Danny Lennon: Hello and welcome to Sigma Nutrition Radio, the podcast that brings you evidence-based discussions with the world's leading researchers in fields related to nutrition and health. I am your host, Danny Lennon, and you are listening to Episode 129, and on today's podcast I'm delighted to have Chris Masterjohn on to discuss glycation and oxidative stress, which were topics central to Chris' doctoral research when he was completing his PhD in Nutritional Sciences at the University of Connecticut, and he's one of the most well-read guys that I've ever come across in this particular area and his depth of knowledge in this particular area is remarkable as well as another number of different areas within nutrition as well. And to be honest, Chris is probably one of the most intelligent guys I've had the pleasure to chat to and I've been a massive fan of his work for many, many years now, and so I'm just really delighted to have him on the show today.

While this will be quite an in-depth podcast, so we're going to dig right into some details, get down into some pretty nerdy stuff, I think there are still some massive takeaways for even those of you who are not as interested in the nitty-gritty details that we might get into. There are some huge takeaways. Particularly, we'll try and probably pull back and get those into kind of a nice summary, and concise, but while we're going through the podcast it can get quite deep, so please do bear with it because there are a number of absolute brilliant gems to find in this episode and I

think it's one that a number of you will refer back to again and again and, as you'll see, plenty of really, really cool stuff in this.

So the show notes to this episode are going to be available at SigmaNutrition.com/episode129, and if you've not already done so you can also sign up to receive the transcripts to each podcast episode for absolutely free and we'll send over to you as a PDF every week once the transcript is out, and you can do that if you either go to the show notes page or if you just go to SigmaNutrition.com it should be easy enough to find that link. Let's not waste any more time and let's just dive into this week's episode with Chris Masterjohn.

Hey Chris, welcome to the show.

Chris Masterjohn: Thanks, Danny, for having me.

Danny Lennon: Let's kick things off by giving people who maybe aren't as familiar with your background some kind of context for this whole conversation, particularly as a lot of your doctoral work focused on some of the issues that I would like to raise later in the show. So what are the CliffsNotes to give people? What is your background both in academia and kind of what has led you along this journey?

Chris Masterjohn: Sure. So I have a PhD in Nutritional Sciences from the University of Connecticut and while I was there I studied glutathione, which is the master antioxidant of our cells that we make on our own from protein, and its role in preventing the accumulation of methylglyoxal, which sounds like a big name but it's basically a potentially toxic by-product of energy metabolism that's thought to play a major role in the development of diabetes and its complications and actually a lot of other degenerative diseases. And currently, currently I'm Assistant Professor of Health and Nutrition Sciences at Brooklyn College. In between those two things, I did my post doc at University of Illinois at Urbana-Champaign, and before I got into grad school and then once I finished school, my real passion was the fat-soluble vitamins. And a lot of people know me for my work on how vitamins A, D and K interact to promote health but why imbalances between those vitamins might actually contribute to disease when they're not kind of put in the right context and taken together.

And that was something that I became really passionate about. Just from my personal experience, I had always been interested in health throughout my life, but I didn't do very well in my experience with veganism. And that drove me to understand the work of Weston Price, who was a pioneer

in nutritional anthropology, and one of the things that he really emphasized was that throughout most of our history as humans we've eaten foods that were really rich in fat-soluble vitamins, and kind of coming to an understanding of how to get those fat-soluble vitamins played a major role in my own turnaround in my health and so that's been something that I've written a lot about and that I kind of made kind of an interest of my current research.

Danny Lennon: Yeah, and for me personally the discussion around fat-soluble vitamins, particularly when we're looking at vitamin D, is of personal interest because that's what I did my own master's thesis and research on…

Chris Masterjohn: Oh, wow.

Danny Lennon: …the area of vitamin D, and so I've been reading your work on that for a number of years now particularly when, like you said, we mentioned the synergistic effect with, say, K2 or vitamin A. And that's a whole topic that hopefully we can revisit sometime in the future because there's so much cool stuff in the area, but for today I wanted to focus in on another area that I think you're perhaps really well-known for and have put out a ton of work over the years on, and because even recently I've really enjoyed your commentary on the topics of glycation, oxidative stress and the related areas to those. And like I mentioned, you've been talking about this stuff for years now and kind of been writing about it and putting work out on it, but even in recent times particularly with the podcast and on your blog, have been doing an amazing job of distilling those ideas into some clear messages, both on how it relates to dietary choices and then clearing up some misconceptions that some folks may have on how different dietary components affect these processes.

So I think perhaps a good place to start this whole conversation is on the topic of oxidative stress because it's one that's super-important but again maybe has some differences in how either people understand it, the model they're working off or maybe people just aren't even familiar with this idea in general, and I think if we get clear on that now it will give a nice framework to the rest of the conversation today. So just to get us all on the same page, what exactly is oxidative stress and what is the kind of new kind of framework or new model or the most updated model of what oxidative stress actually is and what should we understand about oxidative stress?

Chris Masterjohn: So the concept of oxidative stress dates back, I mean, really earlier than a couple of decades ago, but I think it became popularized in the 1980s as a major idea of how aging and degenerative disease comes into play. And I think under the old framework that is now starting to fade away, at least in the research community, oxidative stress was defined very simply as an imbalance between oxidants and antioxidants. And so you may ask the question, well, what are those?

So an oxidant in chemical terms is something that takes an electron from something else, but in more intuitive terms I think we could think about oxidation by things that we can see. So, for example, if metal rusts it's oxidizing, and do you notice that when metal rusts it not only doesn't look very pleasant but it can also corrode the metal and make it start to lose its function? And so we could look at all the different types of things that we find in our own cells and all of those are vulnerable to oxidation in a similar way. And so there's an analogy between those processes. We're not literally developing rust but we are literally having cellular molecules that are losing electrons and are losing their normal structure and function.

Now, in the old framework that came out of the 1980s, we would have said that's oxidative stress or oxidative damage and those are basically interchangeable terms, and what it all comes down to, having the right balance between oxidants that are either caused by exposure to environmental toxins and pollutants or just the natural processes of metabolism within our body versus antioxidants that we could consume in foods, and I would say popularly people tend to think of antioxidants as vitamin E, vitamin C and the polyphenols that are found in fruits and vegetables. Now, as time has gone on, we are starting to see that it's actually a lot more complicated than that because, actually, oxidants that are produced during normal metabolism we are realizing play essential roles in cell signaling and actually are part of normal healthful physiology to produce those oxidants, and oxidative stress is better defined as when the production of those oxidants or the accumulation of those oxidants occurs in the wrong context or in the wrong amount, and usually the major biological results of the oxidative stress are not oxidative damage but are actually disruptions in the normal cell signaling processes, because it's actually the case that many of our proteins, enzymes and receptors are actually modified where they can be oxidized and their function either gets turned on or off or just changes in some way and that's a normal regulatory process.

So if you look at 100% of the oxidation reactions that are occurring through these—when I say oxidation reactions, I'm discounting normal energy metabolism. So, like oxidation of glucose produces energy, I'm not talking about that. If we look at the oxidation reactions produced by reactive oxygen species that have traditionally been seen as harmful, probably over 99% of those reactions fall into the category of cell signaling and some less than 1% fall into the category of actually damaging something. So the new idea about oxidative stress is that you're changing how things are regulated in a way that contributes to the pathology of disease and, actually, I would argue that you're not even disrupting the cell signaling. Quite often, what you're doing is you are properly signaling a context that is bad.

So if you take the case of obesity, for example, now you can be metabolically healthy and be obese but obesity is strongly associated with metabolic dysfunction, and when you look at the metabolic dysfunction that is caused by obesity what you will see is that reactive oxygen species are just governing how much energy will the cell take up, and in a healthful person that signaling pathway is operating exactly the same as in an obese insulin-resistant person. But in the obese insulin-resistant person, what that pathway is communicating is that there's too much energy and more energy than the cell can handle, so all the energy molecules like glucose and fatty acids build up in the blood. In the healthful person, the exact same system is operating but what their reactive oxygen species are communicating is that there is enough cellular capacity to take in that energy and use it.

And so I think the new idea, where we're going with oxidative stress, is to sort of…almost to get away of the idea that there's this fundamental damage and dysregulation and actually to see the system as one that does what it's supposed to do and promotes health when the environment in which it's operating is a healthful one, but which does what it's supposed to do and unfortunately produces disease when it's operating in a disease-producing environment. And that's giving us a much more sophisticated and nuanced idea of what we can do to support antioxidant defense.

Danny Lennon: Okay, let's talk about that concept of oxidative stress as a signal of energy overload in the cell. And just to kind of relay this for people and so we get super-clear on this, are we saying then that we have a case where we have some sort of energy overload, so too much energy coming in, that means that we're going to get an increased amount of oxidants? So these oxidants are being produced because we're metabolizing energy? So we're

increasing the amount of oxidants that are produced. That increase in oxidants is then going to communicate to the cells, “Okay, we need to decrease energy retention here,” so in other words, stop molecules that we can derive energy from from coming in. And you mentioned examples of, say, glucose or triglycerides. These things we can then metabolize for energy. So we're sending a signal to decrease bringing in glucose or bringing in triglycerides, etc. into a cell. Is that an accurate reflection of what this chain of events is?

Chris Masterjohn: I think that's true and totally accurate, but I would go a step further and say that the responses to incoming energy are not just about overload and the results of that signaling are not just decreased energy retention. So that is one part of it, but basically the mitochondrion, which we often call the powerhouse of the cell where most of our ATP is being produced, the mitochondrion is the major metabolizer of energy and it is one of the major sources of oxidants in the cell, and the key oxidants that are produced in quantity are superoxide, and then most of the superoxide is relatively quickly converted into hydrogen peroxide. And so probably most of the cell signaling is downstream from that, is coming from hydrogen peroxide. Maybe some of it's coming from superoxide.

So in a normal healthful person, you will always get this small fraction, considerably less than 1% of oxygen being consumed that's converted into superoxide and hydrogen peroxide, and that will increase when an increased demand is placed on the mitochondrion. But that increased demand isn't necessarily from cellular energy overload. That increased demand can also be because of exercise. And when you're exercising, you're producing more reactive oxygen species in the mitochondrion but the context is totally different. What they share in common is a bigger demand is placed on the mitochondrion, but in one case you have an excess of energy, in the other case you have an energy deficit.

So what ultimately happens as a result of exercise and of eating too much food are totally different nature. But if you look at what is downstream from those reactive oxygen species, one of them is that the energy in the cell is directed towards fatty acid synthesis instead of coming down into the mitochondrion to fully be burned for energy. So step one is you take what energy the cell has and you convert it to fat, and that relieves some of the burden on the mitochondrion. Step two is you stop taking up energy into the cell, and that's not just glucose but it's also fatty acids. You will inhibit the entry of fatty acids into the mitochondrion, you will inhibit the entry of glucose into the cell, and that inhibition will be applied both to

insulin-dependent glucose uptake and to noninsulin-dependent glucose uptake. So you're basically inhibiting any of the energy retention, but you are also stimulating mitochondrial biogenesis. So you're making more mitochondria in response to hydrogen peroxide signaling and you are also increasing every aspect of antioxidant defense and xenobiotic defense. Xenobiotic defenses are a detoxification system against foreign molecules.

So you have this whole suite of responses to the reactive oxygen species that are decreasing energy retention and also increasing your capacity to burn energy and also increasing your capacity to burn energy cleanly. And if you take the context of the person who's exercising and who's generating reactive oxygen species through exercise, that reactive oxygen species response, the hydrogen peroxide response, is actually part of the fitness adaptation, right? So if you're an endurance runner, you are going to get more mitochondria to help you deal with that energy load, and part of—I'm not saying everything, but one of the mediators of that response is hydrogen peroxide signaling. If you are a healthful person and you have a trillion cells and four, five or six or seven of them are not taking up glucose or not taking up fatty acids, you're just allowing other cells to take up that energy and it's normal. If you take someone who's obese and are developing metabolic dysfunction, what you have is the preponderance of the cells in the body are all rejecting energy molecules coming in and that's where you get a fundamental disease process. But you've taken the exact same thing that's causing fitness in the person who's exercising and that same thing is causing metabolic dysfunction in the person who is on an obesogenic diet in an obesogenic environment.

Danny Lennon: Right, okay. So then can we think of this response that we're having, whether that ends up being what we deem as a good or a bad thing that happens in response to this increase in oxidants, can we essentially think of they're really both the same thing in that they're just some sort of adaptation to the signal of increased oxidant production? So on the one hand where we get a beneficial change, we get that from, say, doing some exercise and that increase in oxidant production leads to mitochondrial biogenesis, so we create more mitochondria which, therefore, in the future may improve exercise performance because we have more mitochondria to metabolize energy. But then on the flipside, something we potentially see as negative like, say, insulin resistance, are we then saying, well, that's again just some sort of normal adaptation to this increased signaling of this increased oxidant production in that, yes, while insulin resistance in our own minds is deemed as bad and something we don't want to happen, in

the context of thinking about a cell and how a cell handles energy that is just an adaptation that while, again, like not good, is still much better than the alternative from the cell's point of view, in other words, of allowing more energy to come into the cell and having to continue to drive glucose through mitochondrion and oxidize it? So, essentially, insulin resistance is just the best-case scenario in that circumstance and that is better than the alternative of putting more energy into the cell. So whether we end up with insulin resistance or a benefit from exercise, it's just some form of adaptation to increased oxidant status?

Chris Masterjohn: Yeah, absolutely. I mean, think of this from the cell's perspective. That cell may be refusing energy and, you know, from the—I think we're really biased by the fact that we look at everything through blood draws, right? You go to the doctor and you see hyperglycemia, and you say, "Oh, there's too much glucose in the blood," but that blood is one compartment in your body. Think downstream from the cell's perspective. That cell, that whole suite of responses is all based on the mitochondria experienced some increased demand, what can it do to survive the demands that it expects in the future? And if that mitochondrion says, "Well, I don't think I can handle this workload but I'll do it anyway," then that is where you get oxidative damage because you have this constant load of reactive oxygen species that can't be dealt with. So if you think back to what I said before that over 99% of what the reactive oxygen species are doing is communicating cell signaling, that's only true because they're communicating that cell signaling that relieves the pressure on them. If they didn't communicate that, then the alternative is a total disaster because what you would have is widespread oxidative damage of all the cellular components.

Danny Lennon: Okay, so let's start digging into some of the details here and we've already mentioned a few important terms, i.e. oxidative stress; earlier you mentioned your work on methylglyoxal and glutathione; we've mentioned that term glycation. Now, all of these things are going to be interrelated and super-important so, before we start digging into them, how can we get super-clear on what these terms mean and then their relationship?

Chris Masterjohn: I think probably the average person, the first thing that they're going to want to separate in their minds when they think about glycation is the concept of glycation and sugar because, I think, because of the way that the word sounds and the way it's traditionally been used, people are a lot more likely to confuse glycation and sugar than they are glycation and oxidative stress. So let's start there. If you take the term glycation, quite

obviously it derives its name from glucose, and originally the word was used to distinguish the nonenzymatic and seemingly nondeliberate or automatic spontaneous process of a sugar binding to a protein, and to distinguish that from glycosylation, which was seen as the purposeful and, you know, I'm anthropomorphizing a little, but the deliberate or enzymatic regulated addition of sugar to proteins and lipids and other things like that.

Now, what we have understood in the decades that have ensued since it was named is that most of the advanced glycation end products which are—let me back up a step. This was originally identified outside the body, and so the prototype of glycation reactions is the browning of foods, and if you have a food and you heat it, what you will get is glucose and proteins in that food binding together and they go through a series of reactions where when they first bind together you call that an early glycation adduct, and then when eventually it reaches the end point where you call the end product an advanced glycation end product or an AGE, and that process, those AGEs, are what contributes to the brown color and the tastes that we associate with brown food. Those processes happen within our body, and so we can measure blood or we can measure any other tissue and find AGEs in the tissues, but in our body most of those AGEs are not formed from sugars directly binding to proteins. They're actually formed from small aldehydes that are about 20,000 times more reactive to those proteins than is glucose, and methylglyoxal just happens to be the number one out of those small aldehydes. So if you take most tissues probably in healthy people, definitely in diabetes, most of the AGEs in tissues are derived from methylglyoxal, and there are actually at least 10 other small aldehydes that form AGEs in the body but quantitatively the bulk of them are coming from methylglyoxal. So I think the first thing to distill there is that when you're talking about glycation in the body, you are not talking about something that’s specific to sugar, and in fact if you look at where methylglyoxal comes from, it does come from glycolysis, which is the metabolic pathway from which we derive energy from carbohydrate, but it also comes from ketogenesis, which is one of the main metabolic pathways from which we derive energy from fat. And it can also, and I'm not sure how important this is, but there is at least one amino acid, threonine, that's capable of generating methylglyoxal as well.

So if we consider that methylglyoxal is the principal former of AGEs in the human body, and then we see that it can be formed from carbohydrate metabolism or from fat metabolism, then we separate this idea that glycation in the human body has anything specific to do with sugar

because it doesn’t. So I think that's the major thing that we need to define in the terminology.

With oxidative stress, I would say that there actually is a very good analogy between glycation and between oxidative stress. So everything that I said to you before about oxidants playing a regulatory in the body and that regulatory role being able to contribute to both health and disease depending on the context, you can make a strong case that all of that is true for methylglyoxal, and we can talk about that in more detail if you want but I would just say those are more similar than they are different, even though you wouldn't say that methylglyoxal is an oxidant. You might call it, well, a small aldehyde, a dicarbonyl, a glycate or whatever you want to call it, and you might call that glycative stress. So it's a different molecule than superoxide or hydrogen peroxide, but overall the principles are very similar between the two.

Danny Lennon: Right, okay. So we have a situation where we have this compound methylglyoxal which is going to react with amino acids or a protein and that is going to end up forming this thing we call an advanced glycation end product or an AGE. And so once we have that, why is it typically deemed that these AGEs are potentially detrimental to health or what is that chain of events that leads to an increase in AGEs that potentially is going to impact chronic disease risk in the future?

Chris Masterjohn: Well, it's generally, I mean, very similar to reactive oxygen species. It's generally thought that there's a broad range of degenerative diseases that involve a glycation component. And we could say certainly that this is most researched in the context of the development of diabetes and its complications, especially its cardiovascular complications but also some of its other complications including neurological complications, and arguably the complications of diabetes are much more caused by glycation due to small aldehydes than they are even to hyperglycemia. And I'm not saying that hyperglycemia is a totally innocent bystander here, but I actually think that what’s going on in diabetes is the hyperglycemia is a response to poor intracellular insulin signaling. And it so happens that insulin doesn’t just bring glucose into the cells and thereby lower blood sugar but it also is the most important agent to protect against the accumulation of methylglyoxal, because what you will see is that insulin will bring glucose into the cell and drive it through glycolysis, and in glycolysis, methylglyoxal is mostly likely to form when you have accumulation of the intermediates in the middle of the pathway. Insulin doesn’t just bring glucose into the cell and put it into that pathway. It

actually stimulates the enzymes that drive glucose all the way down through the pathway. So glucose protects against the accumulation of the intermediates that generate methylglyoxal. Glucose also suppresses the release of fatty acids from adipose tissue, suppresses their entry into the mitochondrion, suppresses ketogenesis, and then on top of all that, the way that you derive methylglyoxal from ketogenesis is that acetone, one of the ketone bodies that's responsible for ketone breath, is converted in a two-step process first to acetal and then to methylglyoxal by an enzyme called cytochrome P450 2E1 or CYP2E1. Insulin suppresses that enzyme. So if you take two people with equivalent ketogenesis, if one person has higher insulin signaling, that person should have less methylglyoxal generated from the ketones.

And some people may be asking, well, why would you even have that variation because what you need to do to get ketogenesis is suppress insulin signaling? One case where I…I don't think it's been directly studied in this context, but one case where I can imagine it being relevant is take a traditional ketogenic diet which is based on the extremely low levels of carbohydrate and, to a relatively similar degree, protein, and versus an MCT-oil-based ketogenic diet where what you're doing is allowing greater level of insulin-stimulating foods in the diet because medium-chain fats have an independent contribution to ketogenesis, I would expect, and I've never seen it studied, but I would expect that if you compared those two, insulin levels would insulin signaling would be higher on the MCT-oil-based diet because it can include more carbohydrate and more protein, and I would expect that you would generate less methylglyoxal in that diet simply because of more insulin.

And then finally, to tie this all together, insulin actually directly promotes the detoxification of methylglyoxal and that's because insulin increases the synthesis of glutathione, which we mentioned before was the central antioxidant but also a central detoxification molecule. Glutathione helps detoxify methylglyoxal with the participation of several enzymes. Insulin also stimulates the enzyme, the rate-limiting enzyme in that metabolic pathway. So what you have altogether is that insulin suppresses methylglyoxal generation from glycolysis, it suppresses generation of methylglyoxal from fatty acids, and once you form methylglyoxal, insulin helps you detoxify it. And so if you look at why are methylglyoxal and AGEs so high in diabetes, I don't think it's because of the hyperglycemia per se. I think it's because of the poor intracellular insulin signaling in all these other pathways.

And so if you take someone without diabetes, what does that mean to them? Well, it's unclear at this point. We have one very small, not controlled pilot study where they took, I think it was 12 people, they took them, they had no control group, and they gave them Dr. Atkins' New Diet Revolution and they said, "Here, read this and do it, and then come back." And so they measured ketones, they measured acetal and methylglyoxal—acetone, acetal and methylglyoxal—in their blood before and after the Atkins diet and they found that acetone, acetal and methylglyoxal were all elevated after they went on a diet and they were more elevated in the people who had substantial evidence of ketogenesis and presumably compliance with the diet.

So, on the one hand, that seems to suggest that carbohydrate restriction actually raises methylglyoxal levels, but there are two problems with really concluding anything solid from that. One is that that study had no control group. In particular, they had no control weight loss group. So, on a low-carbohydrate diet and losing weight, methylglyoxal rises. What happens to it on a low-fat diet where you lose a similar amount of weight? If you're losing a similar amount of weight, you have a lot of…you obviously have a decrement in insulin signaling from a lower caloric intake and you obviously have a similar amount of fatty acids flooding into the liver, so presumably this could also be an effect of other weight loss diets.

And then the second thing is, where is the dividing line between physiology and pathology? We alluded to before and didn't really talk about it, but there are a lot of reasons why you would expect to want methylglyoxal to rise during caloric and carbohydrate restriction because of its regulatory roles, and so is that rise on the Atkins diet, is it physiological or is it pathological? They didn't even show that those people developed more advanced glycation end products, but they certainly didn't show that the Atkins diet causes diabetes.

So there's a lot of room for debate and for further research in flushing out exactly where the dividing line between physiology and pathology is, but there is in general I think reasons to warrant caution. When I see that, I don't immediately condemn the Atkins diet, but I do say, well, insulin plays all these positive roles in the body, so I am very skeptical that you want insulin to be constantly chronically maximally suppressed. I think we do need carbohydrate in the diet to take advantage of some of insulin's properties.

Danny Lennon: Yeah, and I think that's a really, really important point that I just want to pull back on and recap for people just so we're kind of clear on that. Essentially, we're saying insulin signaling is important to the antioxidant defense system we have in our body because it does a number of really important things, number one being that insulin signaling is going to increase the synthesis of glutathione, which is this max sort of antioxidant. Secondly, you talked about how insulin signaling is going to suppress the generation of methylglyoxal, and not only that, it also stimulates the detoxification of methylglyoxal. And all of these things then can combine and aid in our overall defense against AGEs or the potential damage that AGEs can do, so tying it back to this important role and protective role of insulin signaling.

So if we then start relaying that back to the impact of dietary choices and in particular this whole discussion around carbohydrates, there was the research you mentioned that in fact diets that have a higher degree of carbohydrates, or at least the unrestricted that contain carbohydrates, are likely to promote possibly lower levels of methylglyoxal and then therefore have a better protective effect against damage that could be done by AGEs. Now, I think it was important that you mentioned that, again, it's only kind of like a pilot study, there's not a ton of research, it's relatively weak so far, but at least based on the research we have in front of us, there's a slight lean in the direction of having a decent degree of carbohydrate in the diet is going to be protective. And I think even more important than that, even at the very least, even if we can't say that just yet, at the very least there's nothing to suggest and in fact there's research that shows the opposite, but there's certainly nothing to suggest that going on a heavily carbohydrate-restricted diet, very low levels of carbohydrate, the idea of restricting it as much as possible to keep glucose down and to keep insulin down as much as possible with the reason for that being that we don’t want a lot of glycation to happen, is…there's nothing to base that on, right? So this idea that you want to restrict carbohydrates purely because carbohydrates and sugar is the thing that's causing all this glycation is something that doesn’t really play out or that we've seen, right?

Chris Masterjohn: Yeah, I would say, you know, I'm so immersed in this that my thought process is kind of like, okay, what is the next frontier in research? And sometimes I can't forget what it was like for me seven or eight years ago before I studied this for my doctoral work and before I read hundreds of scientific publications on this stuff. Where I was seven or eight or

certainly 10 years ago was I only knew about glycation from books that were promoting carbohydrate restriction on the basis that more carbohydrate means more sugar to bind to more protein and form more glycation in the body. So I would say that outside of the research world, I think glycation is very frequently invoked as a reason to avoid carbohydrate, and when you actually immerse yourself in the science, that doesn't make any sense at all.

So I'm not saying there's no good reason for someone to restrict their carbohydrates, but it definitely should not be on the theoretical basis that more carbohydrate means more glycation because the science, even if it doesn't lean all the way in the other direction, is at least leaning in the opposite direction, saying "more carbohydrate at least within a reasonable range means less glycation." So I would say take that reason to restrict carbohydrate, throw it in the trash, and then decide for yourself whether you have other good, better reasons to restrict carbohydrate before making your decision.

Danny Lennon: Yeah. You know, Chris, I think this just all relates back to the importance of taking a step back and looking at the overall complex nature of human biology and looking at these interrelated systems, because so often we see the point where people draw erroneous conclusions or put out something that's misleading or have an idea in our mind that's a misconception is generally when they take a zeroed in focus on either one particular role of one particular nutrient or one particular function of one particular hormone, etc., etc. And I think that the best example of this is generally insulin because a lot of the time, particularly in people that are trying to promote very low-carbohydrate diets for everyone, the idea is that in order to create a better fat-burning environment you have to lower insulin, and they zero in on one function of insulin at one specific time point and, yeah, they correctly say that when insulin is elevated you will get a downregulation of the fat burning or the fat oxidation processes and therefore kind of promoting fat storage at that time, and then they extrapolate that out to try and insinuate the idea that that means that you are going to be storing body fat all the time or you can't burn it or that insulin is inherently bad based on that one role, that one function at one particular time instead of looking at, well, what is the net energy over the course of, say, 24 hours, and then also remembering all the other functions that insulin has, that it does so many other things as opposed to simply being this thing that stops fat oxidation, right?

Chris Masterjohn: Yeah, I would totally agree with that, and I kind of want to hammer this point home because I feel like it's been said so often that insulin promotes fat storage that I've probably said this before but I want to say it over and over again. See, the problem with this concept is that it's true. It's totally true that insulin promotes fat storage. The problem with this is no one who invokes that seems to be looking at what the net effect on energy metabolism is. So insulin promotes fat storage and yet promotes burning carbohydrate for fuel, and I have never seen any clear evidence that it promotes fat storage to a greater degree than it promotes burning carbohydrate for fuel.

So the way that I see this—and I think this should be the default position until clearly documented otherwise—is that insulin, if it's increasing in response to carbohydrate, is shifting you toward carbohydrate metabolism and away from fat metabolism because you're preferentially burning carbohydrate for energy. If you're in a caloric balance, then insulin's promotion of fat storage is going to be net balanced by its promotion of an equal amount of carbohydrate being burned for energy. If you're in a caloric deficit, then you're going to, no matter how much insulin you have, you're still going to lose weight because in that context it's shifting which macronutrient you're burning for energy based on how much of each that you have, but it's not altering your net caloric balance.

Danny Lennon: Oh, I'm just so glad that you made that point, Chris, and it's something that I've written about in quite an extensive article here on the site before and mentioned a number of times particularly in seminars that this whole idea of trying to correlate fat oxidation with actual changes in body fat loss is a major mistake people are making in that you can do a ton of different interventions that will increase your fat burning but has likely no effect on whether you're losing body fat or gaining body fat over time unless you look at the overall net energy situation, and I think it's just such a critical point that people miss. I mean, depending on the type of meal you choose at breakfast, whether you consume a bowl of oats versus, say, you drink a bulletproof coffee with 80 grams of dietary fat, if you drink that bulletproof coffee then, yeah, you will have a higher degree of fat oxidation than if you ate the oats, but whether you're going to lose body fat over time is going to be correlated back to that energy situation at the end of a period of time as opposed to simply fat oxidation during a meal, and I think it's a big mistake that people make of not seeing that fat oxidation or the kind of slang term fat burning is not the same as actual body fat loss. So if someone tells you a certain intervention will increase

your fat burning, that does not necessarily mean that it's going to increase your body fat loss and it still comes back down to an energy balance situation. So I'm just really glad you brought that point up and, again, it just hammers it home for people.

One thing that I did want to pull back to when we're talking about this relationship between oxidative stress, glycation, and then these potentially protective roles that glucose and insulin can play, do you have any reasoning or idea in your mind why you think it is that our bodies coordinate this protection and set up this system in such a way that the protection against oxidative stress and glycation is dependent on glucose and insulin?

Chris Masterjohn: So I think, you know, what I try to do here is I try to think what can bring all of the different things that insulin is doing together into a framework that we can use to understand why it would have evolved that way or why it makes sense for those things to be coordinated, and so I will preface this by saying that, obviously, the degree to which we do this is taking facts and moving it into a more meta position where this is my analytical construct and so there's some subjectivity to that. But I really think that we have to do that to make sense of anything in the body. Otherwise, we just have this disorganized set of facts that don't really mean anything.

So when I look at this, what I see is that it seems to me that the body is going to coordinate energy-intensive processes that promote health based on the energy available to do that, and I see the two hormones that are acting as, and of course there are many auxiliary signaling molecules, but I see the two central players as leptin signaling and insulin signaling, and leptin is influenced by a number of things but it's most strongly influenced by your level of body fat, and insulin is stimulated or influenced by a number of things but it's most strongly influenced by your acute intake of carbohydrate. Many people would point out that protein also stimulates insulin but it doesn't stimulate net insulin signaling in most pathways like carbohydrate does because protein also stimulates glucagon or at least certain—the net effect of eating protein is going to be to have more insulin and more glucagon, and not every pathway that insulin is involved in is antagonized by glucagon but the bulk of them are. So it's really acute carbohydrate intake that's most strongly influencing insulin signaling.

And if you look at body fat and carbohydrate intake, what you see is that body fat is this massive storage depot that primarily reflects our long-term energy status. Carbohydrate is this very miniscule storage depot that

primarily reflects our short-term energy status, right? So you can take people and put them on a low-carbohydrate diet and high-intensity exercise and in a matter of two or three days you can deplete their glycogen, and then you can put them on a high-carbohydrate diet and rest and in a similarly short time you can fill the glycogen back up. You can't do that with fat. I mean, there are people who spend years trying to lose a fraction of their body fat – there's just a healthful person who doesn't need to lose any weight, has 30 times more fat than they have carbohydrate.

So when I look at this I say, okay, naturally the body is going to sense adipose tissue mass as a reflection of long-term energy status and is going to sense carbohydrate or glycogen storage or cue carbohydrate intake as a natural reflection of short-term energy status, and when is the body going to invest? It's going to invest when it feels secure that long-term energy status is replete and that at this time it's a good time to invest. And I think, you know, actually investing I think is sort of a really good analogy for this. Like if you have a long-term savings account and then you have a monthly budget or you have a weekly budget or however you organize it. If you're trying to make decisions of some long-term project that you want to invest in, you probably shouldn't be doing that if your bank account is at zero and your credit cards are racked up. It doesn't make any sense for you to do that and that's your long-term financial pool. At the same time, you may have your savings account maybe sort of overflowing with whatever and you may have investments and whatever, but if you have a back month and that month you couldn't meet your bills, you're not going to pour a lot of money into your investment accounts; you're going to do what you need to do to meet your short-term needs. So I think it's very similar with the human body. We don't want to be overweight but we want to have adequate body fat, but then we also want to give our body the sense that in this moment, at this time, we have all the energy that we need, and at that moment that's when the body will prioritize investments in long-term health-promoting processes.

I mean, imagine that if you have a chronic infection, are you going to invest in fertility? Are you going to invest in protecting your skin from wrinkles? Are you going to invest in making sure that your hair doesn't fall out? Are you going to invest in making sure that that day what you did was minimize your potential to develop atherosclerotic disease 20 years later? No, you're going to fight the infection. If you have high adrenal output of cortisol because of psychoemotional stress, because your body perceives that there's some fight or flight risk, are you going to invest in

those long-term processes? No. Your body is saying, “There is an energy deficit right now. Deal with it.” And so I think in carbohydrate restriction it's not exactly the same as either of those, but it's something analogous where your body is not satisfied that the demands for energy are adequate because insulin as a measure of short-term energy status is so low that it is not prioritizing the long-term investments. That's the basic framework that I use to tie it together.

Danny Lennon: And I think if we start trying to pull this all together and wrap this thing up, Chris, we've got pretty deep on things today and nerded out on some really great stuff, which I absolutely love. But if we are trying to go and pull all this information together and maybe pull it into a summary that will leave listeners with some tangible thoughts on this whole area, what key messages do you feel are important to keep in mind on this issue that we should take away from this whole conversation?

Chris Masterjohn: I would say the first takeaway point is don’t use glycation as a basis for fearing carbohydrate, and I would say as a general principle we want to stop demonizing foods, particularly natural foods that have always been a part of historical human diets, and we want to be able to make our dietary decisions without fearing or demonizing the foods, and I think that gives us a clear collective mind when we're looking at this.

And then, I would say the second thing is don’t associate carbohydrates and insulin resistance so strongly that you throw out the baby with the bathwater and focus on carbohydrate restriction so much that you make yourself sensitive to insulin without actually having any insulin or any quantitatively meaningful insulin output to contribute to these pathways. So in that case, I would say recognizing that you want to see carbohydrates as something that have potential benefits in and of themselves so you can find the right amount that's right for you, that is a real big takeaway point there.

And I would say, depending on who’s listening, in terms of giving yourself really good glutathione status, a few key things that people can do without going into the minutiae too much are, number one, try to maintain an optimal body weight and body fat percentage, and I know that you've had other guests that have really talked through that, so breaking out into other information to utilize to optimize body composition is one of the top two or three things that you can do. And then I would say the other one is eat a broad spectrum of nutrient-dense foods. So focus on unrefined whole foods, but don’t exclude any of the food groups and make sure that it's

balanced, because there are so many different nutrients that support antioxidant defense and that support glutathione status that the number one thing that you can do without thinking too hard about it is eat a lot of fruits and vegetables but also eat animal products to get your protein and also eat starches or fruits or whatever is the best way that works for you to get your carbohydrate.

And I would say if there's one thing that for a lot of people an adequate light bulb won't go off in their heads, it's that when I say don't restrict food groups, I say that in the context of what humans have always historically eaten. So right now what we define as normal already restricts major food groups. For example, think about what is in an animal when the animal's slaughtered? You got organ meats, you have bones, you have skin, you have muscle. I would say what we have defined as normal is to just eat the muscle tissue. If you are eating bones and skin in terms of whatever way is palatable to you, but one of the most common ways to do that is with bone broth nowadays, but there's also collagen supplements and a variety of other ways to attack that or sardines with edible bones, etc., etc., I would say make the organs and the bones and the skin—eat nose to tail is one of the best ways that you can kind of go beyond what's normal and actually eat the full spectrum of food groups that our ancestors have always seen.

If you just incorporate those principles, then yes, you may be in a situation where you want to run blood tests or work with a healthcare practitioner to tweak something that isn't working, but just those few principles I think can give you 80 or 90% of your mileage towards good glutathione status.

Danny Lennon: Cool, yeah. And just on trying to improve poor glutathione status via dietary means, one question that I've got from a number of people relates to intravenous glutathione administration. Do you see any use or benefit of taking glutathione intravenously?

Chris Masterjohn: I would say that as a prophylactic that's pretty silly, but there clearly could be clinical applications where it would make sense to do that. So in theory, if you look at how glutathione synthesis is regulated, I mean, first of all you have to have the precursor. So you have to have the right amino acids, you have to have the protein in your diet. But second of all, you need to have insulin signaling telling you that you have sufficient energy to make glutathione. Making glutathione is ATP-dependent, so it's an energy-intensive process. That means you have to have a good metabolic rate. That means, you know, anything that involves ATP involves magnesium,

so you need good magnesium status. But in general, you only make as much as you need because the second regulator—or there are two other regulators of glutathione synthesis besides insulin. One is oxidative stress, so when oxidative stress increases you make more glutathione to protect against it, and the other is glutathione itself acts as a negative feedback loop. So if you have—oxidative stress is the signal that you need glutathione. Insulin is the signal that you have enough energy to make glutathione. Glutathione is the signal that you've already made enough glutathione.

So in general, when you have those factors optimized, you may call the glutathione that you need and there shouldn't be a reason to put, so you know, override that system and put in extra glutathione. But, here's the thing. In a rare case, you may have a genetic polymorphism that hurts your glutathione status and something like that makes sense, or you may have a severe disease case where the disease is depleting glutathione and typical dietary means just aren't enough to cut it, or much more commonly than either of those, you may have a metabolic problem making enough glutathione. So we mentioned before, diabetes, you see enormous decrements in glutathione status. You see decrements in glutathione status with aging. You see it in smoking. I would be really surprised if…I don't recall seeing the studies offhand but I'd be really surprised if obesity-associated insulin resistance was not also outside the context of diabetes driving poor glutathione status. In those cases, you have a breakdown of the regulatory pathway. So if you are insulin-resistant, your cells are perceiving that you don't have enough energy to make glutathione. So even if you have oxidative stress telling you you need glutathione, and even if you have low glutathione telling you that you haven't made enough glutathione, you don't have good insulin signaling telling you that you can make glutathione, and that's the case where you want to step in and say, "Well, maybe in this case my glutathione status is not poor because my body doesn't perceive the need for it. It's poor because my body perceives that it can't make it," and if it can't make it that's the case where you want to provide exogenous glutathione.

Now, if you look in foods, there are actually some dietary strategies that I would use before I would step into something as extreme as intravenous. One of those is to look at foods that contain gamma-glutamyl cysteine. And so the first step in glutathione status is you take glutamate and you take cysteine, you put it together to make gamma-glutamyl cysteine. If insulin signaling is poor, you will not make gamma-glutamyl cysteine.

And so even the supplements that people use like n-acetyl cysteine, that's just an effective way to deliver cysteine to your cells. If insulin signaling is poor, you're not going to do anything with that cysteine to make glutathione. So if you can consume gamma-glutamyl cysteine in foods, then you can override that problem, and in that case what you want is whey protein. If you're trying to get it directly from dairy products, you can't eat cheese because cheese doesn't have the whey proteins, and if you're getting it from whole milk, actually raw milk has about twice as much gamma-glutamyl cysteine as pasteurized milk does. That's a whole can of worms debating the safety of raw milk, but that's a fact.

The other thing that you can do is use whey protein. So even though whey protein is pasteurized in the processing, it concentrates those specific whey proteins. And usually, I would say nowadays most…a good-quality whey protein is actually bragging about the specific proteins on the label that contain gamma-glutamyl cysteine bonds. So whey protein would be one way of doing that.

And then finally, you can actually consume exogenous glutathione in foods. Pretty much anything that is rich in cells, because glutathione is intracellular, is rich in glutathione. And to take that to a practical level, things that are specializing in energy storage like a potato that's rich in starch or a grain that's rich in starch or a seed that's rich in fat or adipose tissue of an animal, that's not going to have a lot of glutathione, but all of the low-starch, low-fat fruits and vegetables and the lean portions of meat are all good sources of exogenous glutathione. So I would say in that case, unless you have a specific clinical condition that is well-known to respond to intravenous glutathione, if you just have evidence that you have poor glutathione status, try food sources or supplement sources of gamma-glutamyl cysteine and try managing your diet to increase lean protein and fruit and vegetables and see if that can help, and then if that can't help, then you can move on to things like glutathione supplements or liposomal glutathione or intravenous glutathione or whatever to try to fix the problem.

Danny Lennon: Perfect. That sums things up really, really well, Chris. Thanks for that. Before we get to the very final question, maybe you can let people know where they can track you down online, find you on social media, and then a bit about the podcast as well.

Chris Masterjohn: Yeah, great. So for years I have had a blog called The Daily Lipid and overwhelmingly my fans, when I asked, suggested that I should name my

podcast The Daily Lipid. So The Daily Lipid podcast is available in your favorite podcast app and the show notes are posted on my blog, The Daily Lipid, as well as all my other writings. So one way to, if you do this through a computer, obviously you can subscribe to the podcast in your favorite podcast app, but on the computer if you go to blog.cholesterol-and-health.com, that's my—or even, to be honest, if you just google The Daily Lipid it should be the first link, and there you will find links to anywhere you can listen to the podcast, you will find the show notes for the podcast, and you will also find links to literally everything else that I write elsewhere.

People who want to find me on social media can find me on Facebook, Twitter, Instagram, and Snapchat, and on all of those I would say, more easy than writing down my username or handle, I would just say search Chris Masterjohn in any of those social media outlets and you'll find me.

Danny Lennon: Perfect. And for everyone listening, I will link up to everything Chris just mentioned there in the show notes to this episode, which will be at SigmaNutrition.com/episode129, and if you go there you'll get all those links as well as an ability to get a transcript for this episode as well, and yeah, that's all there. And just while we're on it, I have to commend you, Chris, that your podcast is probably the only nutrition podcast that I go out of my way to listen to every episode, and so I really recommend you the information. It's really, really high-quality, and so I thoroughly recommend that people check that out.

Chris Masterjohn: Thank you.

Danny Lennon: Oh, no problem. It's 100% completely deserved. And with that, let's get to the final question that we'll end the show on and it's simply, if you could advise people to do one thing each day that would have some benefit on some aspect of their life, what would that one thing be?

Chris Masterjohn: I think there are so many things that we each should be working on that are different, but the best thing that would apply to everyone is to take, if it's a daily thing, take 10 or 15 minutes a day to reflect on what you're doing and why because I think that many of us are on autopilot and the main reason that we do everything is because that's what we did the day before and the day before and the day before, and then the number two and number three reasons that we're doing everything are because that's what we heard was good or that's what someone else said, that's what everyone else was doing. And so I think almost all of us, if not all of us,

could really benefit by just taking a little bit of time and actually thinking through, “Why are we doing the things that we're doing?” and being as specific as possible about the answers. Because if we say, “Well, I'm doing this instead of that because I don’t have time,” then you really want to say, “Well, why don’t I have time?” and then maybe you find out that you're just prioritizing things differently than you should be. And I think with that one thing, everyone can really find the thing that's particular to—in that generalization, people will find the particular things that are specific to them that they should be doing.

Danny Lennon: There we go. Absolutely, yeah, perfect. And that wraps up our show for today. I want to say thank you, Chris, so much for taking the time out to come on the show and even more so for the really, really high-quality information you've brought here today, and hopefully when people get a chance to go through all, there will be a ton of value I think that people will get from it. So thank you so much for your time and thank you so much for the information. It's been awesome.

Chris Masterjohn: Thank you so much, Danny. It was great being on the show.

Danny Lennon: So that is our episode for this week, Chris with some absolutely astounding and fantastic information, and I feel this is going to be one of those episodes that many of you will listen back to two or maybe even three times to pick out all the details and the gems that were in this one because it was just so extensive with some really, really good information. And I think it was a great example of when you take someone who is a researcher in a very specific field and is able to give a very accurate account of the evidence that we have in that field, you can see how it's counter to maybe some of the misleading scientific-sounding sound bites that some people can use to try and push a certain case. And one good example from today’s show is how many people who are very dogmatic about, say, low-carbohydrate diets, can use glycation as a reason to restrict carbohydrates saying that glucose is going to cause glycation and therefore oxidative stress, but when you see someone who's actually immersed in this field, you can see more of where the truth lies. So I think this is one of the reasons why I think it's so important for us to talk to the researchers in those fields and to continue with trying to spread an evidence-based point of view. So hopefully you are able to pick up some really good information. Like I say, we got pretty deep in this one, so it'll probably take a couple of listens to get all the truly great stuff out of this.

And in the show notes, I'm going to link up to more of Chris' work, which you're going to find more context what we talked about today, where to connect with him online, but you'll also have the option to get the full transcript to this episode as well as all the other episodes for absolutely free when you go to that show notes page over at SigmaNutrition.com/episode129. So again, that might prove useful to go back and to pull even more information from this particular episode.

If you want to find me on social media, then either just search for Sigma Nutrition on Facebook, follow me on Instagram at my handle dannylennon_sigmanutrition, or you can find me on Twitter as well, and the rest of the social channels should be listed on the website.

And that brings this episode to a close. I really hope you enjoyed today's episode and got something useful from it. And if you did, I'll be extremely grateful if you just shared it around on social media or let someone you think can get some use from it, if you let them know about it, post it over to them in a message and just tell them to take a listen, that really does help. So let's try and help get good solid scientific information out there to counteract all the kind of nonsense that we may come across.

And that's it for our show. I will talk to you next week. Over the next few weeks we've still got the listener Q&A to come, we've got an episode with Menno Henselmanns still to come, so I'm super-excited about those. So make sure you are subscribed. And that is it. I will talk to you soon.

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