DANNY LENNON: Today on the podcast, we are going to be talking about plant based diets and diabetes; in particular, we're looking at this, I suppose, hypothesis or proposal or claim about low fat plant based whole food diets and their ability to treat diabetes, or to lead to diabetes remission or reversal, and there's a number of different sub claims we can look at. And this really came out of a number of you who have listened to some of our episodes on dietary interventions and diabetes, and also our episodes related to vegan diets and plant based diets, and asking about, particularly, there's going to be some examples we'll talk about specifically that most of the questions have centered around, but these ideas that using a plant based whole food diet has some sort of unique benefit for diabetes treatment or remission, and may be superior to other types of dietary intervention. So that's what we really want to walk through today. Of course, there's probably the best place to start, as usual, is a few kind of key definitions throughout this what is, as we've discussed in many diabetes episodes before, one of the key distinctions is what do we mean by reversal, what do we mean by remission, what are we talking about in terms of treatment, like, what is the end outcome we're actually discussing here. And so, I don't know if

there's, in addition to that, there's other definitions that we might want to start off with, but what do you think Alan are some of the main kind of core concepts we need to get in mind when we're having any discussion around diet and diabetes?

ALAN FLANAGAN: Yeah, so I think the operational definitions that exist around remission and then reversal, and often those terms are used interchangeably, but we really kind of need to distinguish between the two, and then, of course, the specifics of the dietary intervention that we're talking about, because as we go through today, listeners will notice that there's a lot of shape shifting that goes on in the arguments in relation to certainly vegan or plant based diets and diabetes, when most of the claims are made in relation to a very specific type of vegan diet, low fat vegan diet, and most of the supporting evidence doesn't even use that type of diet, but at the outset, remission typically is defined as the maintenance of a HbA1c. HbA1c is a marker of longer term glycaemic control, and so, how well an individual is managing fluctuations in their blood glucose levels, and it's expressed as a percentage for the most part, and the maintenance of it is generally considered over like a three-month period. So HbA1c levels under a threshold of 6.5% for at least three months, and no concomitant medication use like Metformin, for example, or exogenous insulin to manage blood glucose levels during the period at which HbA1c levels have been maintained below 6.5%. That's the definition of remission. Reversal is different, because it's speaking to something potentially kind of more underlying and mechanistic, and it largely is a concept that has emanated from Roy Taylor's research; and it's a concept that would be dependent on the restoration of beta cell function, and first phase insulin responses. And this is something that we've seen in Taylor's research, although it is clear that there are, what we would call responders and non-responders. So there are some people who, from a particular intervention, and that usually

is related to magnitude of total weight loss and reduction in visceral and liver and pancreatic fat in particular, restore the capacity for normal insulin secretion. And there are others that despite achieving that level of weight loss may not necessarily achieve that restoration of beta cell function. And we'll get into the reasons potentially underlying why some people respond and non-respond later, but there are two important definitions. For the most part, most research is looking at remission as an outcome, but there are often claims then made by various programs that exist about reversal and they use the language of reversal. And unless that's being specifically quantified as restoration of beta cell function, then that language really shouldn't be used. And so, mostly we're looking at remission as a marker because remission is more, shall we say, kind of, readily quantified, i.e., the HbA1c level and whether someone is using medications or not is easier to quantify then whether first phase and insulin secretion has been restored.

DANNY LENNON: Right. And I think that's important for people to bear in mind, number one, when we're looking at any kind of research in this area of, especially now there's been more of this consensus around what remission is, and having that as an outcome that's mainly going to be looked at, versus if someone comes across a website or social media post, and someone's making a claim of reversing diabetes or a cure for diabetes through a dietary intervention, kind of, looking in to see, well, are they actually using correct terminology for to actually be reversed, you actually, as you've just said, need to have this restoration of beta cell function, as opposed to just putting symptoms into remission. So with that, let's maybe talk about some specific claims first to kind of frame this for people. And as I mentioned at the outset, there's a couple of places that people have pointed me towards that tend to come from the vegan or plant based community that have talked about diabetes in particular, probably the most commonly cited that I see is, first, a

program called Mastering Diabetes, which I wasn't that familiar with before people had put me onto that. And then second, we can kind of talk about Neal Barnard's work, and there's kind of two sides of this, we'll talk about some of his studies that he's actually published in peer reviewed journals, but, of course, he also has a book for the Gen Pop, which is quite popular amongst a lot of people that will make certain claims as well. As an example for people, if you are to look at the website for this Mastering Diabetes program, they talk about this as being, "The best lifestyle to reverse insulin resistance and get your blood sugar levels back to normal being a low fat plant based whole food diet". So that's essentially what we're looking at – is this claim actually accurate, that this is the best diet relative to other types of diets, that's the first thing. They specifically state things like our method is scientifically proven to lower A1C, body weight and reduce medication use, however, when you look on the site, the reference they give is actually just a small pilot trial that the creators of this program were authors on, which is just a retrospective, essentially, online survey in Nature, a small percentage of people who had completed their program filled out a survey, I think, like 9% of people actually responded. And through that, then they're coming up with a percentage of people who lost weight, who dropped hemoglobin A1C, decreased medication use, and that's some of the statistics that are then cited on this website. So that in itself as a piece of supporting evidence probably doesn't back up that claim...

ALAN FLANAGAN: Red flag.

DANNY LENNON: So what we can maybe do, as opposed to, like, deeply critique this study, I'll link to in the show notes if people want to look, but there's really not much to say apart from it's just basically an online survey that is incredibly limited. We can maybe look at, okay, taking it at a broader view and taking it in the best faith possible, is there something to this idea that a

whole food plant based diet could, in fact, be better than other dietary interventions for putting diabetes into remission, because that's the kind of interesting question to ask. So maybe as a starting place, before we get into any trials, we said there, probably a good place would be to look at some of the epidemiology in this area, and what associations do we see, where does some of this even thought process or these hypotheses come from, and what are some of the kind of big epidemiological trials or the most commonly cited that you may see from this type of claim that you think could shed some light on these associations?

ALAN FLANAGAN: Yeah, well, at the outset, we mentioned the importance of kind of operational definitions, and this really is important when we're talking about the dietary aspect of it, so the claims that are made are made in relation to a what we would call whole food plant based diet. Right? Now, that's not a kind of generic term, that term is denoting a very specific macronutrient composition of restricting total dietary fat intake to around 10 to 15% of total energy, but 10% is generally the target that is desired from this type of diet. It's exclusively made up then of, obviously, plant based foods, so all dietary protein really comes as a byproduct of an emphasis on legumes and whole grains and pulses. So that tends to top out at about 10 to 15% of energy, and the remainder is to carbohydrate. So, on average, the intervention certainly try and aim for around 75% carbohydrate, 15% protein, 10% fat intake. So that's the actual specific whole food plant based diet. Now, this dietary pattern is almost non-existent in epidemiology, and so, this is particularly important because a number of review papers that one might read, particularly as it comes from the researchers in this area, will tend to use epidemiology on vegetarian dietary patterns, which vary widely in the epidemiology of vegetarian dietary patterns from lacto vegetarian, lacto, ovo-vegetarian, pescatarian, and various iterations, semi-vegetarian. And often these are dietary patterns

that are not exclusively vegan; certainly, none of the aforementioned dietary patterns are exclusively vegan, and they're certainly not necessarily dietary patterns that are restricted to just 10% of total fat. Nevertheless, the epidemiology of vegetarian dietary patterns is generally positive, and we see significant reductions in risk for diabetes as an outcome, and we've seen that in the Adventist Health Study 2, which is one of the kind of most well executed large cohort studies that we have operating currently, well validated dietary assessments, more representative with a higher proportion of African Americans than, for example, other big US cohorts like the Nurses' Health Study, which are almost 98% white Caucasian.

So the AHS-2 is a really good work of nutritional epidemiology and significant reductions in diabetes risk amongst vegetarians compared to what they would term non-vegetarian. So this would be a more omnivorous dietary pattern. We've seen similar associations in the European Prospective Investigation into Cancer, which is EPIC. There's a sub-study of epic called EPIC called EPIC-InterAct looking specifically at type 2 diabetes, and this has looked not necessarily at quantifying vegetarian or non-vegetarian patterns, but more broadly speaking, kind of, food based correlations within dietary patterns. So higher intake of fruit and vegetables, lower intake of processed meats, sugar sweetened beverage, all associated with lower type 2 diabetes risk, nothing particularly earth shattering there from a nutrition perspective. There's been other reviews that have focused more on a priori dietary indices, which we've discussed with a previous episode with David Jacobs, which is where you're coming up based on prior knowledge with a dietary pattern conducive to health. So things like the Alternate Healthy Eating Index, which basically scores out of 110, based on achieving certain levels of intake of fruit and vegetables or salt, or otherwise is positively scored for

good foods, negativity scored for foods associated with adverse health outcomes; or the DASH diet, Mediterranean diet scores, and again, each of these varying iterations of a just broadly healthy dietary pattern are all associated with lower diabetes risk. And generally, what we see with this epidemiology is consistent with dietary pattern research, food components, groups of foods are more informative than any single food and risk. So the total diet pattern matters more than necessarily any specific isolated foods within it.

The Rotterdam study is quite a nice study to look at in relation to this because it used a plant based dietary indices or a dietary index. There are various different ones, so it used a validated one, and Ambika Satija and others have used from the Harvard epidemiology group, but they also had blood measures available, and they were able to determine a validated marker of insulin resistance, which is known as HOMA-IR. And they had a couple of time points that they were able to prospectively look at insulin resistance over time, and the association of that insulin resistance or HOMA-IR with the plant based diet scores. And again, higher plant based diet index scores were associated with a lower HOMA-IR, so lower insulin resistance, 13% actual lower risk of type 2 diabetes, although no significant reduction in risk of pre-diabetes, but ultimately, overt diabetes lower in risk and lower insulin resistance.

So, as a summation, broadly speaking, the vegetarian epidemiology which is what these studies are looking at, finds a reduction in diabetes risk. These dietary patterns are very varied in terms of their actual food compositions, but tend to have some no brainer combinations such as higher fruit and vegetable intake, whole grains, lower processed meat consumption, lower refined grain consumption; but critically for moving on to discuss interventions that purport to use or do indeed use a whole food plant based diet, that

is 10% of energy from fat, 75% carbohydrate, protein entirely from plant sources, that that dietary – that there is no such dietary pattern in the epidemiology. It is largely an intervention, a deliberate intervention that was born from largely, primarily Dean Ornish's research in the early 1990s. So the epidemiology is positive, but the epidemiology is by no means, A, even exclusive to vegan diets, exclusive of all animal produce, and it's certainly not necessarily epidemiology that, although positive, is a reflection of this particular whole food plant based dietary pattern, although it is, broadly speaking, positive in relation to vegetarian and other healthy eating index patterns.

DANNY LENNON: Right, yeah. And that's the, I suppose, the crucial thing that then sets us up to ask, well, what is it about these certain dietary patterns that may be showing this reduced risk of diabetes. So probably, unsurprisingly, these higher intakes of vegetables and fruits have positive effects on reducing diabetes risk, then we see, again, vegetarian maybe relative to non-vegetarian diets that can potentially be beneficial. But again, we have to ask, well, what might be going on there, what's the case. But as you know that these epidemiological studies aren't specifically looking at the dietary pattern in question, so we have to dig a bit deeper to look at that. Of course, if we're seeing something like, something that is trending more towards a vegetarian diet, and maybe less animal produce in the diet, showing some of these reductions in risk, then that can throw up, well, what aspect of the diet is causing this. Right? Is it because these diets have more fruits and vegetables? Is it because they're higher in fiber? Is it because they're lower in saturated fat? Is it the impact of red meat on diabetes risk? There's a whole host of different potential factors going on – is it some combination of those, or maybe none of those. So to walk through this, of those mechanisms that we could look at, where might we start? Would we start on the fiber issue?

ALAN FLANAGAN: Sure, yeah. I think the nutrient composition, obviously a vegetarian diet's generally, but if we're being really kind of specific "steelmanning" the whole food plant based diet, this 10% of energy from fat and predominantly carbohydrate based high carbohydrate diet, then one of the most kind of logical points of departure to consider why this diet might be beneficial will be that it may result in a fiber intake significantly higher than population averages, and even significantly higher than interventions that might have a beneficial effect of fiber, they might often use, say, 35-40 grams, 45 grams a day, and consider that quite high. It's possible to achieve even higher dietary fiber intakes with this kind of dietary pattern. We know from wider research on both whole grains and certain pulses that there is a benefit to peripheral insulin sensitivity, and indeed, there may be some effect of fiber intake on insulin secretion itself. And again, this is slightly less solid than the evidence that would exist for peripheral glucose uptake and peripheral insulin sensitivity, but it's mediated by impacts on what are known as incretin hormones. So GLP-1 and GIP, and they augment insulin secretion, and there's some potential mechanistic plausibility to fiber kind of enhancing GLP-1, and another incretin hormone activity, and so, facilitating adequate and appropriate insulin responses.

So fiber is one potential mechanism. The low saturated fat aspect of these diets, I mean, obviously, total fat has been restricted to 10%. Saturated fat, certainly animal fat is entirely excluded. And this is highly plausible based on a lot of the research that we've seen come out from NAFLD research both Hannele Yki-Järvinen's group in Finland and Leanne Hodson's group at Oxford, and it's quite clear that even independent of an energy deficit, saturated fatty acids have a significant effect on fat in the liver, and can increase liver fat independent of an energy surplus. It's also clear that they mediate not only via increases in

liver fat, but via other mechanisms, insulin resistance, both hepatic and peripheral insulin resistance. So looking at the potential insulin sensitizing effects of a whole food plant based diet, the combination potentially of the high fiber and almost nonexistent saturated fat intake would be certainly two aspects of the macronutrient profile that we would think from wider research could provide quite a plausible explanation for some of the beneficial effects on, say, fasting insulin, or even peripheral insulin sensitivity that we've seen in some of the other research. And then, of course, things like the restriction on refined grains and sugar – again, if we're thinking about the relationship between visceral and liver fat and insulin resistance as it relates to diabetes, the twin cycle hypothesis which we can come back to clarify later, but essentially, this cycle of increasing liver fat, elevated circulating free fatty acids and triglycerides, compounding insulin resistance in the liver, impaired glucose uptake, and then, the liver continuing to pour out glucose rather than actually suppressing glucose production, which in otherwise healthy, normal functioning liver, it would, then sugar and refined carbohydrate obviously come into the equation. Nevertheless, we know from that research that that seems to only be a problem in conditions of overfeeding, and certainly, at maintenance level energy, or even in the context of an energy deficit that sugar and refined carbohydrate may not be as deleterious as the composition of fat in the diet is. But these are all aspects to the macronutrients, and indeed, the food based choices and selection options that make up the whole food plant based diet, that I think would be quite plausible, as potential explanations for a benefit to blood glucose management, and indeed, insulin function and sensitivity.

DANNY LENNON: Yeah, I guess, at this point, and this is something I'm sure we'll spend a bit more time on later on after we look at some of the trials, but really, given any of those potential mechanisms, really we have to then distinguish

between two questions one could ask. Are we asking, could a whole food plant based diet benefit someone who has type 2 diabetes? Because that's one question where we could point these mechanisms and say sure. Or are we asking, is a whole food plant based diet uniquely superior to other dietary interventions? And if so, how can we say it's superior given that any of these potential mechanisms seemingly could also be done with different dietary patterns, in a number of them, there's a number that we can have high fiber intakes, low saturated fat intakes, where we're focusing on making most of the diet from whole foods as opposed to ultra-processed foods as an example? And so, if we can achieve all those through other dietary interventions, can we really say it's superior? And for me, that was one of the things when we look at the mechanisms that get put forward by someone advocating for this type of diet, none of them seem unique, at least, I can see, unless you start getting into claims around protein intake, or maybe dairy protein, or red meat and so on. Even those, they're not necessarily unique to a whole food plant based diet, but at least it's moving more into the direction of you specifically need this type of diet, because if you have these other food components, you won't get the same benefit. And so, yeah, I just struggle to see what question they're actually trying to answer by some of the claims they are putting forward.

ALAN FLANAGAN: And that's why this question I think is one that's commonly on the lips of listeners, and it's a conversation I've had with multiple times just engaging with people on social media is because there's a shape shifting element to this conversation, like, on the one level, we can talk about the diet by its label, and that kind of implies some particularly special effect of this particular approach and macronutrient composition and food choice. But like you said, none of – it might be easier to achieve that level of fiber intake by focusing on this, but it's not exclusive to this type of dietary pattern.

And then, the evidence for specific foods would be way more tenuous than the effects of specific nutrients, if we're making an argument that an isolated food independent of dietary pattern has some sort of deleterious effect that warrants its total exclusion from a given dietary pattern in order to achieve outcomes that would facilitate remission. And I think, ultimately, what this leads us back to is if there's a unifying characteristic between any of these diets, whether whole food plant based or other indeed kind of low carbohydrate, the unifying theme that emerges, the only thing that we can really trace a line through these studies isn't actually in relation to the macronutrient composition or food based makeup of the diet, it's in relation to weight loss, and that ultimately is what we see.

And so, to answer kind of that question you're positing is, if there was something particularly unique to this dietary pattern, then we would expect to see that independent of weight loss, we would expect to see some of these outcomes occurring in the absence of weight loss, because that would remove that potential confounder, and then we'd be going, wow, okay, there is really something to this particular macronutrient composition, or indeed, food based composition of the actual diet; and that's where the rubber hits the road for these claims, because that's pretty much absent – the literature in support of this type of – or even a diet close to this type of dietary intervention.

DANNY LENNON: Yeah, and, I guess, that's one thing we've talked about before in relation to some of these reviews that we'll talk about the benefit of such a diet for diabetes remission, and kind of draw this line of, well, we know weight loss is beneficial for those with diabetes, and then showing a trial where a vegetarian style diet or plant based diet leads to weight loss, therefore, this is the best diet for diabetes, which is clearly not what we can make from that connection. And, as you know, we know from two previous podcast guests that talked about diabetes,

Nicola Guess and Adrian Brown, who are both fantastic researchers in this particular area, both of those have also published review papers in the last few years; and unsurprisingly, note that in terms of dietary interventions for diabetes, the biggest predictor and the strongest impact is from weight loss. And that's like not even controversial at this point, and especially then, if you see claims around reversal, as we'll probably come back to later, that, in particular, where we're talking about getting beta cell function back, that is really only in the area of weight loss versus any other type of dietary intervention.

ALAN FLANAGAN: Yeah.

DANNY LENNON: But let's circle back to that in a bit, I think it's worth, for the moment, whilst I have said that, look, there are these mechanisms that we don't see are unique, someone could make a fair counterpoint, I think of saying, okay, they might not be unique, but we can actually look at trials of using these types of diets versus other types of diets, and if, for whatever reason we see a beneficial outcome or better outcomes with this type of diet, then even if it's through the same mechanisms as other types, it must mean people can adhere to them easier, or these are leading to bigger changes because of, let's say, the degree of restriction of saturated fat as one example. So that's a fair claim of like, okay, if we do have randomized controlled trials that look at these types of diets, and do show that they are better than other dietary interventions, that would actually be some good evidence. So with that said, maybe let's turn our attention to some randomized controlled trials. I think, again, this is going to circle back to a common theme you've mentioned a number of times of trying to find trials where they're specifically looking at the dietary pattern in question. But we can do our best of trying to find something relatively close, or, at least looking at the ones that are most cited. So of that, what are maybe a couple of those most commonly cited randomized

controlled trials, or ones that you think kind of look at this particular question in most detail?

ALAN FLANAGAN: Yeah, so one that I see thrown about the plant based community, possibly only with regularity second to kind of the Ornish-Esselstyn studies, which we won't cover here, because they were looking at cardiovascular disease, but is the BROAD study. So the BROAD study was an intervention in New Zealand – one of the benefits was that it was conducted within a community, and it was quite a low income community. They recruited overweight or obese adults that already had a diagnosis of either type 2 diabetes, heart disease, or had high levels of cardiovascular risk factors like blood pressure and cholesterol. And so, there was 33 participants randomized to a whole food plant based diet. Exactly as we've described, the aim was 7 to 15% calories from fat, 75% carbohydrate, 10 to 15% protein. And again, emphasis on plant foods, vegetables, whole grains, fruits, etc. There was no restriction on energy intake. The intervention group were given a kind of disproportionate amount of support. The control group were just continuing with kind of their habitual or were asked to continue with their habitual kind of diet. And the problem with the BROAD study is if I'm ever to teach a course in nutrition, and highlight one study that is an example of how not to do an intervention if you don't want allegations of bias at every level of your study design and execution, it's the BROAD study. They discussed prescribing, the researchers discussed prescribing with the participants' physicians, that's just wholly inappropriate, and may have influenced the outcome, because in the intervention group, there was a 29% reduction in medication, but massive increases in blood pressure, which suggests that participants were probably taken off their meds prematurely. They also decided that the magnitude of the benefit from the intervention was so great that they ethically had to discontinue the control group after six months and offer the intervention to them. But you

look at the actual magnitude of difference at six months, and it was paltry in relation to the main outcomes, and certainly blood cholesterol levels' difference was paltry between the two groups. So although they published six and 12 months data, the 12-month data from the study is essentially uncontrolled data.

If we're being specific to diabetes, there were two participants out of 33 in the intervention group that no longer met the diagnostic criteria for diabetes, and that was like lower HbA1c in medications, and that was about six and 12 months. But again, at 12 months, we don't necessarily have any comparison with the control group, and one of the things that other factors that may have introduced bias in this study was they discussed the benefits of the dietary intervention with participants before randomization, and then we see improvements in the control group. So it could have been that people in the control group had a level of expectation that was then disappointed and actually made improvements. And so, it's a really poorly controlled study. As far as the diabetes potential goes, it's relatively underwhelming as far as the number of participants in the intervention group relative to the number of outcomes. There was, perhaps the most encouraging finding from the whole study would be that at six months, there was a five millimole per liter decrease of HbA1c, and this brought the percentage elevation of HbA1c down, it didn't entirely bring it into non diabetic range for the intervention group. So some benefits, but overall, the difference certainly between the intervention and control group at six months were relatively minor, and at 12 months, it's essentially uncontrolled data, so there's no real points. But nevertheless, the BROAD study did actually use this specific diet that we're talking about, and is of cited in support of this particular diet, but an honest kind of objective evaluation of the results and the methodological quality of the study, which is appalling in terms of the potential for bias,

it's really underwhelming results as far as the dietary pattern in question goes.

DANNY LENNON: Right. And just to pull back on a couple of those methodological issues that you pointed to, because I think they're worth really emphasizing for people as a kind of a meta point of interpreting nutrition more broadly, you mentioned, number one, this issue of having it discussed with participants beforehand, and then you also mentioned the discussion of prescribing with physicians as well. Can you maybe just again, reiterate both of those and explain why that is such an issue?

ALAN FLANAGAN: Okay, so there's two elements, and actually, we've got a nice contrast in terms of how to potentially manage these issues with the Lyon Diet Heart Study as well. So there's two issues, one is known as an attending physician bias, and then, there's investigator bias. And so, attending physician bias is whereby a prescribing medical doctor or practitioner might alter treatment for a patient, if they know that that participant – if they know that that patient is participating in a comparative intervention study. And the thing about the BROAD study is they openly and explicitly stated that they discussed prescribing with general practitioners, but the general practitioners made all prescribing decisions. Again, in the Lyon Diet Heart Study, as an example, to deal with that, they made sure that the, which was secondary prevention, so all the patients in Lyon Diet Heart Study were in regular medical contact. So they made sure that their doctors were unaware that their patients were taking part in a comparative intervention trial. And that's one way of doing that is you blind the doctors to the fact that the patients are in an intervention study, so that in the BROAD study, introduces a huge amount of potential for bias, and potentially, we see that play out in the study because, like I said, there was a 29% reduction in medications, but it appears that that reduction of medication was premature, because, A, the magnitude of actual

reductions and risk factors was tight, but not only that, blood pressure significantly increased in the actual intervention group.

And then, the second level of bias is what would be called investigator bias. So that's the potential for the participant knowing they're in a study through the investigators kind of conduct to influence the outcome, because you end up having benefits from being part of a study that are unrelated to the actual intervention or treatment. So one of those could be the number of contacts between participants, and the researchers in an intervention group is significantly higher than the number that the control group get. In the BROAD study, the researchers showed the participants in the intervention group the documentary Forks Over Knives like another James Cameron kind of vegan propaganda, which was shown alongside, and this is the quote from the study, an accompanying film endorsing the whole food plant based diet. The subjects were – the participants in the study attended presentations by doctors. Now, we can only imagine what those presentations included, and the lack of objectivity is a foregone conclusion, I imagine. And then, they discontinue the control group after six months, because while the results may have reached statistical significance, it's a really underwhelming clinical significance, and there was no reason to discontinue the control group after six months if we actually look at the results, particularly in terms of cholesterol levels in both the intervention and control group.

So both the potential for, and again, Lyon Diet Heart diet did a nice job of trying to control for this. So, for example, in recruitment, in the BROAD study, they actually explained the benefits of a plant based diet to participants before randomization. That's just an absurdly inappropriate method or approach to randomization. In Lyon Diet Heart, they did a two-step process. So the participants originally

signed consent to participate without knowing that they were signing up for a dietary intervention necessarily, so the consent to participate in this study; and then, after the consent to participate, they were then randomized. So they made sure that then the intervention group signed a second consent then after they were randomized to agree to change their diet, but it meant that the actual participants never knew they were being compared to another group, which could introduce bias when people know they're being compared, the Hawthorne effect it's known as – they know they're being compared and they know they're being monitored, so they change their behaviors even more. So Lyon's Diet Heart Study is a really good example of, you know, people say, oh nutrition interventions they can't, well, this was a single blind study, but they did multiple checks and balances to ensure rigor in their randomization, and in checking the potential for researcher and investigator bias and in attending physician bias. The BROAD study threw all of that out the window in the most blatant way, and it's really difficult to see it as anything other than an entirely biased intervention, both at the level of randomization right through to the actual execution of the study.

DANNY LENNON: So to maybe move on to another one that I think is probably up there with some of the most cited trials on this particular question is one from Neal Barnard 2016 paper, where again, they looked at this low fat vegan diet, so 10% of calories from fat, 15% protein, 75% carbohydrate, and I suppose, interestingly, in this, they compared it with a portion control diet as they termed it, which seems kind of relatively similar to the intake of the vegan diet that they're comparing it to, and kind of put that in line with American Diabetes Association guidelines. So 22-week randomized controlled trial – this one, again, suggesting that there may be benefit or at least is pointed towards that, but there may be some caveats as to why we see some of those magnitudes of difference.

So for some of the results with that, can you maybe kind of give a quick overview, and then maybe some explanation as to what you make of this as being cited?

ALAN FLANAGAN: Yeah, so this is commonly cited by Barnard himself in review papers as well. This is, again, evidence that this kind of whole food plant based diet, 10% energy from fat improves particular diabetes related outcomes like HbA1c, and/or medication use. And in this study, one of the interesting things is they looked at differences relative to people who had either reduced or not reduced medications, and you did see a 1.2% reduction in HbA1c in participants in the whole food plant based diet group, compared to 0.38 in the controlled. And so again, that could be clinically meaningful, depending on their baseline level of HbA1c, but if someone was at 7.5, for example, this would bring them just below the kind of criteria for controlled blood glucose. But you'll often see this cited in review papers without the actual follow-up explanation that's most important, because the analysis did look using a multiple regression of the various components of the intervention that may have influenced HbA1c levels to determine whether it was mediated by diet or changes in bodyweight. And so, they had weight change, they had their baseline HbA1c status, and they had their diet group, whether they were in the whole food plant based diet, or this portion controlled diet, as the potential predictors of the improvements in HbA1c. And this was in people who didn't change medication, so their medication stayed constant; and the effect of diet was not significant, and this is expressed, like, this is in the study. It's not something you have to go digging to find, it's in the text of the results. And so, we're not seeing an independent effect of diet, we're seeing that weight loss improves HbA1c. Well, that's entirely consistent with what we know from wider diabetes research, and there's certainly nothing unique then in this context about this particular dietary intervention. So yes, there was this

improvement in HbA1c in people with constant medication use or their medication use wasn't changing, but there was no independent effect of diet and weight loss was the primary driver of these improvements in HbA1c.

DANNY LENNON: Yeah, so to recap that, it's very important when thinking about this study, and like you say, is right there in the study itself. Of the participants who didn't see a medication reduction in that trial, you see that there was a significantly greater reduction in hemoglobin A1C for the vegan group. You also see that comparing the vegan group to the kind of controlled American Diabetes Association group, you see greater body weight reduction. So in order to see the effect of body weight or to remove that, do we still see this effect, we can look at this regression model that was done; and in that model, the effect shows that there is no effective diet group, it's no longer significant once you account for this change in body weight. And so again, like you say, fitting in with what we know already that body weight changes, if you get a greater reduction in body weight, that tends to correlate to these magnitude of changes, and that can explain why we see this difference between these groups.

ALAN FLANAGAN: Yeah, and crucially, to the kind of bias that you see in the review papers by many of these authors that were mentioning, they won't mention in the review that weight loss was the driver of the outcome. Right? So they'll frame it in a way that makes it appear that the diet was responsible for the HbA1c changes, rather than the diet group lost more weight, and that improved HbA1c. So there's a lot of framing that goes along that people should be aware of with some of these authors.

DANNY LENNON: One to maybe quickly recap on, seeing as we talked quite a bit about fiber earlier, and this is again, one that gets cited a lot, despite it being a study back from the 70s, and this is one I think you went into quite some detail on in

episode 385 of this podcast, if people want to go and listen to that, we did an episode on insulin resistance, and Alan covered this in quite some detail, but it was the Anderson & Ward study. But maybe just here to recap on some of the main points and how it might fit into this discussion, what is the main thing you would point people to on this study?

ALAN FLANAGAN: Yeah. Well, as far as kind of the claims for this kind of specific whole food plant based diet approach go, as they relate to either the term remission or indeed reversal, this is really the only study that can actually come close to being both the exposure of interest, i.e., this whole food plant based diet, and the outcome of interest. The other studies don't actually have diabetes remission as an outcome, and they're often maybe using a whole food plant based diet, but even the macronutrient composition prescriptions often not achieved entirely, for example, in the Barnard study we were previously mentioning, 17% was as low as participants got their fat intake. So this study is now 43 years old. It remains a very interesting study, but it really hasn't been replicated. The study was in men with insulin dependent diabetes as they would take it, so they were type 2 diabetics who were taking insulin, and it specifically was – it wasn't called a whole food plant based diet back then, it was called the high carbohydrate high fiber diet. So 10% or less calories from fat, 70 from carbohydrate, but they aimed specifically for 65 grams of fiber a day; and these were inpatient studies largely, where the patients and the participants were maintained at their body weight. So this is a study in which weight loss is not necessarily a confounder, as it is in the previous study that we mentioned. And half the participants were able to discontinue insulin use entirely, so they no longer relied on an external insulin shot to manage their blood glucose levels; and the remainder also, there was varying degrees of reduction in the actual dose that they needed. So on average, the daily dose decreased from 26 units to 11 units on the high carbohydrate

diet, and there were significant improvements in their actual blood glucose levels after a meal measured over three hours.

Now, this then gets kind of taken up as evidence of reversal or remission, however, the key distinction between the Anderson study, and the reason why I don't think we can place too much stock on us until it's replicated in a modern context, is because of the characteristics of the participants. The participants were lean participants, they did not have visceral adiposity, they were not overweight. This was a type 2 diabetes occurring at a time without the complications of type 2 diabetes that we associate in the modern context. Indeed, the whole genesis for Roy Taylor's twin cycle hypothesis is that diabetes now is a condition which is exacerbated by the development of visceral fat, the development of fat in the liver, the overspill of that fat from the liver into other visceral organs, the pancreas, in particular; and it's actually getting that fat out of the pancreas, out of the liver, reducing significantly visceral fat via reductions in total body weight that is the evidence that we currently have for kind of reversal, quote-unquote, in terms of restoration of beta cell function.

But we can't make those inferences from the Anderson study, it's not possible to extrapolate those lean participants using exogenous insulin to today. And sure, based on wider research that we have, there's potentially this effect of such a high fiber intake on peripheral glucose uptake and insulin sensitivity, potentially hepatic insulin sensitivity, and there's potentially the effect on incretin hormones and actual augmenting first phase insulin secretion, but we don't know, because the study is 43 years old. So I find the Anderson study perhaps the most intriguing of any of the literature on this potential dietary approach. I'm very open to the potential for this kind of prescription to have a meaningful impact in diabetes management, potentially independent of

weight loss; but until that study is replicated, I just don't think it's particularly appropriate to cite it in the context of the type of pathophysiology we have for diabetes in 2022.

DANNY LENNON: So there you go, someone please go through that study, if you are looking for something to do. With that maybe last couple of things to note, and some that specifically focus in on insulin or insulin secretion from the beta cells, as we've noted already that this is something that may be of interest. And some of the more recent trials that are looking at plant based diets, vegan diets, etc., come from Hana Kahleova and one of those is 2016 paper. There's also some kind of reviews that mentioned some of their other work. Maybe if we look at the 2016 Dean paper, can you maybe just mention why this gets talked about, what is it that is particularly cited about it, and what do we actually know from this?

ALAN FLANAGAN: Yeah, so this study used kind of validated models to look at the responsiveness of insulin at a given concentration of blood glucose. That's really the most exciting finding from this study that is often mentioned. So these were otherwise overweight participants with obesity, but they were otherwise healthy, they were non-diabetic. But they did – they were randomized to this kind of whole food plant based dietary intervention versus just a normal control. And there were two primary findings, one is a significant reduction in kind of basal insulin secretion, and then the main finding that's kind of that's portrayed in the figure in the paper is that insulin secretion as a function of the plasma glucose concentration was significantly improved relative to the controlled group over the 16-week period. But when you actually go to the main table of the results for the various glucose and insulin parameters that were used and examined, again, it's kind of, it's certainly slightly more underwhelming, in that there was no significant difference in oral glucose tolerance or insulin sensitivity, oral glucose insulin sensitivity over three hours

after a test meal; there was no difference in mean plasma glucose or insulin, total insulin secretion and other parameters. So yes, this kind of like modeled approach of insulin secretion as a function of plasma glucose concentration seems like an encouraging finding, but the overall parameters of glucose and insulin, both fasting plasma levels and postprandial and responsiveness in terms of total insulin secretion weren't significantly different between the whole food plant based diet intervention and the control group.

So I think if we're taking something from that, that then relates to their 2020 study, which also use this kind of low fat vegan diet, probably the best finding from that study and Hana Kahleova was the lead author on as well is the significant reduction in fasting insulin concentrations. And again, that might relate to certain characteristics of the makeup of the diet in terms of the fiber and whole grain content and otherwise, but at least we could say that that is a rather consistent finding in terms of improved fasting insulin levels. However, both of these studies, it's really important that we're granular with the population; both of these studies, participants were overweight or had obesity; and most of their clinical markers, or nearly all of them, certainly in the 2020 paper were all within normal range anyway. So yes, there was a significant reduction in fasting insulin, but their fasting insulin was well within normal range already. So there's the potential for these findings to kind of be overhyped and over-extrapolated as it then relates to diabetes, because these are not diabetic populations. We're not seeing reductions in, for example, fasting insulin or other parameters that then translate to anything related to remission, because they're already in normal healthy ranges. And indeed, one of the big findings of the 2020 paper that is kind of hyped up a lot is the reduction in liver fat. 5% of liver cells filled with triglyceride, 5% of liver cells of hepatocytes with intracellular triglyceride is the diagnostic cutoff for NAFLD, nonalcoholic fatty

liver. The baseline level in these groups in a subgroup of participants in the 2020 study was 3.2, and it went down to 2.4. Okay, so there is a statistically significant reduction in this, and again, in a review paper, you'll see this cited as evidence that a whole food plant based diet reduces liver fat. But in the paper itself, you'll see that the reduction in liver fat, most strongly correlated with loss of body weight in the whole food plant based group. So it was both loss of body weight and fat mass, which correlated with the reduction in liver fat, and with the change in insulin resistance. And in the paper, and in review papers, the authors will misrepresent the direction of effect, okay? So they will say that it was the diet that improved insulin resistance, it was the diet that led to liver fat reduction. Well, no, it was the weight loss that led to the reduction primarily correlated with the reduction in liver fat, and it was the reduction in liver fat facilitated by weight loss that led to the increase in insulin sensitivity. So yeah, both of these studies have some interesting findings, but again, the magnitude of the effect is often small, and in most parameters, there's no statistically significant difference between intervention and control groups, certainly in the 2016 study, and the 2020 study, while we're talking about improvements all within a range of normal, and certainly nothing that would suggest an independent effective diet that's not related to weight loss.

DANNY LENNON: So that kind of leads us perfectly actually to really the crux of this issue, as we mentioned earlier, that if we're looking at the outcome being diabetes remission specifically, and if someone is putting forward a dietary intervention that is going to lead to diabetes remission, and even if we were to grant that, we see that happen – we have to think about, well, what do we know actually leads to remission. Over and over again, we've so far said weight loss is the strongest driver of that across different types of dietary interventions, and this has been well shown by a number of

different groups now, in particular, then for diabetes remission, and then possibly even reversal, we look at things like very low calorie diets, typically meal replacement type diets like done by Roy Taylor's lab, and from Mike Lean in the DiRECT trial, which then has been replicated in other trials, notably in Qatar. Beyond that then, looking at things like weight loss, and we can maybe revisit some weight loss things in very low calorie diets in a moment, but some of the other trials then have been looked at in this area would include low carbohydrate diets, which we've talked about on maybe some previous episodes, but I think are worth mentioning here, because it shows an interesting comparison to some of the claims that we're seeing around, say, a whole food plant based diet, of we may have certain studies that have now looked at a low carbohydrate intervention for either the management of diabetes, or even possibly the impact on remission. We have things like, let's say, nonrandomized trials like at the Virta Health trial is often cited. But since then, there's been others that have come forward, but notably, I think, it's interesting to me, at least, how people who are very supportive of some of the claims around a, let's say, a whole food plant based diet for diabetes remission, immediately will push back against any idea that the low carbohydrate diet could be a benefit, or at least, they're showing it as like a pseudo benefit. Right?

ALAN FLANAGAN: Yes.

DANNY LENNON: It's helping managing blood glucose, but it's not really doing anything, but our diet is able to help put remission. So I'm wondering how you kind of do see that same kind of contrast and how does that and what line of thinking strike you?

ALAN FLANAGAN: Like all of the absurdity of the diet culture wars, it's just that the cognitive dissonance is quite striking, I mean, one of the biggest claims I'll see is they'll say, well, yeah, like you said, a

low carb diet might benefit short term glycemic control, or yeah, you might see a HbA1c reduction, but I'll often hear people then say, but it doesn't achieve remission. Well, neither does a whole food plant based diet, like, at the level of evidence, there's really no evidence that we have at this point, that the exposure of a whole food plant based diet results in the outcome of type 2 diabetes remission or reversal in a diabetic population. But that evidence literally is not there, it has not been shown in an intervention. So if all we're showing so far is that a whole food plant based diet might lead to reductions in HbA1c, might lead to reductions in medications, well, then in terms of the evidence for low carbohydrate diets, they're on a par. It's very difficult to – and then, so the pushback on that would be, well, we know that low carb diets don't really address underlying insulin sensitivity and you could actually be more insulin resistant coming off it or there's a grain of truth to this. There is transient impairment of glucose tolerance that kind of occur, but at the same time, if someone is able to do this diet and achieve it, well, then the outcomes are largely similar as far as reduction in HbA1c, and reduction or cessation of medication using that approach.

So I find very little to pick up the difference, if I was to really think about the concept of underlying insulin sensitivity and glucose tolerance, then I would probably favor more of the kind of low fat higher carbohydrate approach, simply because of the wider evidence of improvements, genuine improvements in actual peripheral glucose uptake, otherwise relative to some of the evidence for kind of the potential for underlying insulin resistance, certainly peripheral insulin resistance on low carbohydrate or ketogenic diets, not really to be something that is addressed by the dietary pattern. You're controlling blood glucose levels, and taking the need for peripheral insulin sensitivity and glucose uptake out of the equation somewhat. Nevertheless, if we're just thinking about the outcomes, it's really difficult

to see how one is touted as evidence for remission over the other, when the actual outcomes we have are relatively similar.

DANNY LENNON: Yeah, one of the other areas that I think is interesting to ponder, because there isn't really much good evidence right now, although I know a few groups are working on is in relation to dietary protein, and I think, particularly in the last couple of years, Nicola Guess, in particular, has talked quite a lot about this like, this is a really useful hypothesis to explore, and may explain why we're seeing some real benefits observed by people that may be following a low carbohydrate diet or other types of diets where you see an increase in dietary protein, and how that could potentially be of benefit. And interestingly, that's commonly seen as a negative by some that put forward a whole food plant based diet, particularly in the context of diabetes, and it's one of the reasons why they would say that a low carbohydrate diet, for example, is so inferior to a whole food plant based diet for diabetes is because of the protein content of a low carb diet. Although now that seems like, well, there's actually some reasons to suggest this can be beneficial, and I know some groups are undertaking a number of trials on high protein diets as a potentially beneficial, although right now, I don't think we have enough evidence to really make a strong conclusion on that, although I do find that area quite interesting.

ALAN FLANAGAN: Yes, and I think that, you know, and I've heard Nicola and others talking about this, the potential benefit seems to have a mechanistic plausibility as far as the, particularly with certain types of proteins, and whey protein has attracted a lot of interest in this particular area, because it seems to exert almost potentiating effect on first phase insulin secretion. So it may be that capacity to preserve first phase insulin secretion which is crucial, because it's the loss of first phase insulin secretion that ultimately is the kind of nail in the coffin as far as type 2

diabetes goes. So I do find that the potential for protein generally, and certainly for specific types of proteins to have an influence on supporting the maintenance of healthy insulin secretion and function to be quite an interesting area. But like you said, the mechanistic evidence has been shown in a number of trials, but human outcome data is kind of what we're waiting on.

DANNY LENNON: Right, yeah. So being those more insulinogenic proteins, and like the way that you mentioned which we know has strong impact there, and yeah, that's interesting. So, I mean, a few the final things to know, I guess, is that in relation to these dietary interventions so far, we've talked about weight loss being this main predictor of remission from diabetes, and really the only thing that has hinted at this reversal has been large scale weight loss via something like a very low calorie diet done like with Roy Taylor's group and so on. And beyond that, we have seen some work that's suggestive of remission, but I think the larger question that we posit at the star is if someone's making a claim that a specific diet is superior to other dietary interventions, then, number one, do we have any evidence for that, and, number two, how is that diet superior to others, in what way, why would it be superior to those. And I don't think we have enough evidence in any way based on what we've discussed so far to suggest that a whole food plant based diet is superior to any other diet, or to all other diets, I should say, in relation to diabetes remission, which is a claim that sometimes is heard.

ALAN FLANAGAN: Yeah, exactly. There was, as a kind of summary, there was Roy Taylor's group published a paper in 2018 in cell metabolism, and Taylor was the lead author on it, which looked at the remission and the relationship with various characteristics of what the participants achieved, physiological and metabolic characteristics that were achieved, and how it related to beta cell recovery. And as a kind of summation in the responders, those were

people who achieved restoration of first phase insulin secretion, versus the non-responders who did not. The responders had an average of a 15-kilo weight loss maintained, got liver fat down to less than 5%, so below the diagnostic threshold for fatty liver, had a significant decrease in synthesis of very low density lipoproteins and triglycerides. So the liver was not exporting more triglycerides in VLDL, which improves the overall kind of postprandial, and indeed fasting circulating kind of lipoprotein landscape or profile. They got blood glucose levels to less than 126 milligrams, and they got HbA1c to less than 6.5, and so, all of those characteristics together, you saw an increase in first phase, a restoration of first phase insulin secretion, and an increase in maximal insulin secretion. The non-responders lost less than 10 kilos of weight loss, conversely, didn't get liver fat down to less than 5%, so liver fat stayed over 5%. As a result, they still had an increase in synthesis of triglyceride and VLDL1 triglyceride in circulation. That would exacerbate insulin resistance in the liver and have knock-on effects as well then for cardiovascular kind of risk as far as lipoproteins go. Blood glucose stayed over 126 milligrams, HbA1c didn't come down to below 6.5. So again, all of those characteristics combined, you see no restoration of first phase insulin secretion, and no change in maximal insulin secretion. So we know what these kind of characteristics are, but these characteristics, in terms of the underlying metabolic physiology, really appear to be contingent on magnitude of achieved weight loss, and, as a result, that weight loss facilitating quite dramatic reductions in visceral fat, and particularly, fat within both the liver and the pancreas. And there's also potentially the relationship with duration of diabetes, and that's something that has come out in some of Taylor's research that the longer one is from a diagnosis of type 2, the harder it may be to actually achieve a restoration of first phase insulin secretion, and there's some evidence that perhaps people who are within

six years of a diagnosis might have a better chance of actually achieving what we would call, quote-unquote, reversal, i.e., this restoration of beta cell function. But as far as remission goes, the hyperbole from both diet camps, both kind of plant based in relation to this whole food plant based diet, and from the kind of low carb ketogenic, it really is divorced from the veracity of the evidence in support of both. And yes, both diets might achieve reductions in HbA1c; yes, both diets might achieve reductions or cessations in medication use; but both of those outcomes based on current evidence appear entirely contingent on that diet facilitating weight loss. And at this point, we have no evidence that there is a specifically independent effect of diet on any of these particular outcomes and certainly on remission itself.

DANNY LENNON: Yeah, I think that in itself is a perfect summary of everything we need to encapsulate with this episode. So I think that might be a good place to leave things there.