Introduction and Ben Bikmanu2019s Background

Hey, Ben, good to have you here. Thanks for coming. And thanks for joining us. Yeah. My pleasure. Thanks, Jason. Yeah. So, Doctor Beekman is a good friend of mine.

We've known each other a while, and it's, he's, one of the smartest guys I know. Honestly, he's really, you know, looked at really in a deep way, the, sort of root causes of disease.

And, he's not a physician. He's a researcher. And, I just want to maybe go back over a little bit of your background about how you sort of got to where you are, and, and then maybe your book, why we got sick, which is really very insightful about, sort of root causes and, sort of, where we stand because our focus here is longevity.

So, you know, obviously trying to avoid why we get sick is so important. So, yeah. Why don't we start there. Yeah. Yeah. So as you noted, I am a biomedical scientist and a professor.

My research focus as a scientist is to study insulin in as one main theme. And in addition to that my lab focuses on mitochondrial function. We do a lot of mitochondrial work but it's all somatic of trying to get a better understanding of the metabolic influence in chronic disease.

You know, for example, you know, we have, published a few papers over the past couple of years looking at some of the mitochondrial problem, in Alzheimer's disease.

We have published a handful of papers looking at the differential effects of insulin versus ketones on fat tissue metabolism. So all of these things are just, offshoots of our central focus, which is to just understand the role of metabolism in disease.

And my my evolution is you mentioned just providing a brief overview there, was actually one that started with an interest in muscle tissue. But then in the late 90s, I stumbled across a paper that had just been published that documented how fat tissue, was as it grew, as it expanded, was capable of secreting pro-inflammatory proteins, and that these pro-inflammatory proteins called cytokines, were then capable of causing insulin resistance, which was this foundational problem with type two diabetes.

All of this was an AMP, was a total revelation to me that I was certainly aware of the twin epidemics of obesity and type two diabetes, but I had not even been interested enough to start to learn about what was the bridge connecting them.

What was it about this fat tissue that was causing insulin resistance? The foundational problem with type two diabetes and that that the there wasn't there was two things that really set me on the path that I'm still on to this day.

One was the the learning that inflammation, had, metabolic consequence. And that was in fact something that I went on to study for my dissertation work in my postdoctoral work, my fellowship.

Fat Tissue, Inflammation, and Insulin Resistance

But at the same time, what blew my mind at the time was learning that fat tissue is an endocrine organ. That was an absolute, revelation to me. I had I had not been taught that before, even though in hindsight there were hormones that had already been identified from the fat tissue, the most famous of which is, was of course, leptin, and still is.

But I didn't know that at the time. And it it set a curiosity, this, this burning wonder in me to want to learn more

about fat tissue. And so what had started as an academic career that I thought would be mostly devoted to muscle tissue.

And we do muscle work, it really quickly became a career that was more interested in fat tissue. And then to kind of really make the long story short, during my postdoctoral work, we had a protocol that required us to be injecting, low doses of insulin in animals, and yet they were fed.

So the animals that were getting the higher levels of insulin, they could only eat as much as the other animals that were not getting insulin, they were just getting like a placebo, a saline injection.

So they were eating the exact same amount, and yet they had much more fat than the other animals did. And then I, that was a challenging thing, and I assumed we'd been making we'd been there had to have been some mistake that the animal technicians were letting them get more food, and we really had to scrutinize, the protocols and confirming in the end that, no, they weren't getting any more food.

They were eating the exact same amount of food, and yet they were somehow fatter. And then it was a couple years later, that when I got hired as a professor that someone I went to church with, I was sharing this with them.

And he said, you sound a lot like this guy, Gary Taubes. And then I read Gary's book and came out of the closet as a calorie skeptic. And that and that and the rest is history.

And, you know, I love that because, you know, I went to medical school in the 90s, and that was sort of the prevailing wisdom to assess that the fat cell is this sort of inert sack of doorknobs sort of thing.

Right. So it's this idea that there's no regulation. It doesn't do anything interesting. You know, it's like if you have, you know, extra doorknobs, you throw them in the sack and you can take them out of a sack, you can put them in the sack, but the sack doesn't actually do anything.

And that was the idea with fat cells. Right. And that's, that was the prevailing wisdom. And I think to some extent probably is because when you listen to some of the people talk, even so-called experts and stuff, it's like, oh, they clearly have no idea that the whole thing is completely regulated by hormones, predominantly insulin, because it's not a sack of doorknobs.

There are times that it's the fat cell can store fat, and there's times that they can release, that they can't release fat all the time, and it can't store fat all the time.

There's a sort of hormone that lets it go in, like like lets the energy go in. That's the energy go out. And the fat cell itself has, endocrine effects.

And that's, you know, that's something that I think is just so important. Like it's if you don't understand that. Yep. That's that's why there's so much misconception that, oh, you can just eat a few more calories and it's just going to go into fat stores.

Yeah, yeah. Situation. Yeah. That's exactly right. And people like to assign a certain intelligence to cells that is not warranted. A cell doesn't have the intelligence to act on its own.

And it doesn't know what to do because it wants to play nice with the rest of the body. But how can a fat cell know what's happening in the intestines?

It. Because the intestines will tell it. Or how can the fat cell know what's happening in the blood? There will be a signal. One cell type will tell another cell type.

Okay, here's what's going on. And this is what I need you to do. And and type one diabetes is the most, unavoidably obvious example because as much as there are, a handful, it's a small handful of hormones that do have an influence on fat cells.

Thyroid hormone has an influence. Cortisol has an influence. Progesterone has an influence. And yet all of those variables can be present. And if we remove only one, none of them matter.

In type one, diabetes is the perfect example. And it also completely breaks apart this whole idea that if there's a lot of energy in the blood, in other words, lots of calories one the fat cells will just take it in.

But it so in the type one diabetic, if they are, if there's no insulin there, there's this it seemingly impossible situation based on just a purely caloric view because the blood is filled with calories, a glucose levels.

There's ten times too much glucose free fatty acid levels in the blood are through the roof. There's even tons of amino acids in the blood, which the fat cell isn't going to really use anyway.

But suffice it to say, every the cell, the blood is loaded with calories, and yet the fat cell can't take in and store a single speck of it because it has to wait.

It's an obedient child, which I pretend I have several loaves. Sometimes because my kids are so rambunctious, but the fat cell is waiting for its orders.

It's waiting to be told what to do, and in the absence of insulin, it can not. Not only can it not hold, pull in, and create fat, it cannot hold on to any fat.

And so even though the blood is filled with calories, the fat cell just continues to let its own calories out. This is why to me, people want to try to complicate the issue.

Now, neither of us is saying energy doesn't matter, but insulin is an absolute unavoidable signal that tells the fat cell to store fat. Now you need the calories to create the the substance of that storage.

You know you can't have one without the other. If you try to increase insulin without having, a sufficient amount of energy, then the person just becomes, the central nervous system shuts off because you've locked all the energy away and there's nothing left for the brain to eat.

The person goes unconscious, so that's incompatible with life. Alternatively, you can have calories through the roof, and if there's no insulin, you can't store that energy.

And once again, it's a death sentence, albeit slightly slower than the other paradigm. I just mentioned. So you have you cannot have obesity without both.

But we, you and I, I know where you and I are so aligned is that we focus, we beat the drum that no one else that so few are willing to beat. That yes, energy matters.

You must have a sufficient amount, but there must. It must be preceded by a stimulus telling the fat cell what to do with that energy. And that's insulin.

Yeah, absolutely. And the funny part about it is that every cell in the body is the same way, right? Like, no, because, you know, there are thousands of cell like trillions of cells actually, but thousands and hundreds of cell types, probably.

It needs to be coordinated. So therefore you must coordinate it with signals. And most of those signals are hormonal signals. And in this case it's the insulin.

So in type one diabetes of course there's no insulin. That's the pathology of the disease. And that's where if you don't have insulin that's the fat cell can't take in those calories.

And therefore people, you know, even with all those calories they just lose weight. They they, they become extremely skinny until they die basically.

Why Too Much Insulin Drives Disease

So what happens in this situation, in this situation, the opposite situation where you have too much insulin. What happens there. Yeah. So then this is what I like about this segue.

Is it. It allows us to present the paradigm that type two diabetes is the opposite problem of type one, that I think it's one of the great, tragedies of modern medicine that we have lumped these two total opposite diseases into one family because they share one single thing in common, namely, that they both can eventually manifest with high glucose levels.

But how they get there is two exactly opposite scenarios. So it's unfortunate because then we believe they need to be treated the same way, which just compounds the problem.

So when there's too much insulin, you now start to create insulin resistance. So I would I would say there are two things that I'd want to emphasize here.

And then the conversation can proceed on either of these as you see fit. So on one hand chronically elevated insulin causes insulin resistance. I have I have published reports on this, many other basic scientists have published reports on this.

Clinicians have observed this. The the were with type two diabetes. There's there's I think it's important to note that in type two and true type two diabetes, insulin never drops to zero.

That does not happen. It has been really really high. Some times it comes down a little, but it is still multiples higher than it ever was before they started on that disease progression.

So the idea this, this kind of cleverly false language of insulin production becomes insufficient to control glucose. Well, that's a pretty subjective term.

It's they're still loaded with insulin. And by putting the type two diabetic on even more insulin, they become more insulin resistant. So a point that I was getting around to in distracted myself is that every cell type we've used in the lab, muscle cells, liver cells, neurons, brain cells, if they are exposed to even physiological but higher, chronically elevated levels of insulin, they become insulin resistant.

You can create all whether it's cells, whether it's animals. I've done that and published those results, whether it's humans that's been published in all three commonly used biomedical models cells, rodents, humans.

If you increase the insulin and keep it there for a period of time, they become insulin resistant. And lest someone think, well, I'm not a dish of cells or a rodent, I'm a human and I eat when I want.

Yeah, but you probably eat a lot of starches because 71% of all calories consumed globally are carbohydrates. And you're probably like the average individual nowadays who eats about six times a day.

And considering that it can take insulin up to 3 or 4 or five hours to come back down to normal, depending on how much you ate and what you ate and how insulin resistant you are.

It's not a stretch to assume that most adults and children are probably spending every waking moment in a state of elevated insulin because they wake up in the morning.

Insulin has finally had time to come down overnight, and then they spike it with starchy, sugary breakfast. And then right when the insulin is about to start coming down, they spike it again with a mid-morning snack.

And that just continues until their evening snack. And now they're going to bed. Hypoglycemic and hyperinsulinemia. And they're not sleeping well. But anyway.

So one chronically elevated insulin causes insulin resistance. Let's, let's let's pause on that moment for a moment, because I think it's a it's a really, really important point because this is, the crux of the matter.

So and a lot of doctors simply don't understand this. And I think it's actually crucial insulin resistance. We all agree. Everybody in the world pretty much agrees is a problem.

If you're insulin resistant, then you're much a higher risk of all kinds of other diseases heart disease, cancer and all this stuff that. So if you take the next step and you say, okay, insulin resistance is a problem in everybody, what causes it then like nine out of ten doctors will be like, we don't know.

It's like, what the hell, right? You don't know. So insulin resistance being such a huge problem and it's been, you know, syndrome X Gerald Beaven identified it like at least by the 70s.

So we're talking about 50 years of sort of medical research. And you're telling me that and it's, you know, three, 4 or 5 times higher. Diabetes is three or 4 or 5 times higher than it was in the 70s.

In certain countries it's like 10 or 20 times higher. So it's like you have this huge, like epidemic. You've been studying it some 50 years. You've known that insulin resistance is a problem 50 years.

So what causes it? And the answer is we don't know. It's like, okay, well do you have any idea. And again I've asked lots of doctors this by the way. They are like I have no idea.

I asked trainees this and they have no idea because they've never been taught. And I'm always thinking, why don't you actually think about this problem?

Because if you think that the problem is hyperinsulinemia, right, which is too much insulin causes insulin resistance, then it's, it's a it's an important link because if you say too much insulin causes insulin resistance, therefore the the answer for a lot of these problems is to help lower insulin.

And how are you going to do that? Because up until recently there were really no drugs that did that. It was epic. Now can do that, but in a different manner. Right.

So that's such a crucial point that that that the hyper insulin image, the too much insulin problem is, is what we should be focused on. Because again, as you point out, it's been done.

Like if you want it, if you think too much insulin causes insulin resistance, do a study, take people, infuse insulin, see what happens. You know what every single study shows?

They get insulin resistant. You can even take insulin comas, which are these insulin producing tumors. You take them out. So you take a condition where you have too much insulin and they return it back to normal.

What happens? That insulin resistance completely disappears. And it's like, okay, well, yeah, there's something so intuitive about it. If if you just think about it for a moment, a person very quickly comes to the, the, oh, I see, it's just it's an inconvenient, fact because it challenges so much of how these issues are treated, but too much of something causes a resistance to that something.

That is how biology that is one of the fundamental biological principles. If there's an incessant stimulus, the cell, the body by extension, or the tissue by extension in the body by extension will attempt to reduce the response to that, to that signal, assuming just kind of placing it into the background and it becomes deaf to the signal.

In other words, in this case it becomes insulin resistant. And that and that's important because this is a sort of fundamental biological principle. And it's a protective response. Right.

So the cell is protecting itself from too much insulin by becoming resistant. And you see this everywhere, right? Is you if you're, you know, listening to loud music, what happens.

You go deaf. Why. Because your your ear needs to protect itself from the loud noise. So therefore it goes a little deaf. So in that even still, Jason, if you allow me to insert into that metaphor, what do you do to try to continue to hear the music?

You continue to turn the volume up? Yeah. And I mean, bringing it back to insulin resistance, it becomes this vicious cycle where the pattern of eating lots of refined starches and sugars, eating so frequently is pumping up the volume to get to some early 90s music, references.

But then it's you're becoming deaf. So? So. And then what do you do? I want to still hear this. The cell wants to continue to respond to insulin. And so the body will start to have this compensatory response and increase insulin, which further promotes insulin resistance.

And so it becomes a vicious cycle. Exactly. The time it seems obvious that you should pump up the volume, right? Because it's like, hey, I can't hear.

Yeah, I need to pump up the volume, but that's the exact wrong thing to do. And in fact, that's what was done, right? If insulin is too high, it causes insulin resistance.

We saw that insulin resistance and said we need to pump up the insulin. So we gave people insulin. You told them to eat six times a day. We told them to eat lots of low fat, high starch foods.

That is the equivalent of making that insulin higher so that you don't have to overcome this resistance, but it actually makes the underlying problem worse, not better.

You actually have to do the opposite, even though it seems a little counterintuitive, if you will at the time. But it's it's actually the only way, and the only way really is to look at that sort of underlying root cause of, of, disease, which is that, okay, too much insulin.

Let's lower insulin as opposed to, oh, while the insulin isn't responding, let's pump up the insulin, which is such a, you know, it's it seems so obvious to you and me, but unfortunately, I think like 99% of the medical institution thinks it.

You should just sort of give more insulin. Sort of. Oh yeah. Yeah. They've really tried to make that written. Yeah, yeah. And the way they justify it is and I say this with sympathy, unless it sounds like either of us is being too harsh, you only know what you've been taught.

And so unfortunately, these clinicians and the average individual has been taught that glucose is the marker that matters most. And if you see metabolic health and its consequences when it goes poorly through a glucose centric lens, then it is easy to justify pushing up the insulin even more, or not even measuring the insulin, as we both know is is more common is common.

It's common that a clinician doesn't even think about measuring the insulin, that they will just look at that glucose and they say that's the marker that matters.

So we just need to lower that glucose at all costs, even if it means increasing the insulin because they have no awareness of one, what insulin levels actually are in the patient or two, they have no appreciation that chronically elevated insulin is highly pathogenic.

Metabolic Syndrome and Its Mechanisms

And I think that's the part that also sort of stuns me, is that if you look at some of the basic research of chronically elevated insulin, it's not good for you.

Oh gosh. No. Oh no no. In the irony. Right. These type two diabetic patients, they if you put them on insulin and you're needing higher and higher doses in the midst of having optimal glucose levels, the more insulin you're giving

them, their risk of dying from heart disease triples their risk of getting Alzheimer's, doubles their risk of dying from cancer doubles.

This is I know you're very familiar with this work and the listeners need to be, but that's just proof positive that it's not the glucose that's killing these patients in the in type two diabetes.

Because even while you're struggling and fighting mightily and successfully keeping glucose in a generally acceptable range, the more insulin you have to give the patient to do it, the more all of these chronic disease, they get fatter and sicker and die faster.

Yeah. I mean, we'll come back to, obesity and diabetes in a second. But even for diseases like cardiovascular disease, for example, you can look at insulin and what it does, and you can bathe these cells in insulin.

And not only does it, you know, it causes a lot of problems like smooth muscle proliferation and inflammation and all these things because we know that, you know, and again, I sort of shudder sometimes because everybody has this idea that coronary artery disease, which is the blockage of the coronary artery, is like getting clogged with cholesterol, but it's like, again, I went to school in the 90s, even in the 90s, we were taught that that's a foolishly simply thought.

This is and that's not what happens at all. In fact, what you get is chronic damage. That's why you get to see them at birth. Bifurcations in the arteries, right?

But it's a response to injury, thing. So what happens is that there's injury to these, to the lining of the cell and then under the condition of high.

And so you get a lot more of the smooth muscle proliferation. You get the, the sealing off of the damage, the inflammation and then the damage that's covered up by this cholesterol cap and so on.

So even if you study the effect, the isolated effect of insulin on sort of atherosclerosis, it's pretty obvious that it's really, really bad. There's actually 6 or 7 different mechanisms.

I remember I looked at one paper and they're talking about it. It's like, okay, well that makes sense. Insulin is a hormone. It's a natural hormone. Everybody says, oh, I think it's evil.

No, no, no, it's a natural hormone. But if you don't have it, you'll die. Yeah, exactly. It's like thyroid hormone. Like I have nothing against it. But if it's super high, you need to bring it down.

And so as the saying, if insulin is too high, you need to bring it down. Like, what could be more simple than that? People, so over complicate this whole thing.

It's like. But the effect of insulin on coronary disease, on, on on, atherosclerosis is it's been around for. Oh yes, the 90s. So yeah, it's like, I invite anyone. Yeah.

I invite anyone to find a paper that has looked at predictive variables with heart disease. And there's inherent flaws in those studies because they're always correlational, always correlational, which is a basic scientist I kind of look at with some disdain and scorn.

I want mechanism, and you just don't find that in these kinds of studies. But be that as it may look through all the correlational studies that will measure a marker of insulin resistance and LDL cholesterol, and compare which one has the more statistically significant connection, which one has the greater predictive value every time it's going to be the insulin resistance.

And in fact, most of the time the LDL cholesterol levels won't even reach statistical significance. They they they have to get tossed to it's an inconvenient little side line in the in fact, I remember some in the abstract, they will say something like, we've been unable to explain these results because they're so married to the idea that LDL

cholesterol is the singular causal variable here, that when the house of cards tumbles, they don't know how to explain it.

Well, the explanation is because it's not causal. Yeah. And they ignore the triglycerides and it's which is in that same cholesterol panel, but somehow and are always much more significant.

Right. So they're usually twice two times as significant. And insulin resistance is like ten times more important than LDL cholesterol. Right. And yet again, some people say it's because of the, you know, the pharmaceutical influence.

But we focus like so much on LDL, like there's people who are out there saying, oh, it's the one true cause of atherosclerosis. And I was like, oh my God, I know I'm insane.

There's such there's such inconvenient data, though, because some of the most consistent findings, speaking of longevity, which I know is a an emphasis with with this conference, this gathering here, it's, one of the most predictive or consistent variables with the longest lived humans is the highest levels of LDL.

And boy, that is an inconvenience, right? I mean, it is I know it's the it's the people with one of the most common themes. They'll say that uric acid is low blood glucose levels are normal good range.

And wouldn't you know it? Inconveniently, LDL tends to be high in these long lived people. Their immune system is a little more robust. They have a lower risk of infection.

They have a lower risk of, blood based cancers. They we can't. Jason, it's sort of there's a tragedy here. But I in another timeline within the multiverse, which I don't I'm being a little silly here.

I can imagine one version of history where LDL with it's even in our current timeline, it is well known to have a powerful influence in the immune system and a positive influence in some other place in time.

LDL was initially identified as a hero of the immune system, which it is. Rather than being maligned and vilified incorrectly. I would add, as a villain of the cardiovascular system because it that is not a, a reputation it has earned based on the data that has been a convenient finding.

And, and reached was able to integrate itself into the framework of modern medicine without really despite many ardent claims against it even at the time.

And yet it just was so entrenched, it's hard to see it getting kicked off its place. There's so much interest in keeping it where it is as this villain of the cardiovascular system.

And again, that causes us to just pay no attention to the substantial body of evidence that exists now, finding how important LDL is in optimal immune function.

Yeah. And I think that, you know, a lot of it is based on, the statin data, of course, but statins have other effects. And that's that's always been the sort of, argument.

So then people have started to say things like, oh, every time you lower LDL, things improve. And it's like, that's completely not true. You know, Sglt2 is is one class of medications that raises LDL, right?

It raises LDL. And what does it do to heart disease? Oh, it improves it by quite a lot. Yep. And people always forget the whole, hormone replacement therapy, one of its purported mechanisms.

But to, prevent heart disease. Remember, you know, 30 years ago was a big thing, was that a lower cholesterol or that by like 25, 30%? So they're like, oh, give people give these postmenopausal women hormone replacement therapy and lower their cholesterol and, you know, prevent heart disease.

Of course. Then when the real studies came out, like the randomized trials, it was like, oh, it doesn't prevent heart disease at all. It might raise it and it might raise breast cancer risk.

By the way, right now, all of a sudden you didn't hear anything about the cholesterol effect. Right. And it's like, okay, well, there's just so much data that's that's not consistent, like even the starting data.

The problem with a lot of the statin data is, I think the same problem with evidence based medicine in general, which is that the, the doctors and the researchers have basically sort of prostituted themselves to the drug companies to do the study.

You need money, and the drug company will give you so much money. But at the same time, we know that if a drug company sponsors a study, you're like ten times more likely to find a positive result.

Yeah, you data any way you can to to tell a favorable story. And I'm, I'm sympathetic as a as a scientist, I can attest to the frustration that it is to get science paid for.

It is a brutal process. And so I can see the temptation to get into bed with that kind of money. But it absolutely. I, I think I'm thrilled that you bring that up.

It's a topic that, can make us be accused of being conspiracy theorists, but, but but I think that there's a little bit of naivety involved in that sort of perspective that, you know, money talks and and it goes a long way in science as it does in every aspect of life.

Yeah. For sure. Getting back to insulin. So, you know, let's talk about insulin and the metabolic syndrome. How does it like from a mechanistic standpoint, how does it influence the metabolic syndrome, which is not just obesity and diabetes because they're clearly linked.

And just as an aside, this is the thing that bothers me like crazy. If you ask an endocrinologist or a trainee or some other doctor, you know, you know that people who are obese have more type two diabetes.

That's again, not for dispute. And you say why? They'll be like, I don't know. And then it's like, okay, well, obesity is a state of hyperinsulinemia type two diabetes is a state of Hyperinsulinemia like, do you think that's like, yeah, yeah.

And there's a very move, you know, and so metabolic syndrome is identified as this sort of cluster of five, things, which includes type two diabetes, obesity, abdominal obesity specifically, but also, hypertension, hypertension, triglycerides, low HDL.

Yeah. That's the five things. Yep. And they all cluster together. Right. That's the that's the important finding of metabolic syndrome is that when you have one you very much more likely have the other.

And when you have multiple, your risk of cardiovascular disease sort of jumps with each like hugely with each one. Right. How does insulin play a role in the metabolic syndrome?

Because I think that's crucial for today's population, because metabolic diseases are by far and away the most important thing we know. We need to. Yeah. In fact, I completely agree.

In fact, just to help the listeners appreciate the scope of this, you know, why would guys like Jason and I be spending time talking about it? As a for me, as a biomedical scientist, why would I have devoted my whole career to studying insulin resistance?

It's because it is the single most common health problem worldwide. And Jason, you very aptly mentioned Gerald Raven, who we absolutely must give credit to for the metabolic syndrome.

It used to be called syndrome. It also used to be called the insulin resistance syndrome.

Fatty Liver, Lipogenesis, and Fat Cell Growth

But that's not quite as sexy as calling it the metabolic syndrome. So I apprec I can appreciate the justification for the name change, but I also groan because I fear that it somewhat confuses the issue, because if you just call it metabolic syndrome, you don't really appreciate that they all have one thing in common, namely chronically elevated insulin and insulin resistance.

And those two things always go together. If anyone tries to tell you that there's insulin resistance without hyperinsulinemia, they don't know what they're talking about.

Those problems go hand in hand. You really cannot separate them. So with the obesity aspect of maybe I'll end with that one because, it's such an interesting effect.

On the fat cells directly. But with hypertension, you, you alluded earlier to the in the evidence with insulin and heart disease. In fact, Gerald even identified multiple mechanisms that explained how insulin resistance and hyperinsulinemia.

But I'm kind of repeating myself cause hypertension, including forcing the kidneys to retain salt and water, which is increasing blood volume too much, which increases pressure.

It induces the growth of and the narrowing of the blood vessel wall itself as another mechanism. And then maybe just one more that I'll mention is that chronically elevated insulin also activates the sympathetic nervous system.

And so that's resulting in even more constriction of the blood vessels and the heart beating harder and faster. In fact, as a little tangent, one of the reasons I feel so strongly about people not snacking on starchy, sugary fruit foods in the evening yes, it's the insulin bump, but that, combined with the hypoglycemia, is a powerful stimulant of the sympathetic nervous system.

So the person's lying there at midnight wondering why their heart is beating so hard and why their body temperature is so high and they're so uncomfortable.

It's not that they're anxious about something, it's that they went to bed hypoglycemic and hyperinsulinemia, and now their sympathetic nervous system is telling them it's not time to rest.

It's time to fight or flight when they're trying to rest. So we have the hypertension and then we have the, elevated blood glucose. That, of course, is very much, going hand in hand with the insulin because glucose is the primary stimulus for insulin.

And that's one of Insulin's most famous jobs, is to try to bring that glucose down. But as the muscles become insulin resistant, that's the main consumer of glucose.

And now it can't pull in as much. It's not pulling in because it's not responding to insulin. Insulin normally tells deliver to hold on to glucose to store it for later and not to release it when insulin's high.

But the liver's getting a little death to that signal, and now it's releasing glucose when it should be holding onto it. So that explains the hypoglycemia.

And then the dyslipidemia, the high triglycerides. Boy, insulin tells the liver to make fat. And it does so very, very well. So if insulin is up it's telling the liver to start creating triglycerides and packaging them into the triglyceride rich lipoproteins, to be dumped into the blood with the VLDL and the LDL now mentioning LDL, though, it's it's conspicuously absent in the metabolic syndrome, which I think is a testament to kind of how irrelevant LDL is.

Just one more evidence then the final point with HDL insulin accelerates HDL intake back into the liver. And so it's forcing the the liver to be clearing the blood of HDL more rapidly than it would otherwise.

So it's just one more evidence of insulin resistance. And then having a control over that a little bit more. I like that the Novo like with Genesis because I think we we don't talk about this enough because as you said, like 95% of cholesterol stuff is LDL.

But that's not actually the most powerful predictor like in that cholesterol panel, the classic cholesterol panel of HDL, triglycerides and LDL. It is like the weakest link, right?

Oh yeah. It's by far and away. And we know this for a long, long, long time. Despite the outsize attention, HDL and triglycerides, which actually always go hand in, they almost always go hand in hand. Right?

When triglycerides go up, HDL goes down. It's almost like it's it's far more predictive of future heart disease than the LDL. So, so maybe mechanistically, it might be good to go for sort of fighting the Virgin over life agenesis and that packaging your mention of the VLDL, because I think that doesn't get enough, sort of, look action.

Yeah, yeah, yeah. Well, the liver, I like to refer to it as the soccer mom of nutrient metabolism because it can handle everything that comes at it. And it will it will hold on.

And it's the ultimate giver as well. You know, like, if the body, it's sort of sampling the body saying, hey, you're getting a little low on glucose. Well, I've got some here for you and I'm going to give it up.

Hey, we need to rearrange and and store some. We got extra energy coming in. I'm going to turn it into fat, and then I'm going to send that out and so that the body can burn it or store it.

Which, which the, you know, the fat cells can do. So with regards to lipo, Genesis, the liver can essentially take any excess carbons. Mostly that's going to be from glucose, but it will only happen if insulin is telling it to.

So this once again this is another phenomenon where insulin is telling the liver it's basically able to tell the liver, hey, we we have energy now. And it's a moment of, of abundance.

Let's sort of package this up and concentrate these carbons into a concentrated energy and fats, the most concentrated form of this. So take all these carbons a lot from glucose, turned it into stored form of fat.

And then let's send it to the fat tissue for example, or to the muscle or anywhere else the body wants to be holding on to, or even burning fat. That is lipo.

Genesis, the process of taking some carbons and starting to link them together. But you do not have lipo. Genesis. In the absence of an insulin stimulus.

And so insulin will be up and then it tells the liver make these triglyceride rich lipoproteins. I basically need some vehicles to take these fats around.

I'll hold on to some. And so the liver will get fat. But I also need to share some. And hopefully the fat tissue will take some of this up, you know, just as an example.

And so it will pass. Let's let's yeah. So I think that's a really key point that I just want to emphasize again too, that it's like you need insulin. This is one of the genes job, right?

It's not that it's a bad thing if if you're, you know, have a lot of food to eat and you're going to be facing a winter of, you know, no food, this is very, very good.

This is not, you know, something insulin is not moving. That is this job. The problem is it's too high. Right. And and the key is that insulin is a hormone.

It's a nutrient sensor. It tells you that food, as you say, is currently right now in abundance. We need to store some away, just like a bear will store for the winter.

It's the same idea. It's a good protective mechanism. It's a normal thing. It's just too much of it in the modern world. Right. So I think that that's really important because fatty liver is another disease that's gone through the roof.

Right. So you have too much glucose the carbons. And you could have too much protein too. But you have all this excess glucose and then a lot of insulin in response.

And how's the liver. Let's store it away. How are we going to store it? Well, we need to make meal fat. So yeah, this is de novo lipo. Genesis, which is de novo means from new like Genesis means creation of fat.

So it's the creation of new fat from glucose that's like that's like the verbatim translation. Yeah. Me. So it's like, well, obviously if insulin is a key player in de novo Lipo Genesis, it's going to create all this new fat and you're going to get fatty liver.

That's that's why fatty liver appears all the time in conjunction with, you know, the type two diabetes, with the epidemic of obesity, with the epidemic of diabetes, because it's also a manifestation of hyperinsulinemia, which gets back to the sort of excess carbs and fatty liver, of course, is now probably the most important liver disease, bar none.

So 20, 30 years ago, it was sort of down there. Hepatitis B, hepatitis C have actually largely receded because of, you know, sanitation and vaccines, you know, so those have gone down, and now all you're seeing is a huge wave of like a massive epidemic of fatty liver disease, even in children.

Even in children. Yes. Yeah. So hepatitis is the technical name, and it's like, that's crazy, because in 1980, it was actually practically unheard of, like the first case reports started that in, in 1980, I think inciting liver disease, is called nonalcoholic fatty liver because you can get fatty liver in alcoholics.

But there was this guy, this janitor, I think, who was drinking 20 Coca-Cola the day that he had fatty liver, swore he never drank a drop of alcohol. And they said, wow, this is so interesting.

I'm going to publish this now. Of course we see it. You know, every second patient has fatty liver disease, right? So I think that that fatty liver disease is a key component of the whole thing.

It's not part of the the metabolic syndrome which goes along with, okay. So now you have this liver with all this packed fat, you've made all these new fat, these triglycerides.

So what happens to that? Yeah. Yeah. Well if insulin's up insulin is going to stimulate the, fat cells to activate an enzyme called lipoprotein lipase.

And so if we sort of continue the journey, the elevated insulin and the sufficient fuel is making the liver fat and it's making the liver share that fat, which in and of itself isn't a bad thing, but in the presence of chronically elevated insulin, you can't burn it.

You're forcing the body just to continue to store it in the fat cells. Now, with the high insulin telling it, it's basically the insulin is basically telling the fat cell, hey, there's going to be some busses, some school busses of some fatty little children coming by, and I need you to pull them in.

And that is what the lipoprotein lipase is doing. So when lipoprotein lipids get stimulated by insulin, now when all of these triglyceride rich lipoproteins, these fatty loaded lipoproteins are coming by, the fat cells are pulling it in and they're pulling it in as individual fatty acids, but in the in the same presence of that elevated insulin, that fat cell itself is going to start storing more of that fat and basically joining it back in to a stored form of fat, which is the triglycerides.

But as people like to, focus only on that aspect and they will say, well, that's the only way fat cells get big by circulating fat. And that is absolutely not true.

That even that same kind of glucose stimulus that those glucose carbon building blocks that the liver was using to create fat, the fat cell can as well.

Now, some of the confusion has come where you have influencers, influencers who are saying this sort of idea that the glucose isn't a, building block for the fat cell to create fat, it's because they're looking at studies that we're only looking at enlarged fat cells.

It appears to be this sort of shift where the smaller the fat cell, the more it is able to be pulling in the glucose and turning it into fat. And so it does that very, very well.

So that same glucose that's making the liver fat can also be making the smaller fat cells fat. In contrast, when the fat cell starts to get bigger then it is primarily a function of just pulling the fat in.

The glucose is a much more modest contributor to an already enlarged fat cell, and that itself might be a reflection of the insulin resistance that can happen at fat cells.

And in that sort of brings us back to that fifth and final part of the metabolic syndrome, which is the obesity aspect where insulin will not only so as the as the fat cells get bigger and bigger.

So maybe I'll take one step back where the, the, the listeners may be interested to know that the humans can get fat through two different processes. We can get fat or, two different people could be gaining the same 10 pounds of fat.

So they've each gained two college roommates. They were buddies in college.

LDL, Heart Disease, and the Longevity Debate

They get back together ten years later for a reunion. They've both gained 10 pounds. In fact, more likely it would be 20 pounds. But let's just go with ten.

And. And one of them is just a little chubbier. But he's doing fine. He's still generally healthy. His blood pressure's normal. He doesn't have any other sort of signs of the metabolic syndrome.

Whereas his roommate, who also gained 10 pounds of fat, he is now type two diabetic. He has fatty liver disease. He has hypertension. What could explain it is very likely how they gained that 10 pounds of fat.

So more important than the mass of fat that someone gains, it's the size of their fat cells. And there's there's some interesting ethnic shifts here. Like one of the reasons I did my fellowship in Singapore was because the government of Singapore was interested in why Europeans and Chinese Singaporeans had such differing propensity for metabolic problems at such different body fat levels.

So let's say the one roommate who gained the 10 pounds and was still healthy, let's say he's sort of a typical kind of European Caucasian guy, but his roommate was a sort of Chinese typical kind of Chinese ethnicity guy.

They've each gained 10 pounds in these two ethnicities tend to be on the far ends of the spectrum, where Caucasians tend to have a little more ability to make new fat cells.

And so this guy gained fat, and yet he has more fat cells, but they're all still a little more modestly sized. So they're generally relatively small and small fat cells still have a lot of room to grow.

And so they are still sensitive to insulin because insulin wants fat cells to grow, it wants everything to grow. And but when the fat cell starts to reach a point of maximum dimension, it must start to limit its growth, lest it literally pop, which will be a very messy where the membrane of the cell cannot hold on to its size anymore.

It's the water balloon that's getting overfilled and it's about to burst. That tends to be, say, the other roommate,

where in his body he has a very limited capacity to make fat cells.

In fact, he's made them already and he's not making more. This is actually how most people get fat across all ethnicities. But now his fat gain is happening because each of his fat cells is getting really big.

That's called hypertrophy as opposed to hyperplasia where the fat cells are multiplying and the larger the fat cell gets, the more two things happen that create a particularly problematic metabolic scenario.

One, it becomes insulin resistant. So now rather than it still is taking in fat, although it's not taking in glucose as much. That aspect has become a little resistant.

But it's not a it's not a universal phenomenon, a cell can manifest with selective insulin resistance where some things aren't listening to insulin anymore, but some things still are.

So the hypertrophic fatso can still take in fat, but its insulin resistance is manifested by it's also leaking out fat. Insulin can no longer force the fat cell to hold on to the fat.

And so as much as it's still force feeding some fat in, it's now also letting some fat out. And that creates this phenomenon referred to as ectopic lipid deposition or the body's now storing fat where it shouldn't be storing it, including in the liver or the muscles or the kidneys, where there's high levels of fat in the blood, these free fatty acids, normally the body would burn those, but if insulin is up, it has to store it.

It can't burn it. And so we start storing all of that fat in all kinds of places that aren't suitable for long term fat storage. So the fat cell becomes insulin resistant to try to restrict its growth.

But then second, which compounds this problem throughout the entire body, the overfilled fat. So starts to get it starts to push itself and its neighboring fat cells further and further away from capillaries from in the life giving blood, because cells need to be within just a few micrometers of a capillary in order to get all the oxygen that it needs and give off its CO2 and other metabolites.

But the fat cell can expand to 300 or 400 micrometers, which is well over ten times the distance that it should be from a capillary, and thus it starts to suffocate, or at the level of the cell we would use the word hypoxic.

It becomes hypoxic. Interestingly, one way the hypertrophic fat cell can correct the blood flow is flushing the system with pro-inflammatory cytokines, these pro-inflammatory proteins, because some of them act like a trail of breadcrumbs.

And then the capillaries will say, oh, okay, there's some cells over here. I need to grow out too. So it will stimulate the synthesis of new blood vessels to try to correct the hypoxia.

The tragedy here is that these two things that the hypertrophic fat cell has done to ensure its own survival, namely, become insulin resistant to stop growth, become very inflammatory, to correct the blood flow deficiency, also happen to compound and exacerbate the metabolic problem throughout the entire body.

As as mentioned, now we're storing fat in all kinds of unsuitable places. And second, we've activated these immune pathways which in their own right are capable of causing insulin resistance.

So the body suffers all for the sake of the fat cells trying to survive. That's fascinating. I mean, it really explains a lot about sort of what's been happening in the world, really.

But also the differences with the, different ethnicities, because we see this actually clinically a lot where you might have, usually a Caucasian who's, you know, quite overweight and not diabetic in the least.

Yep, yep. And on the flip side, you have some, you know, Chinese or Indian person. I have we have a lot of Indians who are like this too. Yes. And their BMI is like 24 and they've got terrible diabetes.

They're getting heart disease. Yeah. Very. The skinny fat the skinny family. Yeah. Yep. Yeah. And it really explains a lot about that. So you know I think that that's really important.

You know when we're thinking about these, diseases and how to avoid them, right then, you know, keeping in mind this sort of insulin, levels, insulin, you know, the sort of key role this plays because I think, you know, to me, this sort of insulin versus calories debate is not a real debate because they work really at different like completely different levels. Right.

Like obviously a calorie is not a hormone, like it's just a, it's just a measure of energy. You know, if you have carbohydrates versus proteins versus fats, they have different hormonal responses, right? Insulin is a hormone.

So it has completely different. Like you can't compare them right. On the one hand that there's an overlap because if you're eating more calories, if the diet is fixed then you're going to have more hormonal effect, right.

So there's always an overlap and that's where the confusion comes. But I think you've done a great job in trying, you know, and really pinpointing sort of what the important, aspects of chronic disease are.

You know, in the, in the 21st century. I mean, this is really what we need to focus on because it's just not like, heart disease, cardiovascular disease and cancer, like, are the two biggest killers of Americans, like, by a long shot, right?

There's other things such as infections and stuff, but they're really much further down. So if you want to talk about improving your health, it means avoiding these diseases.

And I think insulin is one of those key factors. So, you know, I just want to wrap it up by saying thanks. And, you should check out, Ben's book, Why We Get Sick is super, super insightful, written sort of for the layperson.

So it's it's a really great book. And, do you have anything else on the, on the horizon? Yeah. Yeah. Jason feck thanks. Yeah. So in fact, Jason was kind enough to write a foreword for that book, so I still appreciate that.

In my Why We Get Sick book and the really the reasoning for it was I just thought not enough people were having this conversation that that there was one medical variable insulin resistance that just was not being highlighted sufficiently.

So I have a follow up book called How Not to Get Sick. But also, I tried to create all the content I create. I try to compile it at insulin iq.com. So people can find me there.

Yeah, that's a great resource. And also on YouTube, I've seen some of your you do the little little piece. Yeah. My metabolic classroom. Yeah. And that's like you channel. Yeah.

Or if you want to conferences those are always those are always very enlightening. So I always learn something. So thanks so much, Ben, for, for being here.

Oh, my pleasure. Thank you.