Transcript

Danny Lennon: Here we are a big welcome to the podcast to professor Glenn McConnell. How are you doing today?

Glenn McConell: Oh, I'm great. How are you Danny?

Danny Lennon: I'm doing very well. And I'm excited for this chat. I've been enjoying reading through some of your publications, and also some of your wider science communication work, which we'll probably mention later in the podcast.

So I'm excited to put a number of questions to you, but maybe as a good place to start for people listening to give them some context for our discussion. Can you maybe introduce them to your background, the your work in the field and anything else you think might be relevant?

Glenn McConell: Ah, well, I don't know how far you're gonna go back, but yeah, I did my undergrad at Wollongong uni, was a while ago, so like 1986 to 89 believe or not. And then I went to Ball State. So some people may know David Costill. He was a bit of a big name and exercise physiology at Ball State University in Indiana. And then PhD at Melbourne University with Mark Hargraves, who is also a pretty big name in carbohydrate metabolism.

And then I've been out on my own. So yeah, like a lecturer, all that sort of stuff at Monash university. So this is all in Australia. And then university of Melbourne, then I ended up like a full professor out of Victoria university. So it's all in Melbourne. We have a whole bunch of, as you probably know, a whole bunch of exercise sort of universities in Melbourne.

Yeah. But then strangely enough, I actually ended up taking a package a bit of a long story, but yeah December, 2020 I finished up and yeah, maybe we'll get to it. Like you said, how I've started podcast and whatever, but yeah, carbohydrate metabolism is the main thing I've been doing. Looking at regulation of glucose, uptake, exercise, things like how exercising increases in some sensitivity all sorts of bits and pieces around there.

Danny Lennon: Yeah. So that there's plenty of fertile ground for us to get through. So I was thinking maybe as the best place to start, we can start with some basic concepts, explain those a bit in some maybe general, maybe even oversimplified terms for people. And then from there that will set the stage for some of the details.

So maybe if we start with insulin, glucose levels and this whole connection, because people hear about this, but maybe we need to exactly explain what's going on. So from maybe a, like I said, a brief overview level maybe even simplified for the sake of keeping it concise, how would you first introduce people to the idea of insulin and how it regulates glucose levels? What's a simple way for people to think about the connection between these two things.

Glenn McConell: Okay. So, when you have a meal you're taking in all sorts of things, right? Depends on what you eat, but there's gonna be some carbohydrate in there gets broken down. It's mainly glucose ends up in the blood and then the pancreas picks up that glucose. So, I mean, there's this kind of complicated regulation, but basically the pancreas sees the glucose and releases insulin because you need to have a signal. So you can take up that glucose and store it or use it for energy.

So, if you've had your breakfast, the glucose goes up in the blood, the pancreas releases insulin that then tells the muscle to take up glucose. So that's the major site of glucose uptake. And then the liver also takes it up. You can get some converted to fat, whatever, but that's basically what happens there.

Danny Lennon: So when we refer to the concept of insulin sensitivity, what are we actually talking about there?

Glenn McConell: So there, what I was describing is what should happen, what normally happens. So is the insulin tells the tissues to take up the glucose, but when you're insulin resistant, , which is like the flip side to insulin sensitivity.

So if you think about your insulin sensitive, it means your your tissues are gonna respond really well with the insulin. So it'll take up a lot of glucose, but if they're not responding well, you say they're insulin resistant. So it's just the same. Say, you can say this person is very insulin sensitive or, this person is insulin resistant, right?

So how well they respond to insulin? So a person with type two diabetes, for example, they will have the glucose go to the blood. The pancreas will release insulin, but the tissues won't respond to it properly. So the muscle won't take it up properly. Also you won't switch off the liver, so the liver's pumping out glucose.

It won't switch off properly. So the glucose ends up being elevated in the blood and stays elevated. And when you become insulin resistant, it means you actually need to releasemore and more insulin from the pancreas to get the same effect, if that makes sense.

Danny Lennon: Yeah. And to maybe just to build on that, and you've answered that this next question in part is when we have this loss of insulin sensitivity and specifically, let's say we'll focus in on the muscle because we can talk about different tissues a bit later on, but if we're focusing on muscle, as we'll discuss in relation to exercise, there can be this loss of insulin sensitivity, or essentially it becoming a bit more insulin resistant.

And you've noted there a couple of things. One is that there's these potential immediate kind of consequences of that. And that could be for what happens to maybe fuel use and exercise or postprandially and then there's also maybe long term consequences. So, cause I was wondering, could you speak a bit more to that, of when there is a loss of muscle insulin sensitivity or muscle sensitivity, why is that important?

What are the, some of those immediate consequences and then maybe what are some of the longer term consequences of

Glenn McConell: that? Yeah, so I mean the muscle is the major side. So if you even just think about how much muscle there is, there's a. Muscle compared to the other tissues. Well, obviously, unless you're, morbidly at diesel or something, so it is the major site of glucose disposal.

So, the glucose is taken up by the muscle and converted to glycogen. It can also, be used for energy. So indeed you'll find after a meal, you'll see, you have a hundred oxidation goes up, so you're burning a bit more carbohydrate you'll store someone's glycogen. But if you're not doing that properly, then the glucose stays elevated.

Then that can have, as you said, sort of acute and chronic effects. So chronic effects are, damages tissue, you get increased kidney disease, increased heart disease, all sorts of things from the increased glucose. But then, if you're talking about exercise, I guess it's a bit of a different ke or fish because surprisingly people that are insulin resistant.

So for example, obese a lot of obese people and people have type two diabetes, they have normal glucose Subary. That's the thing that's really important because they have problems with their insulin, stimulating glucose uptake into muscle, but their contraction stimulated glucose uptake is totally

Danny Lennon: normal.

Yeah. So just to jump in on that, because like you say, I think this is a crucial point you've noted there that when it comes to this glucose uptake, there's actually these maybe two different buckets we can think about. One is those that are dependent on insulin and those that are independent of that.

Can you maybe just speak to that a bit, bit more and really outline for people what we know about these insulin dependent insulin, independent processes and the main ways they're diff they

Glenn McConell: differ. Yeah. So, I mean, it's literally been shown classic studies in the eighties that if you take out like a mouse muscle, for example, and you contract it, you can contract it with no insulin there at all and it'll take up glucose.

All right. So that's an insulin independent pathway and, we are essentially the same. It's hard to. Study it, because we always have some insulin in the blood. Right. So in a human you're gonna have the insulin plus the contraction. But yeah, the, I think the best evidence of that is like, I just said the fact that, the diabetics or the people of diabetes have problems with their insulin pathway, but their contraction is totally normal.

So what it means therefore is that you've got these. So it starts getting a little bit nitty gritty, but you've got inside the muscle cells. You've got these transporters

called GLUT4 glucose transport four. And when you have insulin, the insulin binds the membrane and then causes like a cascade of like enzymatic reactions and things that cause the glute four to move to the.

and then bring in the glucose, right? And the people with diabetes or type two diabetes, have problems with that signaling, you can literally measure the enzymes and go, oh, that's that enzyme's not getting activated properly and whatever. So the GLUT4, even though they've actually got GLUT4, it doesn't move to the membrane and bring in the glucose.

But then you get those very same people. You exercise them and you measure it. And the four is moving to the member and that, and they are bringing in the glucose and we, and others have shown they have normal glucose uptake. So that's remarkable. So what it means is that during the exercise, because they've got normal glucose uptake, their glucose were actually come down.

Their blood glucose level will come down during the exercise. And indeed a classic study by moose and from Laurie Goodyear's lab in Boston showed that after 45 minutes of exercise, they had people of type two diabetes. I think glucose went from eight down to like five. It was the same. as the control group after the 45 minutes

Danny Lennon: of exercise.

So that's fascinating because that, again, gives us this reason to look at exercise in, in two distinct ways of potentially benefiting someone with insulin resistance or type two diabetes of one. We can think about the long term effects of someone who's continuing exercise and how that can potentially help.

But here, what we've first focused on is that even immediately in one bout of exercise, we're seeing a, an ability for them to take glucose up into the muscle. And what we're really saying then is to take it into the muscle means we're taking it out of the bloodstream. And so you can see some better regulation of blood glucose.

So that's fascinating. So maybe just to recap so that both, I have it straight and maybe for people. Really hear the importance of what you've just said, that if we take this muscle cell, we have different glucose transporters that will allow glucose to pass from the bloodstream into that muscle cell.

One particular type you mentioned were these GLUT4 transporters, which you said are essentially it embedded in the cell and have the ability to move to the

surface of that cell. One way they can do that is via insulin. Now in a situation where someone is insulin resistant, you not to, then we don't get this same kind of movement of these transporters and therefore our poor ability to take up glucose.

But then you notice insulin yes. In response to insulin. Correct. But then in relation to like a muscle contraction, we can see the ability for these GLUT4 transporters to move to the surface of the cell and to take up glucose. He hence having these benefits. Is that kind of fair reflection of that's.

Glenn McConell: Exactly. Yeah. That's exactly right. And it's amazing. Because, people go like medical doctors, you'll say, oh, why is exercise good for people with diabetes? They go, oh, cause you lose weight and whatever. That's absolutely true. Absolutely true. But what about the effect of one bowel of exercise brings down the glucose and then as well, get to it also makes you more insulin sensitive for 24 to 48 hours.

So then they don't actually even need as much insulin. So.

Danny Lennon: Yeah, so there, so we'll come back to the insulin sensitivity and that time period in relation specifically to those GLUT4 transporters after say exercise and a muscle contraction how long does that stay present for how long is glucose uptake improved for let's say due

Glenn McConell: to that next ask question.

Yeah. So it's an interesting one. So, so when you finish the exercise, the glucose re uptake remains a little bit elevated, even if you don't eat. Cause obviously if you eat, then you've changed things. You put the insulin up, but during the exercise, the insulin actually goes down, right? That's a normal response.

And then when you finish despite the insulin been down, the fact that the muscle is used quite a lot of glycogen, depending on the exercise bout, but assuming you've used a decent amount of glycogen, that muscle then remains has takes up some glucose for about four hours, three to four hours, we've done studies and we usually say to be safe, We keep four hours.

So we've done studies where we do one Legg exercise and we're measuring glucose uptake across both legs. And after four hours, you're back to basal three hours, three hours is pretty safe at four. Definitely.

Danny Lennon: So with that in mind, people might be thinking, okay, does this mean there are implications for the timing, particularly of say carbohydrates, that for someone with type two diabetes or prediabetes, where we might be inclined to say, okay, if we can have more of their daily carbohydrate intake coming within this timeframe after exercise, that would actually lead to say better blood glucose management over the day, because they have better glucose uptake for this period of time after exercise.

I, is that something we can. Conclude from this, or is that a bit of a

Glenn McConell: jump? I may have led you a stray a little bit there. I was thinking you were saying if they hadn't eaten. So I thought you were just saying, what's the effect of just the exercise alone. So if you do the exercise, then you don't eat for four hours, which who's gonna do that.

Then the glucose uptake remains a little bit elevated, even though you're not exercising and you haven't had anything to eat. Right. But then when you eat, then the insulin goes up and the insulin stimulates the glucose uptake, just like it always does, but it even does it more when you've exercise. So it's the beautiful thing that the exercise increases, the insulin sensitivity, such that you're taking up more than you would if you hadn't, done the exercise.

So the classic studies and I've been fortunate enough to go to Copenhagen now three times. So, for total of over a year, And worked with Erik Richter and university of Copenhagen where we can do these amazing studies. So we have femoral artery and femoral vein catheters in both legs and we do one ne exercise and then we wait four hours and then we can look at glucose uptake, with a meal or with, or infusing glucose and insulin.

You can look at the glucose uptake and the rested leg and the exercise leg. Yeah. And what you find is that the previously exercise leg has almost double the glucose uptake. And this is a beautiful model because you've got the same person. You know what I mean? It's not like you've got them in one day and they've done exercise in one day.

They haven't, and maybe they were feeling crappy that day or whatever. This is the same person, one leg exercise, one leg, same hormones going to both legs, everything, and same glucose going to both legs, the same insulin going to both. but one has, almost doubled the glucose uptake.

So that's the, sorry. I know you kept saying we're gonna get to that and I keep sort of pushing it, but it just becomes it's quite foremost in my mind, guess.

Danny Lennon: Yeah, that's fascinating. So we have almost doubled this glucose uptake after an exercise bout. So with that, what do we know about the variables around say intensity and duration of that bout how do they change that increase in glucose uptake?

Glenn McConell: That's a good question. Yeah, so I mean, it's, I wish it was this simple. We used to think. And some of us, some people still do think that... we used to think it was pretty simple that it was like how much glycogen you use, because you can imagine glucose has been taken up into the muscle and it can get converted to glycogen.

So it makes sense if you've exercised; so if you've done quite intense, or you've done quite prolonged, moderate, and you've used a lot of glycogen, then it makes sense that would be the main thing then that, that causes the insulin sensitizing effect. And it's gonna store that glycogen. Right. But we know it's probably a little bit more complicated than that, but that's a, that's an easy way, like is a take home, even if it's not like a hundred percent perfect.

So if you think about it, if you've done really low intensity exercise and you haven't burnt much glycogen, because I think your listeners would probably know that if you're doing low intensity exercise, you're mainly burning fat and know, you'll take up some glucose, but you won't be using much glycogen.

So then it makes sense, therefore, that you don't have to resynthesize the glycogen. So you don't have to take up as much glucose. And then if you've done something more intense, so just say you're doing something intense but for shorter period, you'll use the glycogen in a faster rate.

All right. And then when you have the meal, you'll synthesize it because you've used quite a lot, but if you do like, a marathon or something, then obviously you'd be pretty much collection depleted at the end. And then you would take up a lot of glucose. So basically your insulin sensitivity tends to go hand in hand with how much glyco you've used.

Danny Lennon: So let's talk about that in insulin sensitivity in relation to exercise, because we've talked here about some of these acute effects. Are there other things beyond that, that we need to consider when we're thinking about the long term impacts on insulin sensitivity in a human of why exercise is so potent and so important.

Are there other things that maybe sometimes don't get recognized or sometimes left out of the conversation when we're thinking about the benefits of exercise in relation glucose tolerance or insulin sensitivity or anything else like that?

Glenn McConell: Yeah, I guess so far, we've just talked about the acute effects, right? So if you do like one bout of exercise, then you're more insulin sensitive. And we I touched on it, but for 24 to 48 hours the other thing is naturally if you do training, right? So you say, okay, so what's the effect of training versus one about, and the interesting thing is training is essentially a series of single bouts.

Obviously we know everyone knows that, but what I mean is you do the battle of exercise. Your insulin sensitivity goes up, you glute four on the membrane, goes up and then it drops off again and then you do another bout and then it goes up again and it builds on it itself a little bit, but most of the effects you get are a series of single bouts.

Okay. So you do get some changes. Like for example, when you're exercise trained, you actually have moral GLUT4. So not only does the GLUT4 move the membrane, but you've actually got. More group four that can move to the membrane. Right? So there are some building effects, I guess that's the main thing I think there, sorry and then eventually you do lose weight. I just wanted to clarify that thing. Cause I, I don't want to diminish the importance of, because people that are insulin resistant, so obese people, not all of them, but all of them and people with diabetes, the body weight is a major reason why they've got problems with their in insulin sensitivity the body fat and the fact that the fat can get into the muscle and all sorts of things.

So I don't wanna diminish that. I just wanted to point out that it's more than just the losing weight. So exercise per se. So, it's classic studies where they've done like eight weeks of training and people with type two diabetes in controls. They get an improvement in their insulin sensitivity, but they haven't actually lost weight and they haven't changed their weight.

Well, maybe they might have been a slight change of their body composition, but I wanted to make the point that there's so much of it is the exercise itself. and then, the weight loss and the fat loss and whatever is maybe like it's almost like a different etiology again,

Danny Lennon: At this point I wanted to focus in on insulin and this increased insulin action. That seems to be an important component of these health benefits of exercise that you've outlined so far. And the reason why is because so often, particularly in the nutrition space, if you look at enough stuff online, insulin

gets this weird reputation as being inherently bad and any increase in insulin is what you should avoid.

And I think this is largely emanating from, let's say some of the low carbohydrate community circles, but this interpretation then for many people of, "oh, insulin is always bad. Any increase in insulin is bad for me". Whereas a more accurate view. Actually, we need to think about how this is involved in some of these impacts we've just talked about.

So how would you start by talking to me about how we should more accurately think of the role of this hormone and how this increased interaction plays is a role in the benefits we see from exercise.

Glenn McConell: Yeah. I agree with you it is a weird one. I even see people sort of going on all the time about all these glucose spikes and, whatever, if you've got, when you have a meal, your glucose goes up and then, and then your insulin goes up and then it goes down that's normal physiology. That is normal physiology. Where it does become a problem if it's chronically elevated. So if you glucose is chronically up, your insulin is chronically up, then that's a problem. Right? And one thing, I guess we haven't touched on, I thought about it, but it just seemed a bit much at the time was I just wanna explain what actually happens when you become insulin resistant.

So just say you are leading now, right? So you've got, you have a. No drama. Glucose goes up. Incident goes up, it's stored away. So after a couple of hours, your glucose is down your insulin's down. Everything's great. Right? No drama. And again, as you are alluding to, there's no problem with that spike.

But then if you are, if you just say you become your sedentary and you're putting on weight and maybe you're eating crap and whatever, you start to get a situation where you start to become less insulin sensitive, so more insulin resistant. So what happens there? The problem is you have the meal, just say you have the same meal, the glucose goes up.

But the insulin has to go up more because your insulin resistant. So you're making your pancreas work hard. Yeah. So the insulin has to go up more to get the same curve I'm showing you here, but people can't see. So you know, the glucose goes up and then comes down. You might actually have the same exact glucose tolerance curve.

Like it might go up the same and down the same, but you needed more insulin. To get that same response. Does that make sense? So becoming insulin

resistant. So that's the thing that does people's head in a bit because they think about diabetes and they go, oh, I thought diabetics don't have enough insulin. No. That's type one diabetes. They don't have enough insulin. People have type two diabetes. If anything, they have too much insulin. So because they, they had the meal on that. Pancreas is working its buns off, which doesn't, that doesn't work anatomically. So the insulin is going higher and higher. So they've got chronically elevated glucose and insulin for, if you look across the day and that's causing damage to tissues.

So to clarify there, so what's happening is the people with type one diabetes, they have not enough insulin. They've gotta inject insulin and stuff. People with type two diabetes, they have a normal insulin and if anything is elevated, but then what happens is the pancreas eventually gives out.

And then you get to the point. So that's a little bit further on, you've usually got secondary problems, like high blood pressure and various other things going on. Then they have a problem because they're pancreas has had to work so hard and it's unhealthy know, basically you've got, you've got fat in the muscles, you've got fat in the pancreas.

You've got fat in the liver. Things are just not good. This low level sort of inflammation body like whole body. And then the pancrea starts to pack it in. And then you may end up as a person with type two by diabetes later on. You may need to take insulin, but you know, it's a very different situation.

So basically to get to your question, yeah. Having elevated glucose and insulin for long periods of time is gonna do damage. But if you're not, if you're just a normal person, then normal spikes in glucose are insulin are totally fine.

Danny Lennon: Yeah. And that's the crucial point that those acute effects in response to feeding or otherwise of changing in glucose and insulin are not pathological in the way of a chronically elevated insulin or glucose is. So I think that's a re useful way to, to think about it. One other question that people may have at this point is okay if we're seeing these acute benefits to an exercise bout, and we've talked about some of the time course of that and the impacts of duration, intensity or so on, is there a certain threshold, or let's say a minimum effective dose that is easy to kind of prescribe of here's what an exercise bout would need to involve in order to get some of these benefits, or is that even the right question to be asking.

Glenn McConell: Yeah, it's a good question because, you tend to think about physical activity and exercise and sometimes, we think about, okay, walking is

maybe more physical activity. It's not really sort of card carrying official sort of exercise which you tend to think about more of it's sort of moderate or vigorous.

There is a different level of effect on insulin sensitivity of those exercise. Because as I touched on earlier, if you're burning a lot of glycogen, you tend to increase your insulin sensitivity more. Yeah. So in terms of minimum, I guess it depends on the intensity and the duration.

So I'll put it this way. If you do a 30 second sprint, this is classic studies that were done years ago. If you do a 30 second sprint and you do a biopsy before and after it. So this is like a Wingate. So I don't know if people would know, but it's a test where you go flat out on a bike. For example, you goes hard as you can from the first pedal stroke and then you hang on for dear life. Okay. It's called a wind gate test 30 second sprint. And you get your it's measuring your anaerobic capacity and all that stuff. You can use about 50% of your muscle glycogen in that one 30 second bout. Okay. Which is crazy. It would be about the same as it would take if you're doing like a moderate intensity.

So about 70% of your VO2 max that you can hold probably for a trained person can hold for about two hours or more two or three hours. It would take an hour to burn the same amount that you burn in that 30 seconds. Okay. And that's just a good example of showing because the physiology is just totally different.

If you are doing a flat out sprint, you need to use a lot of glycogen and you also use this thing called creating phosphate, which I'm not sure people know about. That's a very different kettle fish. You hardly use any glucose at all. No fat. If you are doing a 70% VO to max, something that can endurance strain, people can hold probably for more like three hours or so.

You are using quite a lot of that. You're using decent amount of glucoses. You're using a little bit of glide cause you, you know what I mean? Like the rate is very different. So you end up using, as I said, the same amount in the 32nd sprint, as you would take you an hour. Doing endurance exercise.

So, but my point there is you would get probably a similar improvement in instance, sensitivity after each, because you've used similar glycogen. If that makes sense.

Yeah, for sure. So where does something like resistance training come in where by and large, depending on what type of training someone is doing, but you could if we, if I think about a typical power lifting training session, for example,

you probably don't burn through a huge amount of glycogen per se, but you do have quite a lot of muscle contraction.

You have a lot of mechanical tension on the muscle. How does that kind of tie into this

picture? Yeah, that's a good question. That's a good question. Yeah. So if you're talking about power lifting training. Yeah. So you are doing like, not that many repetitions, but you're doing like enormous forces. Yeah, that's a good question.

I haven't particularly thought about that, to be honest. I know that resistance training definitely increases in insulin sensitivity. And again, the more muscle groups you use, the more using a bit of glycogen, every, all these different muscle groups. But again I'm probably oversimplifying it.

It's not just the glycogen. So because because for example, if it was just the glycogen, you wouldn't super compensate. So you know how, if you break down glycogen, then you should go back to the exactly where you were if it was just based on glycogen, but we know that you can super compensate. So there's more to it than just the glycogen.

But yeah, I'd like to think any exercise where you've done a decent intensity. You're gonna activate GLUT4, moving the membrane. You're gonna have all those signaling changes going on and you're gonna make the muscle more insulin sensitive. I'm probably skirting around a little bit there cause I haven't thought about, just, if you do like.

Six or seven hard contractions. My feeling is it would be less than obviously if you did like an hour of, sort of circuit training or something like that. Sure.

Danny Lennon: I did wanna ask you the question on some of the specifics related to some of your publications that I was reading in one of those, you were to study that looked at whether that insulin sensitizing effect of prior exercise is associated with increases in skeletal muscle microvascular perfusion.

So first of all, could you maybe explain to people what is muscle microvascular, perfusion, and then maybe why this is important?

Glenn McConell: Oh, good on you. That's the sort of stuff I'd like to get into. I didn't know if it was going too hard. Yeah. So that's the really nifty stuff we did in Copenhagen. So I've done studies here with.

Look, we had FEOR artery and Freal vein catheters across one leg. But over there you can do two legs plus biopsy. We do biopsies here as well, but the amazing thing was, as I said, you could do the one leg exercise. So for an hour. Yeah. And then we put the catheters in so we could measure the glucose up, take across both legs.

We infused insulin, London, glucose, and we looked at glucose uptake. Now the thing was there that everyone prior to that study, pretty much everyone just thought about the muscle itself. So the actual signaling. So now how I talked about you have these enzymes that are signaling to the glute four, the glucose transporter to move to the membrane and bringing the glucose.

Everyone was just looking at that. They weren't thinking about blood flow at all. They'd be taking biopsies and they'd be measuring these insulin stimulated, enzymes and looking at how activated they were and how mu how much activation they had in the rest of leg versus the contracted leg and all this sort of stuff.

And hadn't really thought about the blood flow. And that's really important. Cause if you think about, if you're taking up glucose, you need to have the glucose delivered to the muscle, so is the blood flow the same in the exercise in the meed leg or more or whatever? So, yeah, so what we did there was really nice study.

So yeah, it's this thing called contrast enhanced ultrasound, which is very cool. You basically, you infuse these little micro bubbles, which is smaller enough to go through the capillaries. So they're actually smaller than the capillaries. They're red blood cell size a little bit bigger.

So they go through and what happens is you hit them with ultrasound. so you do a flash of ultrasound and they basically blow up. So then you can't see them anymore. And then you can see them coming back in it. So you can see, as you see them come in, you can see how many capillaries are actually open and also the rate that they're going through.

Yeah. So we were able to do that at rest. And then after the exercise and then after the exercise, when you, they had insulin onboard to stimulate the insulin stimulate glucose update. So, yeah, so we were able to show, as I touched on earlier and, it had been shown as well previously that the exercise leg takes up.

So this is four hours after exercise, the exercise leg, the previously exercise leg takes up, a lot more glucose. So maybe 60, 70% more, up to a double in some

studies. And then we were able to say, well, how much of that was the signaling. So from taking the muscle biopsies and how much was from the blood flow.

So we showed for the first time that there was increase in muscle blood flow in the previously exercise leg. And that was very nifty, because basically what we showed was that sitting there before you had the insulin on board, the signaling was elevated, right. But the glucose uptake wasn't because there was nothing sort of to do, there was, and then when you had the insulin on board, then you had the signaling was elevated.

Plus the blood flow is elevated and then you had the higher glucose uptake. So, you actually need both because the really nice thing was we then gave a thing called a nitric oxide syntase inhibitor, which we infused in the femoral artery. We blocked that blood flow effect because nitric oxide as a vasodilator; it causes dilation and blood flow. So when we gave the insulin and showed the take was higher in the ex previous exercise leg, and it was because of the signaling and the blood flow. So when we blocked the blood flow by giving the nitric oxide synthase inhibitor, the went right back down, and it was the same as the exercised leg.

Danny Lennon: And so presumably that type of finding has implications for how people could have or how they should interpret other research in that field. And certainly that there's, without acknowledging this role of blood flow, we could get into trouble when trying to interpret things?

Glenn McConell: Absolutely. All the studies up till then it was just all muscle. So what was happening to the signaling and that was the beautiful thing because because as I touched on is you do the exercise and then four hours later, the signaling still a little bit elevated, but the blood, but the glucose uptake isn't because you haven't got the blood flow coming in.

And then when you have the insulin then you have the insulin on board that increases the blood flow and increases signaling even more. And then when you block the blood flow, the signaling must still up. It didn't stop the signaling. So the muscle was still saying put the GLUT4 on the membrane let's do this, but because they didn't have the blood flow it went back down.

It was the same as the non-exercise leg. So it shows you need both. Yeah. And yeah, so previous studies would not have considered that. So, it's, it was a big, it was a big deal. And the cool thing about the microvascular flow, which is the term you use. And I didn't actually say it myself.

So that's saying it's not the macrovascular. Macrovascular is like the big blood vessels. So, your femoral artery and all that stuff. This is the capillaries here. So the microvascular. And people had looked at the total leg blood flow, but they hadn't looked at how much it's actually going through the muscle.

And that's what you need to know. Because you can imagine you might have an increase in your total leg blood flow, but it's not actually going through the. So that's why we're, as you can tell, I'm pretty proud of that study. So yeah, I've gotta give, thanks to the guys in Copenhagen; Erik Richter and Kim Sjøberg for having those methods up and going.

Danny Lennon: And that actually reminds me of another thing I wanted to ask you about in relation to some of your work and that specifically on the role of AMPK or AMP-activated Protein Kinase and how this plays a role in skeletal muscle metabolism. First of all, maybe just as a primer for people, can you maybe give a quick explanation as to it its role in, in muscle metabolism, but then secondly, from there, can you maybe just speak to a bit more of some of your writing as to some of the ways you feel people may be of getting it wrong or misinterpreting its role, or at least not seeing that the full picture? Can you maybe speak a bit more to that?

Glenn McConell: Okay. This is one that's been pretty controversial for many years and thankfully. People have come around to my way of thinking. Well, let's just talk about it first. So AMP kinase is AMP-activated Protein Kinase. So I think your listeners would obviously know about ATP. So it's the real currency in the muscle for contraction and energy. So ATP can get broken down to ADP and then to AMP and... then AMP activated protein kinase. So basically if you've got an energy deficit, you can imagine your ADPs are getting broken down to ADP and some gets broken into AMP that gets picked up by this AMP Kinase right.

So it gets activated and then it turns on glucose uptake into the muscle. So basically it's saying we've put an energy problem here, right? Because you're getting this amp, so it's activating AMPKinase and then the AMPKinase is trying to overcome the energy problem by increasing glucose uptake, increasing fat Use and then you obviously are hoping to overcome their energy deficit.

Now that the reason I started off with my sort of gloat there at the start was I was totally on board, saying, okay, AMP kinase, regulates, glucose uptake, fat oxidation. So then we did these studies and I, but I started going, hang on a minute. How can it regulate both? Because you can think about, as you increase

intensity, you use more and more glucose, but you get to a point where your fat oxidation goes down.

So I'm not sure if your listers aware of that, but low intensity, you burn mainly fat. At 65% of VO2 max it's about 50-50. And then as you get harder, it becomes more carbohydrate. So glycogen and glucose and less fat. So that's weird. How can it regulate both? So I did a different intensities, AMP kinases, and showed that it tended to go more as it got harder, obviously you get more of an energy deficit. So it tended to go more in hand with glucose uptake, right? So that was one study.

And then I also thought, well, what's another way of looking at that. You could look at training cause as you probably know, when you do endurance training, you get better able to burn fat and you tend to use less carbohydrates, including glucose. So I did that, but this is where things got weird, because we showed after the training. So we did two hours of exercise at 65% VO2 max in untrained people with biopsies before, during and after, like zero (minutes) , 30 (minutes) , and two hours. And we got tenfold increase in kinase before training.

Right? Then we trained them for 10 days really hard. Came back and exercised them. And people had shown previously that you burn more fat, less glucose. After the 10 days of training, we got that as well, but we had no activation of AMP kinase at all; zero. It was like what? Okay. And then we since went on and did that was 2005.

Then we since went on and did mice, when we knocked out their AMP kinase and they had normal glucose uptake, we had we did trained and untrained at 65% VO2 max and the train got no activation of AMP kinase at law. So after that, we were saying, well, hang on a minute. We don't actually think AMP kinase is critical to glucose uptake during exercise because we've shown these dissociations.

And basically we're sort of laughed at and things for a while. And then thankfully the last few years, other people have shown that as well. People had shown it in mice; AMP kinase knockouts had, but they said, oh, it's probably not what's happening in humans. But yeah, the last few years some people have shown the same thing that you can have dissociations between AMP kinases and glucose uptake during exercise.

So thankfully I sort of vindicated there. So it's a bit confusing but we think AMP kinase is... it's maybe important under some circumstances, but it's not critical for glucose uptake fat oxidation during exercise.

Danny Lennon: Fantastic. So, so let me try and recap over that. So I have everything clear first you started off by mentioning ATP, which people are familiar with as this energy currency. And when we get a breakdown of ATP, we can get that into ADP and then ultimately AMP. And so when we have this, more of this AMP around, because ATP has been broken down, we're essentially getting this kind of signal that well, there's less ATP. So we have a short fallen energy and to try and regenerate energy. We want more ATP back. So we have this signal then from AMP kinase of saying, look, we have this energy deficit because there's less ATP around because there's more of this AMP around. And you then outline that we had this conventional view that AMPK. Was the kind of regulator or directly regulating both glucose and fat use here and exercise and through a number of those different studies you outlined, you showed that there's not only a dissociation with fat, but also with glucose uptake.

And so the kind of position we're left in now is that AMPK is important, but it's not directly influencing these things. At least not in a direct or linear fashion. It might play some role, but it's not directly

Glenn McConell: Yeah. So what a hard one to get your head around because there's a drug called ACAR, which is basically a drug that activates AMPKinase.

And if you give that ACAR to rats or isolated rat muscle or whatever, it increases their glucose uptake and increases their fat oxidation. Perfect. But it, it somehow isn't that simple and now it is actually recognized now that there's more to it, but you'll still see the start of journal articles.

They say "AMP kinase regulates glucose uptake and fat oxidation during exercise". And youre saying, well, not really. There's more to it than that. So there's a whole bunch going on. And this is part of the problem with, well, it's not part of the problem. It's part of the beauty of physiology because there's a lot of redundancy, so redundancy means that, you can, so just say, if you think about breathing, the classic studies were done to where this guy, Michael Kjaer in Denmark, showing that you try and work out, what's regulating breathing, you knock out one sort of regulator and you still have normal breathing. You knock out another potential regulator, you still have normal breathing. It doesn't mean they're not important. It's just something else compensates, because it's so

critical. Right? And it's probably the same with glucose uptake. We think there's redundancy. So if you don't have AMP kinase, something else takes over, you know what I mean? So it doesn't mean it's not important, but so for example, we know during muscle contraction, you get calcium released with each contraction and calcium relates glucose update.

So, maybe the calcium is more important when you're trained or, whatever. And the other thing I should say is that it's not like AMP Kinase is never important. Like if you just have to do like a higher intensity of exercise to get that same. So for example, after training, because you are so well able to maintain your homeostasis and the muscle, because you're so, it's like it's called coupling, your ATP production and ATP use is really nice and tight. Basically when you are trained, you don't get as much of an increase in a ADP and amp. So you basically have to try exercise at a higher intensity to get that same signal if you know what I mean, but it doesn't take away the fact. that you can still have, 65% VO2 max in a trained person. They're still using a bucket load of glucose and a bucket load of fat, but there's no activation of AMP kinase.

Danny Lennon: So it just reminded me as to speak to your previous point where you said, indeed, if you take someone and train them in a certain way, you can actually nudge up that exercise intensity, where they're burning, let's say more fat and less carbohydrate, or you can get to a point where at higher exercise, intensities, proportionally, compared to people who are untrained, they're gonna be able to oxidize more fat than those are not trained.

However, that's still within a certain range. That's not to say that you can just train someone and now they're not gonna switch to a point where at high intensities are using lots of carbohydrate, that's still gonna happen...

Glenn McConell: Exactly. It'll happen at higher... Exactly. And this is where it gets complicated as well, because you talk about the absolute workload and the relative workload.

So just to make sure people are clear on that. So if you think about. An untrained person, they're exercising say at 60% VO2 max, right? That's gonna be a low, absolute workload because they're not very fit, but it's gonna be the same relative workload as a trained person. Right? Because the trained person at 60% VO2 max is the same relative.

Cause they're both 60%, but their absolute workload is higher. Right. So, and that's where, when you start talking about the effect of exercise, intensity on glucose uptake and fat ox or whatever, you've gotta actually think about the

person, how fit are they? What's their absolute and relative intensity. So, so it does your head a little bit.

So basically endurance training increases fat oxidation and reduces glucose uptake at the same absolute and the same relative. So even though you are doing so, just say you are, tour de France cyclist. and you are at 60% of your VO2 max, which is obviously gonna be a much higher workload, your still you using more fat and less glucose than the untrained person.

So you become more efficient in terms of, efficient again, define it. You, when I talk about efficiency, I'm saying you are sparing your precious carbohydrate, which obviously doesn't last as long as the bucket loads of fat that we all have, no matter how lean you are, you have enough fat to last hundreds of hours.

Danny Lennon: Yeah. And this kind of reminds me of some of the adaptations that we can get during exercise or two different types of exercise and how this actually can be dependent on not only the fuel use used during that, but also for example, glycogen stores is a good example. And I think you see a lot of work now being done in the area of, okay if we take situations where we purposely have an athlete, do a certain training session with low glycogen stores, whilst that compromise performance. We know we see these differential changes at the level of the muscle and we might then periodically use them to try and get a certain training effect.

And I think people have tried to do similar with different types of nutritional interventions as well. The same idea of by changing these, this provision of exogenous or endogen. Carbohydrate, we can maybe get different exercise adaptations. Would that be fair?

Glenn McConell: I think it's slightly overblown. So this thing about like, oh, if you exercise with low glycogen, you'll get, greater increases in fat oxidation, long term. And if you, so for example, if you exercise and you don't drink carbohydrate, you let your glucose drop, then you'll, you'll burn more fat and that'll be better long term or whatever.

I think there was a little bit to it, but I think it's maybe not as much as people as people, and as you touched on there, that means the actual exercise you're doing, you can't do as well initially. So, there's a trade off, you know what I mean? It's almost analogous to like exercising at altitude because you exercise at altitude, you can't exercise is hard, so you might lose a bit of a training effect, but you're hoping to get the altitude effect. And obviously you can " live high" and "train low" and all that stuff, but it's the same sort of thing you're missing

out on that particular training bout in the hope that you'll get. But my, I tend to be a bit of a guy who sort of says, well, can we just get a bit simple on that?

Danny Lennon: But I think this is a good example because at least from the outside looking, and my kind of perception of this is that much of these potential benefits are based on mechanisms. Right? Mechanistically we see these changes at the level of the muscle when you do. About of exercise with low glycogen availability. And you don't have, let's say carbohydrate during, or even after, right. Some of these train low strategies. Now of course there are many mechanisms which, are at work.

We see changes in mitochondrial biogenesis or gene expression of the muscle and so on. But when you start looking at actual data and performance, you start to see a lot less to shout about, which I think is what you're alluding to of like, okay, these things might lead to some of these changes, but in the long term, are they actually making athletes better relative to if the athletes just continue to train really well and a few open carbohydrate, are we actually seeing differences?

And I think it's difficult maybe to point to evidence that is occurring. At least from my current understanding.

Glenn McConell: Again, I'm sure some people would totally disagree, but I think... things get a bit too complicated. I think the main thing is be consistent with your training. Be smart with your training, be specific with your training and, maybe worry about all these other bits and pieces a bit less, you know what I mean?

Danny Lennon: Right. One area that I want to ask you about separate from the exercise stuff. Just because I noted that you've contributed to some publications on it, and it's an area of interest for me is around shift work and this potential impact on or potential of shift work to impact insulin sensitivity glucose tolerance, et cetera.

Can you maybe give a quick overview to some of of that area of work and what do we currently know about the role of shift work in impacting insulin sensitivity, glucose tolerance, et cetera?

Glenn McConell: Yes. I mean, there is, there's definitely evidence that shift workers have reduced insulin sensitivity. And I, well, I've touched on this a little bit, but they are difficult studies. You've gotta get people to live. We did had people live sort of five or six days either on like, normal. So wait during the day

sleeping at night or back to front, and you can't sort of have them go both going at the same time, because it just messes everything up because they keep each other awake and whatever.

But basically, yeah, we did a study, which I mean, okay. So we know that shift workers on average are less insulin sensitive and they have more diabetes that is known. Okay. And we were again, just wanting to sort of look at mechanisms and things like that. So we did biopsies and things, but the main point that I wanted to bring out, I guess, is it's a little bit.

To know that well, because shift workers also tend to not eat as well. You think they've, you're just sort of grabbing something and whatever. So even though it's a little bit controversial, there's some evidence they tend to eat more fat and they don't exercise as much and whatever. So, but you know, it's clear like, again, animal studies, aren't always, ideal and you can't always compare them, but when you do animal studies, and you muck around with their shift work or even genetically modify them to affect what's called clock genes, which circadian genes, it does mark up their insulin sensitivity.

So yeah, we we did a study on that and we did show that the shift work reduced in some sensitivity and then we showed, so that was just four or five days of shift work. And the good thing that we did there is that we actually matched the sleeping. Because see, not sleeping as much, also mucks up your insulin sensitivity.

So we actually managed to, we gave them like a longer sleep opportunity than you actually needed if you were just like a normal day shift. And so it meant they were sort of like laying in bed bored, but then they stepped the same number of hours as the people that were doing the shift work, they had trouble sleeping.

And so that was quite nice because we showed that it wasn't the lack of sleep. It was the, it was purely the shift and they also ate the same. So, it covered for that. But again, I don't wanna make too much, it was just, a smallest study five days or whatever but it did seem like the shift work per se caused insulin resistance.

Danny Lennon: Yeah, I because it's such a fascinating area. Like, as you alluded to of course there are behavioral differences. You see, when someone is doing shift work, whether that's food choices or even the availability of if you're working nights and your gym is clothes at that time, then it's more difficult to engage in these different activities and so on.

But there's at least good reason to see that we do see changes based on circadian biology in certain things around glucose tolerance. I think that the, obviously the gaps that are still there is probably to what extent this happens and how much is adaptable and then differences between different types of shift work.

Because there's probably a large variance where and this is something my regular co-host Alan has discussed before of you could see. If we do have the ability to adapt to certain degree of change in circadian rhythm, then for someone who is consistently on, let's say a night shift for an extended period of time, they might be able to adapt after a certain period of time.

Whereas it's the person who maybe changes shifts every three or four days between night days, even that becomes maybe there's no stabilization, right?

Glenn McConell: Yes. There is a level of adaptation. But it's never like you never end up back. So it's not like if you just, forever were doing like the graveyard shift or whatever, midnight till eight in the morning or whatever, you would not adapt the point where you were normal, it would be better than doing the rotating shift, which, makes sense.

And you I'm sure that the other thing I just thought I'd mentioned, I just thought of while you were talking was some nice studies that some people here in Australia have done is showing that part of it is actually the fact that you are eating at the wrong times. So the fact that you're actually awake during the night, if you actually tried to make it that you didn't really eat, I know it's hard, but if you didn't eat during that, so just say you ate at the normal times.

Right. And then, so you basically didn't eat during the night then that, that actually nullifies quite a lot of the negative effects. So part of it is taking on the body is taking on food when the body isn't really expecting it.

Danny Lennon: Yeah. The postprandial response, particularly to fat and carbohydrate is, at biological night, is just screwed up. That you get these differences in that response. And so like you outlined, if someone could feasibly at least in the real depths of biological night, have a period of time where they're not consuming food that theoretically could impart.

Glenn McConell: Yeah. So like for example, I actually did shift where years and years ago before as an academic or anything. And we did used to have these rotating shifts. So it was every week was a different shift. It was ridiculous. And anyway, the mid, the graveyard shift was midnight till eight in the morning. And you could feasibly do that, right? I mean, you could actually eat, so you

just eat in normal dinner, you'd have something to eat like 11.30 and then you wouldn't eat until eight in the morning have like your breakfast.

And, it suggests that would actually, solve some of the problems there, but you know, you wouldn't wanna do it but in theory you could, and then as you said about exercise, like, I didn't really feel like I was a bit of a runner then, but. Didn't really feel like it when you're doing those rotating shifts, either even if the gym was open.

Danny Lennon: Yeah. Yeah. It's very difficult to do it. And that's part of even making recommendations here could be difficult because of the practicalities and but that's a whole other topic that we can probably spend.

Glenn McConell: Well, you know what, I don't know. I don't know if we've got time, but I've got one other major area that we did, which is really cool as well.

Well, it's totally different, but what we did there was so you know how you can be like, Prema, you can be born premature. So that means you are, you're actually small and you're, you didn't go for the whole gestational period. The other thing is you can be born small, right? So that means you're small for gestational age.

So, so just say you even went the whole 40 weeks. If you were born small, it's been shown that you have increased risk of diabetes. You have low bone mass, et cetera later in life. Okay. So there's premature is bad and being born small is bad. So anyway, we did a whole bunch of studies where it just so happened.

When I was at Melbourne uni, there was a person down the hall, Mary Volek; and she was doing all these studies on on "born small". And she had these rat models and I sit there and go, "oh, not another bloody rat, born small study". But then she was talking about how it mucked up... it caused diabetes. And we were looking at mitochondrial function at that time.

And I thought, well, this could be quite a nice model. You could see because there's a bit of a debate. Does the insulin resistance cause the mitochondrial problems or does the mitochondrial problems? Cause the insulin resistance, there's a bit of a debate. What causes what? And I thought this could be nice because you have these rats that are born small.

They become diabetic. They get insulin resistant in diabetic. We could see does their mitochondrial screw up first or does the, diabetes screw up and then the

mitochondria. So we did that and we actually showed the had mitochondrial dysfunction and all this stuff. But anyway, that was pretty interesting.

But then I decided, I said, why don't we exercise these little guys? So these rats are the born small. We exercise them early in life, like just after weaning and we showed we could fix them. We totally fixed them. They didn't get diabetes later in life. It was the strangest thing. But the funny thing was, it was, we haven't talked about this much, but it was the pancreas.

It wasn't, we've talked about the muscle, but the thing is these rats that are ball and small they end up having 50% of the normal cells that make insulin, which is the beta cells. They would literally have 50% of the normal amount at six months when we showed, if we exercised them only for four weeks, right.

From five weeks of age to nine weeks of age. And that was it. We just exercising for four weeks on a treadmill and then back in the cage, nothing else, their pancreas was totally fixed at six months. They had normal beta cell mass. So it's just crazy. Right. So, yeah, so that's a bit of a hard one. So we'd like to do that in humans because you know, manners on rat and whatever and believe it or not, we've done it right with sheep, ran sheep on a treadmill because they're actually more similar developmentally.

See the problem is with rats, their pancreas isn't really developed when they're born and our, and ours is more developed stuff. So you know, how do you compare them? But anyway, I just thought I'd try that out there. So that's and that's super cool because what we've done is we've shown that if you exercise a me in life, you fixed it pancreas.

But then we said, well, what about other models? If the mother's pregnant, she's high- fat fed, the offspring get diabetes. If the father has high fat fed before conception, then the offspring get diabetes.

And we also show it as well there that if you have the high fat fed father, you exercise the offspring early in life. You could fix a lot of their problems. And the same, if you had the high fat fed mother and you exercised her, you could help the offspring later in life.

Danny Lennon: I mean, that's a fascinating thing because it gives some at least hypothetical interventions that we know could have a benefit in cases where at least from a genetic standpoint, someone may start a disadvantage, but it necessarily doesn't necessarily mean that will manifest because something like exercise, which is unbelievable.

Glenn McConell: Exactly. And I don't know if you ever talk about epigenetics to your audience, but that's what that basically is. You're not changing the genetics, you're changing the epigenetics. So. You have these epigenetic markers that get passed on. So that's a whole different kettle fish to maybe get into that.

Danny Lennon: Yeah. Yeah. We can spend a long time getting into that for sure. But before I do get to my final question, Glenn, may, maybe let's talk a bit about what you're currently working on now in relation to the podcast, because there's gonna be a fair chunk of people listening that do have an interest in exercise science and physiology. So can you maybe just tell people a bit about the podcast and kind of the goals of that and what you've been

Glenn McConell: doing there?

Yeah. So I touched on earlier that I basically left academia. I don't know if I'm really left academia. I still have funding for another six month visit to Copenhagen next year, which is great.

But at the moment, I've I basically left academia and thought, what am I gonna do next? And I decided. To start an exercise podcast. So as you would know with your own stuff, there's a lot of crap out there. And I thought, well, people getting their information from sort of influencers and things like that.

And even, some of the people that talk about exercise online, they're not exactly spot on when they, talk about stuff that I know about. And so I thought, wow, this is great. So, because I know a lot of people around the world in the area and I've actually, someone who is still, at the top of my game, but I stopped. It means I actually have the time to do it. So I've lined up basically the who's who of exercise, physiology, exercise, metabolism, and exercise and health, and doing a podcast with them. So. Yeah, it's called Inside Exercise on, YouTube and Spotify and whatever. And if you're on Twitter, it's @inside_exercise.

Danny Lennon: Great. And yeah, for people listening I will link to that in the show notes this episode. And so if that sounds like something you'd enjoy, I thoroughly recommend you go and check that out.

And with that Glen, we're gonna come to the final question. I always finished a podcast on, and this can be to do with something completely outside of what we've discussed. It can be quite a large generic question. So apologies for putting you on the spot with it. But nevertheless, it is, if you could advise people

to do one thing each day, that would have a positive impact on any area of their life what might that one thing be? ,

Glenn McConell: it's probably not surprising. I tend to think of exercise yet. But yeah, one thing would be to get out there and do something every day. Exercise wise. Yeah. Consistency. Yeah, I mean, okay, sure. I'd like to say, do something, moderate to vigorous, but if it's walking, vigorous walking or whatever, I would highly recommend that.

And that's, that was an easy one.

Danny Lennon: So with that, we will leave it there. Professor Glenn McConell. Thank you so much for taking the time to talk to me today. Thank you for the work you've done in the field. And it's was a pleasure to talk to you. So thanks for giving up your time to do this.

Glenn McConell: Oh, well, I enjoyed it. Thank you very much. Thank you.