, we see quite clearly in relation to research that looks at carbohydrate, particularly high fiber diets. And the capacity of high fiber, even potentially some nuance for fiber type, some of the studies using fiber preloads have found a benefit as well, although

the benefit doesn't seem to be to the same magnitude of effect as preloading with whey protein, for example. But the benefit of complex, that broad word complex carbohydrate, high fiber, unrefined, slow digestible carbohydrates that are slow to present to the bloodstream, and also through fiber itself having certain properties able to modify a number of aspects of postprandial metabolism, whether it's cholesterol metabolism or the blood glucose response itself.

DANNY LENNON: Excellent. And as you mentioned John Kirwan there, he'll actually be on the podcast within the next week or two. So that'd be something for...

ALAN FLANAGAN: Yeah.

DANNY LENNON: A timely name drop there. So if we maybe start wrapping this up, I suppose, we've discussed a number of these different dietary modifications that could, or, at least have been hypothesized to have potential benefit in cases where there is established insulin resistance or glucose intolerance; and maybe they fall into different categories of the strength of the current evidence for each one, some are very clear of their benefits; some seem to be beneficial but we're not kind of sure of how that will play out in long term; and then some we can hypothesize of having a benefit, but the actual real world impact is kind of unknown, so to speak. So when it comes to all that we've discussed, from a practical perspective, what do you think are the clear bullet points of what someone should have in their mind of from a diet perspective, when insulin resistance is the case?

ALAN FLANAGAN: Yeah, I think if we're separating just kind of insulin sensitivity in terms of peripheral or hepatic insulin sensitivity, skeletal muscle insulin sensitivity from beta cell function, because in relation to beta cell function, there's obviously a lot of potential kind of, you know,

some evidence in relation to some of these factors, like, we talked about protein loading, etc. But the reality is today really the only direct evidence that we have of the capacity to restore that functionality comes from the very low calorie liquid diet, the Newcastle, the VLCD, related to the magnitude of weight loss of give or take around 15% of body weight. And also seemingly, the potential to restore function may relate to duration of diabetes, so that the closer someone is to a diagnosis, the more chance it seems that they have to restore that functionality.

But moving kind of from that as a more extreme clinical and medical nutritional intervention, in terms of improving insulin peripheral, skeletal muscle insulin sensitivity, and hepatic insulin sensitivity, again, if we're going from a kind of top down approach of best evidence downwards, best evidence is moderate weight loss in this regard, give or take, 5 to 7%. It does appear that 7% is in terms of, if you look at some of the prediabetes intervention programs, either the Finnish or the DPP in the States or the [inaudible 01:04:01] study in China. They seem to suggest 7% more protective over time in terms of progression, but that weight loss is probably – it remains the highest level of evidence that we have for improving overall insulin sensitivity and resistance.

Second to that then, there is the potential for factors like distribution to improve insulin sensitivity, independent of weight loss, and we've seen that with some of Courtney Peterson's interventions using really time restricted feeding in individuals who are prediabetes. So I think that there's a potential utility for the distribution of energy and again, Oren Froy and Daniela Jakubowicz's research, and some of Roy Taylor's additional research in this area. So that I think in terms of reducing the overall magnitude of glycemic incurred excursions, not just in a subsequent meal, but over the course of a total 24-hour period, does

seem to point to a front loading of energy intake in individuals with impaired glucose tolerance, and an emphasis on higher dietary protein intake, in that context earlier in the day, modifying the fat composition of the diet then, I think is also something that even in the context of energy balance, appears to be an important factor for hepatic metabolic health or liver health, in terms of fat accumulation in the liver or insulin resistance in the liver. And in that context, it's very clear that the hierarchy is polyunsaturated, monounsaturated and saturated fat in that order with more deleterious effects of high saturated fat observed in energy balance conditions than you would necessarily see for simple sugars. In the context of energy over excess, then insulin sensitivity is best served by obviously reducing that degree of over nutrition, simpliciter, overall, independent of any specific macronutrient reductions, and an emphasis then in terms of carbohydrate type on high fiber, low glycemic load carbohydrate as a strategy to additionally improve peripheral insulin sensitivity.

So all of these can be in conjunction with weight loss as well, but the diet composition can independently influence insulin sensitivity with or without weight loss, the magnitude of which would be greater with concomitant weight loss. And then, it's a separate conversation almost, but it's worth bearing in mind that the beneficial effect of exercise really in all of this in terms of insulin independent glucose uptake, in skeletal muscle and the improvement of peripheral insulin sensitivity from exercise, resistance exercise in particular, there's a huge place for that, and, in fact, something in terms of level of evidence that will be very good level of evidence, in terms of that our understanding of the role of exercise in facilitating glucose disposal and benefiting.

So yeah, I think weight loss top, second to that then, dietary modifications in favor, from a fat perspective of enriching with unsaturated fat,

poly and mono, in particular. Would there be a benefit to one or the other in that context? You're splitting hairs there potentially. There could be a greater benefit for polyunsaturated fat if the outcome is liver fat. But overall, just for general metabolic health, unsaturated fats generally is probably sufficient characterization, and then carbohydrate enriching with high fiber low GI, and then considering then factors like distribution and timing, and then exercise.

DANNY LENNON: Excellent. A wonderful summary, and, I'm sure, it's going to be very useful to people. Is there anything on this topic that we didn't touch on that you had hoped to mention before we wrap up, or, is that a good place to, at least, leave it for now before – I'm sure, it will crop its head up in future episodes.

ALAN FLANAGAN: Yeah, I mean, because we focused a lot there on composition, and people will probably, again, be saying, but what about this or that diet, I mean, some of those dietary characteristics we just described are consistent with diets like the Mediterranean diet or otherwise, but I think as we established earlier, the kind of overreach by both the kind of low carb keto camp and the vegan plant base camp in relation to their respective diets for "remission of diabetes" which they're not achieving, and there's an overuse of that word, really, in both scenarios, is probably over enthusiastic. There's more potential in the very low fat, high carbohydrate, high fiber diets, but for research that hasn't been replicated in the gaps of 40 years, I think it's a little difficult to stand over that now until it is replicated.

DANNY LENNON: And that's probably again, like you say, a conversation for another day of how people might point to a certain marker that has seen improvement through one of those diets, and confuse that as proof of reversing or putting the disorder into remission, or even in some cases, you may see an improvement in one of those markers, but there may be other things that are

negatively impacted. And that's particularly the case when we look at some of these, I suppose, very high fat diets, but that said, I think, yeah, that's a great place to kind of, hopefully, give people a lot to chew on with this particular topic. So let's turn our attention to the quack asylum before we finish.

The quack Hassan for today, very fittingly, for today's topic, who would you like to add to the list?

ALAN FLANAGAN: I mean, it has to be Tim Noakes. He, I think is probably infamous in two ways, one, within the actual low carb, keto circles where he's revered, which I think says a lot about their general critical thinking capacity as a movement; and then in the rest of the nutrition world where he's Tim Hoax, and viewed of as not much beyond a joke. But everything is about insulin resistance, especially the lipid hypothesis, everything to do with cholesterol, anything to do with LDL, anything to do with saturated fat is basically all wrong, because it all comes back to insulin resistance. He has his own parody account on Twitter, which is Tim Hoax, which I highly recommend, because it kind of says a lot about his some of his posts in relation to – there was one a while ago that did the rounds about him being an expert in everything – I woke up and found out that I'm not only an expert in exercise physiology, but also nutrition and metabolism and epidemiology and everything else in between.

But yeah, he's one of these characters who forms, I would say, a bedrock of the kind of low carb, high fat nonsense really, along with Zoe Harcombe and some others. And none of them have contributed anything original, like, it's all just the same opinions regurgitated, oh the lipid hypothesis, oh it was all Ancel Keys – the kind of industry conspiracy narratives about dietary guidelines, oh it's all dietary guidelines that caused obesity or have been responsible for metabolic disease. And it's the reason, obviously, within those dietary guidelines is

carbohydrates via insulin and insulin resistance. So if it were all that simple, it would be fantastic. We'd have a fairly clear path to solving and addressing the burden of chronic disease at a population level. But unfortunately, despite their protestations, it's not so simple. And yes, while no one would ever argue even in cardiovascular sciences that insulin resistance is not important, so the way, certainly, the way Noakes carries on in terms of like talking about insulin resistance, as if everyone in the wider medical nutrition and science community is somehow sleepwalking past this giant clue. But that will be consistent with the kind of conspiracy theory thinking that David Robert Grimes has talked about where their whole kind of mindset is that like, they're possessed of knowledge that that the rest of the diluted masses are not capable of seeing.

DANNY LENNON: That's the only explanation agreeing with me... they just don't know.

ALAN FLANAGAN: They just don't get it. So I think he's a worthy admission, he joins some good company.

DANNY LENNON: And, I mean, if people, especially after listening to this episode, if they want to kind of hear directly the position that Dr. Noakes would hold, you can check out episode, I think it was 210 of this podcast, along with Martin MacDonald, a debate around some of these ideas. And so, you can kind of hear his position to show that it's not being butchered here.

ALAN FLANAGAN: Well, that was the episode where he famously declared that if you eat over 35% of your calories from protein, you will die.

DANNY LENNON: That is correct, yes, that was stated in the episode. So I agree with you, I think, yeah, very much in the same old as many of those kind of low carb people that I don't know, it's this position where they are so staunchly confident in their position that everything else is nonsense.

ALAN FLANAGAN: And thinking that they're sitting on something that's groundbreaking and revolutionary, and kind of turns everything we know on its head, when it's just the same narrative, it's a story that this community tells itself. And whether you hear it from someone that has a professorship like Tim Noakes or you hear it from just your average low carb blogger, it doesn't change, the gravity of the information, the level of insight, none of it changes, because it's just all the same simple, silly story that creates a certain narrative that allows them within that narrative to then reject any evidence to the contrary.

DANNY LENNON: Excellent. So yeah, I think that's a good way to kind of round this up. We're just coming up to our planned time here. So I hope everyone found this useful. And, as always, feel free to leave any comments or questions on anything related to this discussion. You can do that either through the show notes page, which is sigmanutrition.com/episode384, I believe, or 385, depending on what podcast this is, I think it's 385. Or you can just, obviously, message on social media or there is a contact form on the website that you can also send questions or comments through. If you did enjoy it, please share this around the internet, whether that's your Instagram story or Facebook groups you are in, email it to a friend, etc. If you think people would benefit from this and enjoy this content, please share that. And that also obviously helps the show which we're very grateful of. And that is it. I'll link up to any of the studies we referenced for this discussion in the show notes to the episode, so you can go over there at sigmanutrition.com and get access to all of that. You can also find our other content, including our Sigma statements, and most probably connected with today's discussion would be the one on fatty liver, which Alan produced, and you can find that over on the podcast there. Also, as a reminder, if you are in the UK and you want to get involved in Alan's study, you can email him, I

will put his email address in the show notes of this episode, so please do that and help out with some science. And yeah, that's it from me. Alan, do you want to say anything to the folks at home as they say?

ALAN FLANAGAN: Yeah, folks at home, thanks for listening. And yeah, if you are, or, you know someone who might be interested in participating, like I said, recruitment's going to be open, so if you're stuck for May, because of life, you could always do it in June or July. So yeah, get in touch one way or the other if you or someone you know would be interested in contributing to my sample size.

DANNY LENNON: Excellent. So that is our episode. Thank you yet again. Please spread the word of the podcast, and we will be back in another episode very soon. So hope you tune in for that. Until then, take care.

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