DANNY LENNON: As I was talking to you earlier, at what point did you see that academia and particularly research in this specific field was the thing for you, what got you excited about that in particular?

NICOLA GUESS: So I worked in the NHS for three years and what was evident was the only advice was limit carbohydrate. Now that made sense, the community I was working with was largely South Asian, and people would have type 2, have an entire plate of rice with a Lucozade to wash it down with, so that's kind of a no-brainer. But other than that, there wasn't really much I can do, and actually we don't know that much about the effect of diet on type 2 diabetes. And so I thought the best use of my time I think is to try to understand much more about this and then translate that research to clinics.

DANNY LENNON: So before we get into any of this stuff around type 2 diabetes, prediabetes and so on, it's probably a good idea to get into some clear definitions, so we are all on the same wavelength to know what we're talking about. So with respect to type 2 diabetes specifically, what is the most accurate or a comprehensive way we should frame that in our mind to explain what that is?

NICOLA GUESS: They are all quite long winded. So diabetes is the condition of hyperglycemia, type 2 diabetes we define with a fasting glucose of up 7 millimoles per liter or a two-hour glucose of above 11.1, that's the diagnostic criteria. So one of the ways we diagnose that, if anyone's had any kids and you've had a glucose tolerance test when you were pregnant, you'll know this, we give people a really disgusting sugary drink; two hours after that sugary drink we measure their blood glucose. So if your fasting is above 7 and your two-hour glucose is above 11.5, so 11.1, that's type 2 diabetes. So it's basically hyperglycemia, that's it, and we diagnose it based on clinical risk factors. There is no easy way at all in a GP practice to say that's type 1, that's type 2. Historically, we've done it by age, by weight, but actually it's a little bit – we're learning it, it's cloudier than we thought.

DANNY LENNON: So with that difficulty to diagnose, does that present like a problem for people who may be on the path towards type 2 diabetes and how much, I suppose, underlying damage, for a lack of a better word, can be done before we reach a diagnosis?

NICOLA GUESS: Oh, that's a great question, yeah. So, because it's a continuum, your blood glucose basically, 10 years prior to diagnosis, starts rising and rising and rising. And we diagnose it, like we say on these thresholds, but there is real variability within those thresholds. So basically, a lot of it is people would get some symptoms, so they get thirsty, they'd be urinating a lot and need to drink more water, still be thirsty, still be urinating, they might find themselves losing weight. People typically go to the doctor, and then if you do and you have these measures, then they diagnose you. But you make an excellent point. So half of people, when they're diagnosed with type 2 diabetes, already have some macro vascular damage. So they already have basically cardiovascular disease, they have the stuff we get concerned about. And so, we think that

happens in the prediabetic stage. So people could have prediabetes, there are no symptoms, completely unaware of it, and all of the damage or lots of the damage is being done already.

DANNY LENNON: Right. So we have this kind of progressive disease that's happening, we have this state of prediabetes before, we have a diagnosis of type 2 diabetes. So under the surface, what's going on with this prediabetic stage as someone is progressing along to that point?

NICOLA GUESS: So primarily, when someone is developing type 2, there are two primary pathophysiological factors. So the first is insulin resistance that I'm sure lots of people have heard of, and essentially this is when the tissues, primarily muscle and liver, don't respond properly to insulin. The second thing that happens is that you get defective insulin secretion. So mostly, we think this is about the beta cells, so the beta cells in the pancreas are the cells that produce insulin. What we do know from early studies in people who have relatives with type 2 but also their kids, their blood glucose isn't high, but they have the genetic risk factors for it, they already have some signs of beta cell dysfunction. So a lot of these things are present really, really early on in the disease. So it's defective insulin secretion and insulin resistance. Just to make a couple of points really clear, there's lots of people talking around on the internet that type 2 is insulin resistance, that's the only thing that matters. That's not true. About 60% of the population have insulin resistance and, yes, we need to be concerned about it. But you don't get type 2 unless you also have dysfunctional beta cells. So that's a really important distinction. The seminal defect in the development of type 2 is that the beta cells functionally don't work properly.

DANNY LENNON: Right. I think that was one thing that I was going to ask about of when we have this insulin resistance and this decline in beta cell function,

is that relationship between that they are intrinsically tied together, are they two independent things that once they both manifest we have this issue?

NICOLA GUESS: So this is an incredibly complex question, and it's more complex because these things are difficult to measure. What we think happens is that there's no set way of getting type 2. So let me give you an example. I might have a patient, and I would guess, if they were Caucasian, 50 years old, a BMI of 35, and they develop type 2, that a lot of that, is insulin resistance, is a major part of that. And actually, yes, they'll have beta cell failure or functional failure, but most of it is insulin resistance. And they're quite easy to manage because weight loss improves insulin resistance. Let me give you another example. If I have a patient who's 28 years old, Southern Asian, probably very slim, maybe active, and they have type 2, then insulin resistance is a tiny part of the equation. There's probably a larger contribution coming from the beta cells. So the heterogeneity, the varying character of type 2 diabetes, we're beginning to realize.

DANNY LENNON: When we talk about this decline in beta cell function, how can we frame that, like more precisely, what's going on? In other words, why is that an issue, what is causing some of the pathophysiology that leads from that?

NICOLA GUESS: This is the toughest question in research, because it's really, really hard to measure. There are lots of hypotheses. So some of it is genetic, like I said, if you can find a five-year-old who's perfectly healthy, isn't overweight, and has a defective beta cell function, that suggests there's some kind of early link to or hereditary cause of it. In terms of though what happens when it develops, this is really a vicious cycle. So there are a couple of hypotheses or theories around it. One is called glucotoxicity and the other is lipotoxicity. So glucotoxicity, so glucose, toxicity speaks for itself, it's the idea that glucose itself is toxic. So

above a certain concentration, glucose becomes toxic to the beta cells. So then you imagine a situation where you're developing prediabetes, your blood glucose is going slightly up and it's elevated kind of all the time. That itself starts adding to the destruction of the beta cells. What also happens when you develop type 2 diabetes is you get elevated lipids circulating around the blood, and again this hypothesis is that, okay, so maybe when you start developing elevated triglycerides or fatty acids, they then too start damaging the beta cell. So it becomes this vicious cycle and this is when it's really hard to identify the primary factor going wrong, because there's lots of different factors and they all interact with each other.

DANNY LENNON: Right. So once this dysfunction is present and a risk with this being, may be an over-simple question, why is that a problem, what is it that the beta cells are doing that once we see the kind of function, what is that leading to?

NICOLA GUESS: Okay, sure. So the pancreas produces insulin all the time, it produces insulin in the fasting state, they're not that much. What's really evident when someone starts developing type 2 is the postprandial glucose rise. So the pancreas or the beta cells of the pancreas actually have glucose sensors on them, it's really sophisticated, that they can sense the tiniest rise in your blood glucose. So let's imagine you have half a slice of toast, you maybe have a small sip of orange juice, whatever it might be – when your blood glucose moves as much as 0.3 millimoles per liter, a tiny amount, the senses and the pancreas can recognize that and it starts to produce insulin, and that's really important because it enables the body to anticipate a rising glucose and that you produce enough insulin to control your blood glucose. So let me just go back a few steps. So what insulin actually does is insulin moves, simply put, glucose from the bloodstream into the tissues. So it will take glucose and put it into the muscle where it can be oxidized and used for energy, it

can take glucose and it gets stored in the adipose tissue as triglycerides, and it can help get glucose and fat into the liver and other tissues. So if that's not happening, if insulin isn't working properly, glucose doesn't go to the muscle, it doesn't go into the adipose tissue, it stays in the blood, and that's hyperglycemia. So when you don't have an appropriate rise of glucose after you eat that causes really marked, we call them glucose excursions. And this is how bad it can get. So in a healthy person, I would be very surprised if your blood glucose at any time went above 9.5 millimoles per liter after you eat. We see people with 30 with type 2 diabetes, yeah, because of the combined effects of insulin resistance, but primarily that beta cell defect.

DANNY LENNON: Perfect. I definitely want to get back to blood glucose excursions and spikes after meals a bit later on. Before we get there, we've already kind of given an explanation of the diagnosis of type 2 diabetes, what cutoff points they have. For prediabetes, what are we talking about there in order to determine if someone is prediabetic?

NICOLA GUESS: Okay, so I said that type 2 diabetes is a fasting of 7, prediabetes starts at 6.1. Then I said the two-hour glucose in type 2 starts at 11.1, in prediabetes it's 7.8. So if your fasting glucose is 6.1 to 6.9, that's prediabetes; or if your two-hour glucose is 7.8 to 11, that's prediabetes. But I should add, this is total guesswork, because why do we care about prediabetes, like why have we got these diagnostic criteria, it's because we want to identify people at risk of type 2, and the cut-offs that we have are incredibly poor to predict type 2 diabetes. If you take people within those boundaries that I talked about, about half of people in a year will develop type 2, half of people will stay prediabetic – sorry a third of people will develop type 2, a third of people will stay prediabetic, and a third of people actually go from prediabetes back to normal. So prediabetes is a very controversial – it's not

even a diagnosis, but we have those criteria to kind of guess really.

DANNY LENNON: Right. So that two-hour response is based on like an oral glucose tolerance test.

NICOLA GUESS: Absolutely, yes.

DANNY LENNON: Okay, if I'm picking you up right, we have for prediabetes, it can be when fasting blood glucose is between 6.1 and 6.2 or it could be a case where that two-hour postprandial response in a glucose tolerance test is elevated. Does that suggest then if it's one or the other we could have a case where someone maybe has a normal fasting blood glucose but this really weird response after they have our challenge with glucose?

NICOLA GUESS: Yes, so that absolutely happens, and again it comes back to the heterogeneity of type 2. So prediabetes is really an umbrella term, and it's more a term for public health, because to get people to realize they're at risk, prediabetes kind of sums it up quite nicely, but actually it's an umbrella term for different conditions. So one of those is impaired fasting glucose, like the name speaks for itself, your fasting glucose is elevated. But if you eat something, your postprandial, so your after meal glucose actually is normal. On the other hand, you can have people who have normal fasting blood glucose. So if they went to the doctor, had their fasting blood glucose measured, there would be no concern whatsoever because it would be completely normal; but then you give them something to eat and they get this massive excursion. Do you want to go into the hetero – the pathophysiology of that, the one that's different?

DANNY LENNON: Yes, please.

NICOLA GUESS: So you might be thinking, well, that's like two separate conditions and you're absolutely right, yes it probably is. So what we think happens, if you have impaired fasting glucose, it's because

your liver, but not your muscles are insulin resistant. And that kind of makes sense because the liver's role is primarily to keep you alive when you're fasting, so it can produce glucose and it can produce fatty acids that keep you alive. So it makes sense that if insulin is not working properly on the liver, that's when glucose leaks out of the liver and, boom, your fasting glucose is elevated. On the other hand, after you eat, in the normal state, your muscles take up 80% of the glucose. So postprandially, your muscles really suck out tons of the glucose from your meal. So if you've got muscle insulin resistance, again it makes sense that after you eat postprandially, your glucose is elevated only after you eat. So actually they are probably two separate conditions, and what we're realizing probably and what my work tries to do is figure out how we can target nutrition to the underlying pathophysiology. So insulin resistance in the liver or insulin resistance in the muscle, because they're two very different things.

DANNY LENNON: So if we talk about these spikes in blood glucose or where it gets elevated to a certain point, I think that's probably a good place to clarify a few things, because the way it's often framed it's that anytime someone spikes their blood glucose it's a bad thing per se, and here we've already talked about glucotoxicity, we've talked about this poor glycemic response after meals where blood glucose stays elevated. But how should we think about spikes in blood glucose, so on one hand, are they necessarily a problem, or what is it that makes an elevated blood glucose problematic?

NICOLA GUESS: Yeah, that's a really, really great point. So we know that type 2 diabetes, the hypoglycemia that you see in type 2 diabetes, we know that's harmful, it causes damage to the blood vessels, causes damage to the nerves, etc. In prediabetes again, that evidence is pretty convincing in terms of observational studies, it definitely causes damage and increases risk of cardiovascular disease. Then it becomes, in my

opinion, people are kind of developing a little bit of paranoia about this. So like I said, let's put this into context, prediabetes is if your fasting is above 6.1, and postprandially, two-hour glucose is above 7.8. We don't know much about what happens in between. So let's say, I gave you a glucose drink and 30 minutes after you took the glucose drink, your blood glucose was 11.2. If it comes back down again, I don't think that's a concern. We have no evidence that that might be a concern. So there isn't convincing data that hyperglycemia at some points after you eat is harmful whatsoever. And there's a growing trend of using CGMs, so CGMs is continuous glucose monitoring, it's designed for people with diabetes, it measures blood glucose every five minutes for 24 hours, and it's great for them to keep their condition under control. What you're seeing is that you have perfectly healthy people without prediabetes at no risk of prediabetes, using their stuff and panicking because their glucose, 20 minutes after they eat, goes to 6.8 or something, and that's really concerning because we have no idea it probably doesn't cause any harm whatsoever; because if you took an athlete, like a very, very healthy person and you gave them three slices of bread, their glucose would, as you call it, spike, but it'll come straight that down again, because they are insulin sensitive and they can use it properly. So I think you make a really good point. We need to really differentiate between the hyperglycemia of diabetes and normal physiology.

DANNY LENNON: Right, yeah, that distinction I guess between an elevation in blood glucose versus chronically high blood glucose...

NICOLA GUESS: Absolutely, yes.

DANNY LENNON: So presumably, does the same thing hold true if we're talking about insulin, because a lot of time the same kind of argument gets put forth that if you have this big spike in blood glucose, your insulin goes up, and then these are

problematic. So I'm just wondering, does a rapid response in terms or a rapid rise in glucose and insulin, is that any more problematic versus a more continuous but not as big a spike over the day, so let's say the area under the curve for insulin over 24 hours was the same, but one had these massive increases and then drops again versus one that's kind of just more continuous, is there anything to suggest that those things play a role?

NICOLA GUESS: So that's a really good question. Does everyone know what area under the curve is?

DANNY LENNON: Sorry, I should have explained things.

NICOLA GUESS: I was impressed. I mean, so basically what we're talking about is like, oh isn't it over, like exposure to insulin, so overall 24-hour exposure to insulin. So this is this whole hyperinsulinemia thing, so if you hear someone use hyperinsulinemia without clarifying it, they probably don't know what they're talking about. So let's just take it back to normal physiology. So in normal physiology, in a perfectly slim person, after you eat, like I said, the pancreas is really sensitive to changes in glucose and you should and you do get this pronounced insulin spike. I don't like the word insulin spike but I'm going to use it. So in normal physiology, you get this pronounced insulin spike, it goes up really high, really quick, and then it normally comes back down again, and that's because insulin is very powerful, it's shutting down glucose output from the liver, it's very powerful, it's shutting down lipolysis, so lipolysis is the fat coming out of the adipose tissue and it also really promotes the uptake of glucose into the tissues. So if you have this insulin spike, what that will do is switch your metabolism from a fasting metabolism to a fed metabolism, that's exactly what should happen. Because, let's think about this, if you're fasting, you obviously need glucose coming out from your liver but you have your breakfast and you have some cereal, some toast, the glucose is coming from the

meal. So you want to shut down the release of glucose from the liver immediately, and that's what the insulin spike does, and that's normal. The concern that happens is when, and this is probably two things, people get insulin resistance, so you have that normal spike, but because the tissues are resistant to the actions of the insulin, your pancreas has kind of got to produce more and more. So then it goes from, this is normal spike straight back down again, what happens with some insulin resistance is it goes up and then it kind of struggles to come down, because you've got to produce more insulin to get glucose under control. The second thing is that we know from early tests that people who are developing type 2 lose that spike. So even if you inject them intravenously with glucose, they are not able to produce that insulin spike. So then what happens is the pancreas kind of, you know when you start your car, it doesn't work properly a few times and then it does, that's what happens with the pancreas. So you don't get that initial insulin spike but eventually the pancreas gets it together, manages to produce a bit more insulin, and that's when you get this profile that looks like, it's like pathetic rise here, but then it continues for a long time after you eat. So your exposure to insulin is probably longer-lasting, and that possibly could be damaging.

DANNY LENNON: To shift to some of the dietary interventions, we can look at, to only prevent, manage, and maybe even put diabetes into remission, I wanted to start with that piece on diabetes remission or reversal, and there may be a need to maybe distinguish between some of those terms as well or at least define what we're talking about here, because at least to me sometimes there can be confusion if we're talking about a potential strategy, you can put diabetes into remission or you see places online talking about this strategy will reverse diabetes. And so, I'm just wondering, what is the accurate way to think of diabetes remission versus this idea that something is going to

mean that person no longer has diabetes, and now there's slightly different things.

NICOLA GUESS: Yeah. So in general, remission is a much better term, and it basically means is that you currently don't have the condition of diabetes anymore. There has been a proposed definition and that is that your glucose is no longer diabetic at a diabetic level and you have to have been off your diabetes medications for two months. So that's been a proposed definition, I think it's a fair one; because if we think about what patients with type 2 diabetes want, like most people hate taking their medications. If any of you are or you know people who have type 1 or type 2 diabetes, it can be awful – pricking your finger to measure your capillary blood glucose is actually painful, it's not very nice; injecting insulin every single day of your life is not pleasant. So the desire for people to come off their medications is the primary motivating factor. So people want remission because remission means you're no longer in your medications but glucose is normal. I don't like the word reversal, and I tend to see it used when people are selling something. And to me, reversal means you can go back to your normal life and not be concerned that type 2 diabetes will develop again, and it probably will.

DANNY LENNON: Right, and I think that's the key thing, and that's something that hit me when people used this term reversal, because even if you get someone to a place where they're no longer exhibiting symptoms or, like you said, they're no longer medications, does that mean they can go back to eating kind of whatever and have a response that someone who doesn't have type 2 diabetes has – and I think they're probably completely different things?

NICOLA GUESS: Yeah, so I think that this depends on how you achieve remission, because remission is super new. So if any of you are aware of the DiRECT study; this was a study that came out in the UK last year, where they used very low energy diets and they managed to get at least 50% of people

off their medication; the more weight people lost, the greater their chances of remission were. Now, that remission occurs because you get the first, the insulin spike back. So remember, I was saying, in healthy people you get this insulin spike like this; when you get type 2, it's pathetic like this; what the very low energy diet protocol does, the reason why it gets remission, the predicting factor of why it gets remission, is because you get the insulin spike back. Now, that came out last year, so we have no idea of the long term follow-up or what it looks like. Those data should be out about now, so if one-year data came out December of 2018, so the two-year data should come out now. What is amazing about that study is that they put people on a very low energy diet, so it was about 900 calories on average a day, people lost 15 kilograms of weight, that's an extraordinary amount of weight, at about three to four months, and that's when their glucose went became normal. They follow people up for a year, so they maintained their weight loss. But what's really important is that they weren't still on that diet, they were on the very low energy diet but they went back to a weight maintaining diet, so they were in normal energy balance. So what is striking and suggests there is a legacy effect at the very low energy diet is that they're still in remission at one year.

Now, I expect, at two years, those people are going to have gained some weight, and that's really going to tell us how durable remission is, like how much do you then need to control your weight and control your lifestyle to stay in remission. We don't know that yet. And so if I can just come to low carbohydrate diets, because I have a particular interest in these, low-carb – and there's no studies on this, which is just embarrassing, because there's so much talk and noise – low-carb probably is able to get remission more easily, because if you don't have exogenous, so outside carbohydrate coming into the bloodstream, blood glucose doesn't go up. It's nothing to do

with fixing the pancreas, it's nothing to do with insulin sensitivity. If you go low-carb enough, exogenous glucose doesn't enter the bloodstream, boom, your postprandial glucose is controlled. So I think that low-carb would be better at getting remission than other methods, but there's no study on that yet, a well-controlled study, but that works differently. And one thing with low-carb and low-carb you hear the cure, oh we've cured it, the moment you reintroduce carbs, your blood glucose goes straight back up again. So there's a real distinction between how you achieve remission.

DANNY LENNON: Yeah. So let's talk about some of those specific strategies. First, even before we get into very low energy diets, you talked about that 15 kilogram weight loss, and that does seem to quite trend across the data that it's weight loss can drive these dramatic changes. Is it fair to say that that would be the primary thing or primary target of a dietary intervention for diabetes?

NICOLA GUESS: At the moment, 100% yes, that's really strong data. As you say, if anyone's read that paper, there's this beautiful graph that shows, if you get 15 kilograms or more of weight loss, 86% of people get remission. If you go down to 10, it's about 57, and it's clearly a dose response relationship, the more weight you lose the higher your chance of remission. So yes, my advice to any person with type 2 wanting remission is weight loss, but I think other methods could add to that.

DANNY LENNON: Right. One interesting thing I heard, and be interested to hear if this plays out or not, when we see this pronounced effect of weight loss and improving symptoms and putting remission in place that even if someone were to gain that weight back, it's potential that they could still have a net benefit compared to if they never lost the weight. Is there anything to that hypothesis and what we have to be aware of?

NICOLA GUESS: So we know there is in prevention of type 2, so there are lots of prevention of type 2 studies where people lose weight as they always do in studies they regain it, and your risk of developing type 2, if you lose weight and regain it, is lower, than had you never lost weight at all. In terms of remission of type 2, we don't know that yet, because it's new. But what the investigators of that study are doing is doing some modeling work, looking at the risk factors of patients in remission and seeing whether that results in a reduction in risk over time.

DANNY LENNON: Okay. So when it comes to weight loss – and again this could lead us down a rabbit hole, so feel free to skip this if you wish – but what is it mechanistically that leads to weight loss being such a powerful thing for type 2 diabetes and prediabetes, what is going on that makes it that powerful?

NICOLA GUESS: So it's going to be a mixture of things. Definitely, ectopic fat, so ectopic fat means fat deposited where it shouldn't be. So liver fat is a big player here, probably pancreatic fat, weight loss reduces that really quickly. In fact, if you lose weight, you lose fat from your liver. The second thing is insulin sensitivity, partly linked to liver fat. If you lose weight, if you lose a kilogram or two kilograms or three, you improve insulin sensitivity. There's also a role for inflammation. So people talk about inflammatory factors which we know interfere with insulin signaling. We know that weight loss improves inflammation. So it's definitely multifactorial.

DANNY LENNON: So let's take a look at some of the low carbohydrate interventions because, as you say, a big interest area of yours, and you've paid a lot of attention to that, from an overview level first, why is it so interesting and compelling to you to look at this dietary intervention, and to this point, what do you think is fair to conclude about their role?

NICOLA GUESS: So I think it goes back to the weight loss conversation. So pretty much, with type 2 diabetes now, the advice is weight loss. Whatever diet you have, weight loss is going to help you. Where I think the potential advantage of low-carb is, is that you don't need to lose weight to have probably amazing reductions in your blood glucose. There is a study by Gannon, which I encourage everyone to look at, they've done a series of studies where they were beautifully well-controlled, so no one lost or gained any weight, they measured their blood glucose and their insulin 24 hours, and what they found is that blood glucose went from something like 20 postprandially down to 10, normalized with no weight loss. And that was about a 20% carb intervention or 30% calories from carbs, but they also had high protein. So this is where it gets difficult – people are really anti-guidelines and they think the diabetes guidelines are terrible because of corruption or special interests, they're not actually that – the data are quite equivocal. So protein is important because protein helps the pancreas produce insulin. So I think that study is awesome, because no one lost weight and your blood glucose normalized pretty much, that's remission. But because they gave low-carb and a lot of protein, you can't tell us the carb, so a study we're looking at is going to try to find that out.

There is another study done where there was no weight loss, this was done by Manny Noakes, don't confuse Noakes with Tim Noakes, Manny Noakes from Australia, and this was comparing ketosis as a super low-carb diet; and they had these beautiful graphs because they did a meal tolerance test, that's where you give someone a test that is low-carb and then they give – or a glucose tolerance test – before and after this diet. And what the meal tolerance test showed is that the moment you give someone a low-carb meal, the effect on their glucose is immediate, there's no need to wait for it to take effect; if you go low-carb,

your blood glucose postprandially just goes boom, right down. They followed them up for 12 weeks, gave them the meal tolerance test again, the blood glucose was still low. But they also did the oral glucose tolerance test, and the moment after that low-carb diet, you reintroduce carbohydrate, the carbohydrate goes straight or the glucose goes straight back up again. So what those data show, low carbohydrate diets probably can lower postprandial glucose amazingly while you follow the diet. The moment you reintroduce carbohydrate, your blood glucose goes straight back up again. But that was not done in people with type 2. So there are two really compelling data in other shorter term studies, but unfortunately no one will base guidelines on those data because they're not in type 2 or they also have confounding factors.

DANNY LENNON: Right. You mentioned you're going to look into this distinction between low carbohydrate with high protein versus low carbohydrate with perhaps lower protein, higher in fat, is an interesting one. Where would your hypothesis be on what's going to or would we see distinct differences? And if so, what mechanistically could be the reason why?

NICOLA GUESS: Okay, so let me just explain the study that we have plans, so basically it's a five-week long study, it's patients with diet controlled type 2; we're using CGM, so that's the apparatus I mentioned that measures blood glucose every five minutes continually. What we do is we keep the carb low all the time, so the carbs going to be 20% of calories. We start with seven days on a high-protein diet – sorry, a low-protein diet, 15% of calories – so let me start again. So keep them low-carb all the time. For the first week, we have 15% of calories from protein. We then take it up for two weeks or 30% of calories from protein. We take it down again for two weeks to 15%. So basically, what I want to see and what I think we'll see is low-carb does lower your glucose compared to the normal diet, but adding in protein has an extra

effect on blood glucose. In terms of the mechanism, it's probably because some amino acids help the pancreas produce insulin. There is some evidence – we're planning another study to look at this – that in type 2 diabetes, your beta cells can't detect glucose. So remember, I said you have the sensor that can monitor changes in glucose levels; in type 2 we know that doesn't work properly. But there is some data that suggests that your body, when you have type 2, can recognize amino acids. So if that's the case, and then maybe if you've got type 2 and you follow a high protein diet, your body can recognize the amino acids and produce enough insulin. So I think it's all to do with the insulin secretion with protein.

DANNY LENNON: We mentioned a bit earlier when we have this instant secretion and it's at a super high level chronically, that can be damaging in certain ways. Does that lend value to the idea then that even if we don't see weight loss, if someone's trying to manage that condition and they're very insulin resistant, maybe they're prediabetic or diabetic and they're on a low carbohydrate diet, that has a net health benefit from the perspective of they're not going to be asked to secrete as much insulin?

NICOLA GUESS: If I had to bet, I would say, yes probably. But physiology is extremely complex, and I don't think we know that yet. Like I said, low-carb, there's so much noise around it, it's a real value I think in type 2, but the quality of data out there is really poor, and there haven't been very good studies being done. One study that we're planning actually at the Desmond Diabetes Institute is looking at a low-carb diet on beta cell function because I actually think maybe it could help, because it would go back to what I said about glucotoxicity. If the glucose levels themselves in diabetes are harming the beta cells and low-carb can reduce blood glucose, maybe low-carb can actually help the beta cells function better. So that's something we're going to be testing.

DANNY LENNON: Is there a certain point we can reach with beta cell dysfunction where we just can't go back, that it becomes irreversible, and at what point can we maybe restore function completely or do we know?

NICOLA GUESS: So to give some history to this, type 2 diabetes is a progressive condition, and the reason we know that and we've always thought that is because within 10 years of diagnosis, half of people have to go on insulin; and the reason you have to go on insulin is because the pancreas isn't producing insulin anymore. We also know if you take cannabis, if you take people who've passed away with type 2 diabetes, and compare the weight of the pancreas and the weight of the beta cells to people without diabetes, it weighs less. So in other words, it looks like the beta cells have died. We call this apoptosis. So all of the data together suggests that it's a progressive disease and the beta cells die over time. That's what we've always thought. Then when bariatric surgery came along, so that's the gastric bypass, what was observed was that people with type 2 diabetes got cured essentially, they got remission of their type 2 diabetes within 24 to 48 hours of having the surgery, and that was amazing. Because, like I said, everyone had always thought it was progressive, and so it got people to thinking, well, hold on a second maybe it's not, because you can have people who've had diabetes for 15 years and they come up with all of their medication and their blood glucose is totally controlled. And so it got people thinking why might it be. And so before you have bariatric surgery, you have to go on a liver reducing diet so it's a two-week very low-energy or very low-carb diet to reduce the size of the liver to make the operation easier. You then have to fast prior to having the surgery. After you have the surgery, because it's a major surgery where they reattach your intestines, you can't eat much. You go on a clear liquid diet after the surgery which is like 100 calories a day, if that. Then you go on other liquid diet and that's about 300-400 calories. So

essentially, you are on a starvation diet when you have bariatric surgery for about seven to eight weeks. And so we've got people thinking, maybe it's that that's causing remission of type 2 diabetes, and that's what led to the Direct study.

Now what was observed with the bariatric surgery is not everyone got remission. Even if you lost 50-60 kilograms, not everyone did. And so, like you say, one of the predictors was how long a person had had type 2 diabetes. The longer you have type 2, the less your chance of getting remission with bariatric surgery, and we know the same is true or we think the same is true for a very low energy diet. So the Direct study only included people who'd had type 2 diabetes for six years, because probably after six years, maybe like you say, we don't know whether the beta cells have died, but it certainly looks like maybe, at the moment there is a point of no return, but we don't know when that is yet. Sorry, did I just go off on a complete tangent – I thought like you asked me a simple question and I just gave you a straight...

DANNY LENNON: No, that's perfect. I do want to come back to the Direct trial, but before that, because we've been talking about low carbohydrate diets, I think if people maybe had discussions online or got into debates around this, one that tends to be brought up is the Virta Health trial. And again, there's super interesting things to come from that, there's also some clear limitations which I'm sure we'll get to – and just in case, people are unfamiliar, Virta Health is essentially this group based in the States I believe who have this program which is a ketogenic diet in combination with lots of intensive support regularly for people, and they've basically being collecting data on that. That has been one of you – I've seen people point to as something that's kind of groundbreaking in many ways. What were your initial reactions to some of the results and data that's come from that, maybe you can fill people in on what that might be, and then your

response to that right now or what you thought?

NICOLA GUESS: So Virta basically is an online program, like where they do a ketogenic diet, it's really close one-to-one coaching, and they're basically trying to get remission, like that was the aim, they're trying to get people off their medications. What was really interesting about Virta, so like I mentioned, Direct – Direct was trying to get remission but they did so by rebooting the beta cells and they didn't include people who'd had type 2 diabetes for a long time. What was great about Virta, it was a kind of come one, come all – If you have type 2 for however long, if you're on insulin, if you're on a 100 units of insulin a day, you can go on this program. The compelling data for me from that was that people came off their insulin. So like I said, if any of you know any, if you have relatives or friends with type 2 diabetes who take insulin, it is not a nice thing to do. And so, about half of people on that program came off their insulin, so they had normal glucose and they could come off their insulin. And the other half of people on insulin could halve their dose. So yes, they still require insulin, but they need half as much, and that's really never been shown before. If we think about our National Health Service, any health service frankly around the world, are all going to be bankrupt by type 2 diabetes. If you look at any of your local GP practices or local CCGs, they probably spend in the millions every month on diabetes medications and support. So to be able to have this dietary program that gets people off their diabetes medications is huge. So that's what I found really exciting, the possibility that, yes, you can come off your insulin.

DANNY LENNON: Right, yeah, for sure. And I think when you see the magnitude of some of the changes in those results, that was the thing that kind of strikes you first. But obviously, balancing with it wasn't a randomized control trial etc., etc., but still pretty interesting to see.

NICOLA GUESS: Yeah, so let me just kind of add to that, just to make that clear. So in the Virta trial, there wasn't a control group that achieved the same weight, and this has been what's hindered low-carb being more promoted in guidelines, because they lost 15 kilograms in Virta. So they lost 15 kilograms in Direct, most of them got remission; they lost 15 kilograms in Virta, people got remission. And I'm kind of guessing, this is conjecture, I think Virta did better with people on insulin, because low-carb, lowers your postprandial glucose. But we can't say it's better because there was no control group that lost the same weight which weren't low-carb.

DANNY LENNON: With some of the other dietary interventions that tend to get discussed around this area, things like intermittent fasting, time restricted feeding has been one too. What is current state of the literature, do you believe, on some of these areas? And obviously, it's hard to navigate at this point, but what are your initial impressions of other dietary strategies?

NICOLA GUESS: I don't think we have enough evidence to say at all at the moment. So the trouble with intermittent fasting, it can mean lots of things, it can mean fasting on two consecutive days, one day a week, two days a week, separate. It could mean that you fast completely on one day or take 400 calories. So it's totally, totally varied. That's really hard to interpret. A lot of the observational work has been done, like in Ramadan, when people are fasting all day and then they're eating at night, which isn't necessarily because – when I have friends who do Ramadan, they tend to eat very high sugar, high fat sweets when they break their fast, but that's not what you'd necessarily recommend people do. So that data doesn't look good, and I think it's because people are not following fasting in the healthiest way. For me, the most compelling stuff and the most exciting stuff is coming from time restricted feeding. But there's been one good study to my knowledge in humans. So this was published in Cell Metabolism earlier this year, it was eight

people, this is tiny, eight obese males with prediabetes, and it was beautifully controlled. So one group, if I remember correctly, they could only eat between 8:00 and 2:00 p.m., so 8:00 in the morning and 2:00 p.m.; the other group could eat whenever they wanted, but the weight loss was beautifully maintained through the study. And what they found was that insulin sensitivity had improved and fat oxidation was higher in the time restricted feeding group, which is pretty compelling but, hey, it's eight people, and it's one study in humans. But there's lots of work going on at the moment in that. I think the key is like, anyone in the room, raise your hands if you think you can have a great social life eating only between 8:00 in the morning and 2:00 p.m., like what just happened to your weekend. So this kind of stuff has to be translatable, so people are doing stuff like, okay, what if you fast all weekend – fast all day and then just eat at night, how does that work, because even if something's physiologically effective, it's got to be something that translates to something people can do.

DANNY LENNON: To circle back to what we've said about weight loss being a primary driver or that that primary target for us, is there a certain magnitude of weight loss that comes into this, is any weight loss going to improve things, is there a certain threshold, or how should we think about how much is necessary to see some of these benefits?

NICOLA GUESS: Okay, so that's a really great question, and I can't answer this definitively because we have one remission trial. Certainly, the more, the better with type 2 diabetes. It looks like 12 kilograms or more is necessary, and that's kind of weird because that doesn't make sense that you would think that certain people could lose 5 kilograms and get remission, but it just seems that's not going to happen. And no one understands why this is. Certainly, what's clear, I think from the literature is if you lose 5% of weight that doesn't do anything to your beta

cells, so remember I said, with Direct, that the story there was all about rebooting the beta cells that's why you get remission, and it looks like you need a lot of weight loss to get to achieve that. But why that is the mechanism no one knows. Looking at the data, it looks like, like I said, if you lose a moderate amount of weight, you don't reboot your beta cells. So certainly, for people with type 2 diabetes, I think we need to really reevaluate the kind of weight loss we're recommending to people, because what we've done as dieticians for 20 years is, oh we are trying to eat a bit less, trying to exercise a bit more, lose a bit of weight that's really going to help you, and yes it will. But I think it's pretty clear that's not going to get remission. And what we hear, where I work in South London and Nationwide, is patients want remission, and I think what we need to be working on is ways that we can achieve that.

Let me just say one other thing about weight loss is weight loss is one of the things that's probably driving remission, but the other thing is the rate of weight loss. So if you lose 15 kilograms over a year that's going to be fine, you're going to get remission. But other studies have done a 400-calorie a day diet for seven days and basically found the same effect on physiology. So if you have 400 calories a day, that's tiny, it's mega starvation; but in seven days, you lose about 1.2 kilograms, you don't lose a lot of weight. But that does the same thing to the underlying pathophysiology, it reboots the beta cells. So possibly, if you lost 6 to 7% of bodyweight, but you did so really quickly in two weeks, that might get the same effect on remission.

DANNY LENNON: So could that indicate there it's not just necessarily the fat loss that's going on, it's the degree of caloric restrictions having some other effect mechanistically, or I guess we don't know...

NICOLA GUESS: Honestly, I don't know. It might be, and no one's ever measured this, it might be because

the rate of weight loss somehow influences fat oxidation, like your guess is as good as mine I think.

DANNY LENNON: So we have quite a few people here who are kind of practitioners, whether that's nutritionists, dietitians, a couple of doctors, and so on, people working as personal trainers. Of course the recommendations will probably vary depending on someone's scope, but when they are dealing with people who are either prediabetic or diabetic, where do you feel right now is safe to say, this is the kind of center of the bull's-eye for what we should be doing in practice, how we should aim to set this out if we can find like a theoretical best way for...

NICOLA GUESS: So prevention and management are different, so let me tackle those separately. Prevention weight loss, however, is achieved, if a person can lose weight with low-carb intermittent fasting; whatever the diet might be, weight loss is going to help prevent type 2 diabetes unequivocally. Exercise, by the way, can also prevent type 2 independent of weight loss. But when it comes to management, this is where things get a bit challenging I think, because again, certainly, weight loss is always going to help, but I think there is an ethical obligation. Now that we know that you can achieve remission – physiologically, remission can happen – I feel like every practitioner has an ethical obligation to let their patient know of the interventions and the data that are available.

DANNY LENNON: One other thing that can come in, in kind of pragmatically, is when we look at supplementation, some people will have heard suggestions around, for example, berberine can help with glycemic control. Is there anything that you think is well-established that is useful to include in terms of dietary supplements or there are others that you see promoted a lot that you think are not worth?

NICOLA GUESS: I mean, to be honest, most of the studies done are pretty poor. So I wouldn't say unequivocally there are any that I – actually, I wouldn't recommend any. Actually, one of my concerns about promoting these products, even when there is an effect, I think, cinnamon is one where there's some data which seems to be fairly consistent, but it's about the effect size, and so the effect size is how much does your blood glucose lower if you take some of these products or supplements. And that's my concern, because the effect size on glucose with weight loss is huge, the effect size on mortality with those things is huge, and that's our role as practitioners. And I think my concern with some of those other things is that the effect size is pretty tiny, so statistically, yes, it's significant, but clinically do we really care? So if I have patients who are taking some of those supplements, I might look them up, look at the evidence; if they're not going to be harmful, I don't necessarily say stop taking them if they want to, but I never recommend supplements.

DANNY LENNON: One that's probably going to be more relevant for those involved in medicine would be the role of metformin which I think is what most of those supplements try and mimic we want these benefits but never really get there. But at this stage, metformin or glucophage which people would have seen the brand name, tends to be pretty compelling and safe in general. Would that be a fair way... ?

NICOLA GUESS: Oh definitely, yes. So the metformin can lower your blood glucose by 9 millimoles per mole, so that's A1C, so taking it down to like 48, the effect size is huge, it's an insulin sensitizer. There's good evidence on CVD prevention and other preclinical trials on diseases including cancer, that's preclinical by the way, and very safe. So it's been well-studied, it's cheap, so that would definitely be my recommendation. Lots of people think we should be using it for prevention which I don't have a problem with.

DANNY LENNON: I've definitely seen that for sure. The final question was more about either people who like to monitor blood tests for themselves or get regular checkups or recommending that to family and friends and so on. We have the typical things like fasting blood glucose, fasting insulin. What else do you think is worth people keeping a monitor on, obviously in combination with their doctor, other things we could mention like hemoglobin A1C, the glucose tolerance test? Let's say, we have someone who's maybe generally healthy or is trying to become healthier, hasn't established diabetes yet and wants to just monitor things overall.

NICOLA GUESS: I mean, so this is really hard, so if I had someone who was healthy but had a family history of type 2, because remember you can be 400 pounds and completely inactive and have totally normal blood glucose levels; conversely, you can be an athlete and have type 2 diabetes, and so genetics or hereditary – is a hereditary condition. So if someone had a family history of type 2 diabetes, I would definitely keep an eye on all of those things you mentioned – and I'll come to some of these glucose points in a second. Waist circumference and weight, unfortunately, it's really unsexy. It's just so obvious and boring, but weight is what's driving this, 80% of people with type 2 are overweight, weight loss prevents type 2 diabetes, helps manage it, weight gain increases your risk, that's very clear. So if someone's gaining weight gradually over time, that's a danger, especially if they've got a history of type 2. So let me just come to the glucose, because we're using hemoglobin A1C, it's cheaper, doesn't need fasting, it's less variable in the sense that you don't get day-to-day fluctuations, but it doesn't capture everyone at risk of prediabetes. So fasting blood glucose and oral glucose tolerance test, I favor those. If I had a private practice and I was screening, I would definitely use oral glucose tolerance tests, because they pick up people that A1C doesn't. So remember I said before,

you could have a fasting glucose that's normal, could be 5.2, your postprandial, your two-hour glucose could be 10, it could be 11. A1C might not even pick up that patient, and that's a real concern because it's probably the postprandial excursions that are the most risky in terms of cardiovascular disease and other health risks.

DANNY LENNON: And for that reason, we're starting to see this shift towards more CGM use, this continuous glucose monitoring.

NICOLA GUESS: Yes, I mean, the problem is CGMs are very, very expensive, and they're licensed for the management of type 2. There's been no research done in whether they're useful for prevention. If I have patients with prediabetes, I do actually recommend, if they can afford them, to try and get one, because I think it's useful for identifying postprandial glucose excursions. But we don't know whether just controlling the excursions per se reduces risk. But I think what it does is it helps people to follow a lower calorie diet, and it's about weight loss; so if I put a patient on a low-carb diet, I actually think stuff like CGM is useful because it helps to monitor whether they're following the diet, that helps compliance and that's going to help their weight loss.

DANNY LENNON: Yeah, there's something about that continuous feedback to someone from a behavioral...

NICOLA GUESS: Continuous behavioural feedback, absolutely, yeah.

DANNY LENNON: I think that's what you're probably seeing with a lot of like wearable devices and so on; if someone is like really dialed in to using them, it's probably more so the behavioral aspect as opposed to the data per se a lot of the times.

NICOLA GUESS: Absolutely, it's the nudge all the time, yeah.

DANNY LENNON: Let's get into some questions that people have submitted for you Nicola and see what we can...