



ALZHEIMER'S

THE SCIENCE OF PREVENTION

Episode 5: Diabetes & Alzheimer's



- David Perlmutter, MD: Put simply, diabetes is a condition in which the body has difficulty maintaining normal blood sugar levels. By far the most common form of diabetes is type 2 diabetes and this is a disease that is strongly associated with inflammation and relates to dietary choices.
- David Perlmutter, MD: While we've known for some time how diabetes develops as well as how to treat it, what we are now discovering is that many of the things that cause and worsen diabetes may actually be closely linked to the development of Alzheimer's disease. In fact, this idea is so important that many now refer to Alzheimer's as type 3 diabetes. It turns out that several of the key problems involved in diabetes, like inflammation, toxic levels of blood sugar and problems with the hormone insulin are very much involved in Alzheimer's disease as well. This is really important because it means that by understanding the diabetes disease process we can also potentially lower our risk for developing Alzheimer's disease.
- David Perlmutter, MD: In this episode, we'll uncover the links between diabetes and Alzheimer's disease and then demonstrate how to use this information to create better strategies for general health and to help us avoid Alzheimer's. I'm Dr. David Perlmutter and this is Alzheimer's - the Science of Prevention.
- David Perlmutter, MD: In previous episodes we've learned that not only is Alzheimer's on the rise but it is in fact a disease for which we have no meaningful treatment.
- David Perlmutter, MD: Most importantly we've learned that there are many empowering changes that we can make to our diet and our lifestyle choices that can help us prevent the disease and take control of our health destiny.
- David Perlmutter, MD: We've already reviewed some of the important tools we have available in our Alzheimer's prevention toolkit including dietary changes, proper exercise, avoiding various toxins in the environment, reducing and managing stress, nurturing our gut microbiome and getting enough restorative sleep.
- David Perlmutter, MD: Now let's turn to the pivotal role that blood sugar plays in determining the level of inflammation with the body and how this relates to Alzheimer's disease.

David Ludwig, MD:

Diabetes is by definition the body's inability to manage a lot of carbohydrate. When you eat too much carbohydrate, blood sugar rises too high. The body can't handle it, can't metabolize it.

David Ludwig, MD:

Type 2 diabetes, we know, has genetic determinants, but is not primarily a genetic disease? How do we know this? Because there have been populations that have existed around the world, for centuries, that have had virtually no type 2 diabetes. This epidemic has exploded during the last 50 years, in lockstep with the obesity epidemic, but also with the invasion of our diet with a whole range of processed foods, and especially the processed carbohydrates.

Dale Bredesen, MD:

If you have type 2 diabetes, you have more than doubled your risk for Alzheimer's Disease, because you've got both the inflammatory piece and you've got the piece for the insulin resistance.

Max Lugavere:

If you have type two diabetes, your risk for developing Alzheimer's disease increases anywhere between two and four fold. And type two diabetes is considered a lifestyle disease brought by too many processed carbs and simple sugars and an overly sedentary lifestyle.

Max Lugavere:

This is a condition that is by and large preventable and yet today, 50% of people in the United States have either diabetes or prediabetes, which means that they are on their way there. And Alzheimer's disease shares striking similarities with type two diabetes in the brain, so much so that type three diabetes has been coined to describe Alzheimer's disease.

Mark Hyman, MD:

We know that high blood sugar, even slightly high, not abnormal, increases your risk of heart disease and death and Alzheimer's even if you don't have diabetes. So managing your blood sugar and keeping it within a normal range or an optimal range is really essential if you want to create health longevity and prevent Alzheimer's.

Jeffrey Bland, PhD:

Now we recognize it even before you get to the diabetic level. You start to get varying degrees of increasing risk to injury from sugar causing damage.



Suzanne De La Monte, MD, MPH:

I created the term type three diabetes because at the time I was studying insulin effects in the brain and for a completely unrelated reason we developed a model to see what would happen if you were to knock out insulin from the brain, prevent it from being there. And I was expecting to find effects of what we see in alcoholic brain disease, but instead we looked at the brain and it looked just like Alzheimer's and it was at that point we stopped all research and just focused on whether or not Alzheimer's could be this kind of diabetes thing. And we looked at the human brains and what we found was that there were features of type one diabetes, which means there wasn't much insulin there and as the disease got worse, you had less and less insulin in the brain. And at the same time you had an insulin resistance, which is like what you see in type two diabetes. So they were both going on at the same time and one plus two is three, so we said, you know what? It's both of them, so let's call it Type 3 diabetes.

David Perlmutter, MD:

Having type 2 diabetes or even just having elevated blood sugar increases the risk of developing Alzheimer's. But how?

David Perlmutter, MD:

Let's take a deeper look into the mechanisms underlying exactly how type 2 diabetes and even just elevation of blood sugar can be so harmful, particularly to the brain.

David Perlmutter, MD:

To understand why high blood sugar is so harmful to the brain there are two main concepts to grasp. The first is that chronically elevated blood sugar causes insulin resistance. The second is that it also causes inflammation.

David Perlmutter, MD:

So let's take a look at the role that insulin resistance plays in Alzheimer's.

Sarah Gottfried, MD:

The way I think about health is that it's a much more integrated concept. It's a state of emotional, physical, social wellness, which we can actually define. I would say blood sugar is one of the most important biomarkers of health. What I see in my patients is that they start to develop a problem with insulin signaling. And as insulin starts to get out of whack, their blood sugar rises. What's amazing is that so many people don't know that this is happening behind the scenes in their body. But it's one of the most important indicators of your longevity, your health span, the period of time where you feel like you're in your prime, where you're disease free, and it's also one of the most important indicators of your risk of Alzheimer's disease.

Sarah Gottfried, MD:

So we believe based on some cutting edge data, that probably 60% of cognitive decline is related to how you handle blood sugar. When you eat, your blood sugar goes up with certain foods more than others. Insulin is like an escort, which takes up blood sugar and puts it in three different places, inside your muscles, inside your liver, or inside your fat. So I think of insulin like a bodyguard. If you're a perfect hormonal specimen, if you're like Steph Curry or say Jennifer Aniston or someone who hasn't struggled with their weight or hasn't struggled with insulin being out of whack, then you do a really good job at this. In fact, you send most of the blood sugar that you have in your body after eating to your muscles.

Sarah Gottfried, MD:

What happens is, because of various reasons, sometimes the foods that you eat, such as eating too many refined carbohydrates, sometimes due to stress, sometimes because you took antibiotics and it made your microbiome get out of whack, insulin no longer serves in this really important function. It becomes an overwhelmed bodyguard. So that's also known as insulin resistance. That's where your cells become numb to insulin, and so it's much harder to get that blood sugar that's elevated in your blood after eating inside the cell. So insulin resistance is a state of inflammation, which is associated with many other conditions. Things like diabetes, metabolic syndrome, Alzheimer's disease.

Georgia Ede, MD:

Insulin resistance occurs not just in the body with diabetes but it also occurs on the outside of the brain, it's called the blood brain barrier and that blood brain barrier is a special lining that protects the brain and is very picky and it chooses what's going to get into the brain and what's not going to get into the brain. And if you have a healthy blood brain barrier, only the right things go in. But unfortunately, one of the things that needs to go in is insulin and if you eat too many of the wrong carbohydrates too often, you're going to damage those insulin receptors on the brain that escort insulin into the brain. And when those become damaged and fewer in number, it's harder and harder for insulin to get into the brain. The brain becomes insulin resistant and then the inside of the brain will become lower and lower in insulin.

Georgia Ede, MD:

A high carbohydrate, especially the wrong types of carbohydrates in the diet can damage the brain at any age, so we now see people with high insulin levels and insulin resistance even in childhood. This didn't use to be very common

but now unfortunately it is, so we have young children with obesity and type 2 diabetes and this is really very frightening. And as soon as you have insulin resistance and those things, type 2 diabetes and obesity, are both markers for insulin resistance, as soon as you have insulin resistance, you have insulin resistance at the blood brain barrier very likely already occurring. So it's really, really important to start as soon as you possibly can to change your diet.

Georgia Ede, MD:

Though the risk for Alzheimer's disease develops long before a person has type 2 diabetes. By the time you have type 2 diabetes, your blood sugar is completely out of control, your insulin is no longer able to keep your blood sugar in a normal range. So decades before that, often, what you'll see is insulin level is climbing, it's trying harder and harder to try to keep your blood sugar in a normal range and it's doing a pretty good job at first, and it's working harder and harder and the level's going up and up and you're eating more and more sugar, and it's like "Okay, we got this," and the insulin keeps climbing and climbing. And over a long period of time, at least a dozen years, the diabetes experts say, pretty soon that insulin can't keep your blood sugar in a normal range anymore and your blood sugar starts creeping up and up. That's way out here. So what you want to find out is whether you have insulin resistance back here, because the insulin resistance, not the diabetes, it's the insulin resistance, the high insulin levels that damage the brain.

Max Lugavere:

Today, we are just inundated with packaged processed foods that our bodies don't know what to do with. And it's driving insulin resistance, which is the cornerstone of type two diabetes. And we know that insulin resistance in the body is closely related to the metabolic health of the brain. Given the current state of the evidence, if you want to avoid Alzheimer's disease and possibly even other forms of dementia, then the best thing that you could do is don't become a type two diabetic. And if you are a type two diabetic, well, there are wonderful clinicians and people in the functional medicine space that can pave a road map for you towards getting out of those woods, because it's a condition that now people are talking about as being a reversible condition.

Max Lugavere:

You might have chronically elevated levels of insulin for a decade before you develop chronically elevated blood sugar. And chronically elevated insulin ... insulin is something that is not bad. It's an ancient hormone. It's one of the most conserved hormones throughout the animal kingdom. But it was really

something that our bodies would find elevated on a seasonal basis, or at the very least, on a cyclical basis around the day. Today, our levels of insulin are chronically elevated by the cheap refined carbohydrates that we are chronically eating throughout the day.

Max Lugavere:

So basically, the point is you do not need to be diagnosed as a type two diabetic to suffer the consequences wrought by chronic carbohydrate consumption and chronically elevated levels of insulin. I see in young people, there's this misconception that if you're thin, you are going to be metabolically healthy. We tend to think about metabolic obesity as being something that is exclusive to people who are actually obese on the outside that we can visibly observe. But that's not true. And this is actually a dangerous misconception because chronically elevated levels of insulin can proceed a diagnosis of type two diabetes by decade.

David Perlmutter, MD:

A lot of your work is focused on the importance of regulating blood sugar, keeping blood sugar in check and the role of insulin. How does that relate to Alzheimer's?

Mark Hyman, MD:

We know that if you have prediabetes, you get pre dementia or what we call mild cognitive impairment or MCI. We know that the mechanism in the brain that is driving some of the inflammation, it has to do with what we call insulin resistance, which is driven from eating too much sugar and starch. We know that sugar is highly inflammatory and that Alzheimer's is an inflammatory disease, so we have all these linkages that we put together that make it very clear that a diet high in starch and sugar is bad for you and the bigger your belly, the smaller your brain is actually what the science shows.

David Perlmutter, MD:

Now we'll take a look at the second mechanism through which elevated blood sugar damages the brain and that is inflammation.

David Perlmutter, MD:

How does having a higher blood sugar increase inflammation?

Mark Hyman, MD:

Well we know that having a higher blood sugar drives inflammation and it does it through a number of different mechanisms. One of them is essentially creating creme brulee in your brain, not the creamy stuff but the crusty stuff and it's where proteins and sugars interact to create damaging crust that literally clog up your brain. And they do this by activating receptors. We call it AGE or ages because of the age. And this is

because you have too much sugar and it combines with the proteins and at least this consequence of severe brain damage to this process called glycation, which is what you see with crème brulee or the crust on bread or crispy skin and our chicken. These are all proteins and sugars interacting to create damage.

Mark Hyman, MD:

So what's fascinating is that your hemoglobin, which is a protein, can also be affected by too much sugar and sugar combined with a hemoglobin to become glycated. We call that hemoglobin A1C and that is a marker of your risk of diabetes and of course even Alzheimer's.

David Perlmutter, MD:

You mentioned inflammation. Why is it so bad?

Mark Hyman, MD:

So inflammation is ravaging our health as a nation, as a global community. What it does is creates damage to proteins and to cells, creates free radicals, and what we call oxidation, everybody knows what that is. That's when your car rust or an apple turns brown if you leave it out too long or oil goes rancid, imagine that happening in your body. It's rancid fat in your blood. It's rancid fat in your brain. It's oxidized damage chemicals that cause huge havoc with every function of your body. It's the single final pathway for aging of all sorts, whether it's heart disease, cancer, diabetes, and it's really prevalent in brain disorders. So getting a hold of inflammation, getting a hold of oxidative stress, getting a hold of the free radicals is a critical step in creating a healthy human and a healthy brain.

Sarah Gottfried, MD:

Inflammation may be the most important concept for you to really grasp as you listen to us. Inflammation is this entire cascade that occurs in the body. It's quite complex, but it's the root cause of chronic disease.

Sarah Gottfried, MD:

Here's how I think about it. I think of inflammation like a fraternity party. Here's what I mean. So, when a fraternity party first begins, things are okay. People haven't had too much to drink. Maybe there's really good band, maybe there's some good dancing. So a normal amount of inflammation, when it was first initiated, is fine. But over a few hours as people drink more, as things get rowdier, problems occur. And so we know that there's a period of time with inflammation. There's this initiation phase, there's a resolution phase, which usually happens within a few days. If the resolution doesn't happen, if you're stuck in the middle, that's like a frat party in the body.

Sarah Gottfried, MD:

So by that, I mean, you have all of these inflammatory markers, you've got this problem with not resolving the inflammation, and it's the root cause of every chronic disease, including Alzheimer's.

David Ludwig, MD:

Inflammation is a biologically ancient pathway, which serves a critical protective function. If you cut your arm, or it gets infected, inflammation is the body's response to bring in immune cells to kill the invading bacteria, and to begin the process of wound healing. But inflammation in that setting is self-limited. It goes away as the body repairs its tissues. Another related problem is chronic inflammation, not acute, but chronic inflammation, and especially the kind that takes place within the body, in the lining of the blood vessels and the organs. This process is initiated, importantly, by aspects of our lifestyle, poor-quality diet, too much processed foods, other environmental insults, and when this type of inflammation sets in and becomes chronic, it begins to damage the body's internal organs, the lining of the blood vessels, and even the brain, setting the stage for type 2 diabetes, heart disease, and neurodegenerative diseases like Alzheimer's.

David Ludwig, MD:

Chronic inflammation in the body can start in a variety of ways, poor diet, lack of exercise, stress, and one of the key factors relating to chronic inflammation is insulin resistance, especially related to fat cells. When fat cells start growing, taking in extra calories, for a period of time, the body can handle it just fine, metabolically. But at some point, at a lighter weight for some people, heavier weight for others, fat cells begin to undergo a transition, and they go from a nice, calm metabolic state to inflamed. White cells rush in, the adipose tissue with this inflammation begins to spew out chemicals that spread inflammation throughout the body. When that inflammation goes to blood vessels, it can promote atherosclerosis. When it goes to the pancreas, it can affect the production of insulin, setting the stage for type 2 diabetes, and when it goes to the brain, it can set the stage for Alzheimer's and other neurodegenerative diseases.

Leo Galland, MD:

There are many ways in which elevated blood sugar is associated with inflammation.

Leo Galland, MD:

First of all, inflammation will elevate blood sugar but it's a vicious cycle because the high blood sugar causes damage to tissues, which then aggravates inflammation.

Georgia Ede, MD:

We need to worry about inflammation in the brain because inflammation is very damaging and almost every brain disease you can think of is driven at least in part and often mostly by inflammation. It doesn't mean that your brain is red or swollen or sore, it's inflammation on a microscopic level. So these unnatural food products, what they do is they cause the cells in the body to release lots of little SOS signals and distress signals and free radicals that are damaging, they're like little bulls in a China shop, and they run around bumping into cells and damaging DNA and damaging proteins and left to their own devices, they can actually kill cells from the inside out. So, if that keeps going and going, you can actually have shrinkage of parts of the brain.

Max Lugavere:

Inflammation both contributes to and is a result of insulin resistance in the body. So again, in terms of a diet that's going to mitigate your insulin resistance and inflammation, it's a chicken and egg scenario, but by eating the right foods, by focusing on fibrous veggies, nutrient dense whole foods, you're going to go a long way towards mitigating inflammation in the body, and thus helping your body better process glucose, which is going to promote insulin sensitivity, which is the inverse of type two diabetes, which is going to help minimize your risk for developing Alzheimer's disease.

David Perlmutter, MD:

With the combined effects of insulin resistance and inflammation, there is no doubt that stabilizing blood sugar is paramount when it comes to preventing Alzheimer's disease.

David Perlmutter, MD:

Are there other harmful effects of elevated blood sugar on the brain? You bet there are. Let's take a look.

Georgia Ede, MD:

So shrinkage can occur in the memory side of the brain actually earlier than shrinkage in most other parts of the brain. The memory center of the brain is called the hippocampus and the hippocampus is where memories are formed. The hippocampus is especially vulnerable to big spikes and peaks in blood sugar and it's really sensitive to the same types of forces that cause diabetes, so high blood sugar and high insulin levels. The reason for that is the hippocampus needs more insulin than most of the rest of the brain does. This is kind of counterintuitive, doesn't really sound true but it is, the more sugar you eat, and the higher your insulin levels, the less insulin gets into the brain and it starves the hippocampus of energy.



Lisa Mosconi, PhD:

There's some evidence that having a diagnosis of diabetes or insulin resistance increases risk for Alzheimer's and Diabetes accounts for 67% of all cases of Alzheimer's disease. In patients with diabetes and in Alzheimer's patients with diabetes, there's a commonality in that insulin resistance that then eventually leads to diabetes has a negative effect on the hippocampus, which is the memory center of the brain. So if you have insulin resistance for a long period of time, and you do not manage that, either by lifestyle modifications or medical interventions that eventually may affect your hippocampus, in that your hippocampus it will start aging faster. And we see that in brain scans in the form of shrinkage.

David Perlmutter, MD:

We've covered a lot so far about the damaging role that elevated blood sugar and inflammation play in terms of Alzheimer's disease.

David Perlmutter, MD:

As we move forward, keep these concepts in mind when we talk about how diet and other lifestyle choices relate to Alzheimer's risk.

David Perlmutter, MD:

As we described, high blood sugar and inflammation are without question, toxic to the brain. So let's now talk about practical steps we can take to prevent this process and instead take control over our blood sugar, insulin levels and thereby help to prevent type 2 diabetes.

David Perlmutter, MD:

You just mentioned that if we become a type 2 diabetic, we may have doubled our risk for this incurable disease, at least from a pharmaceutical perspective. How do we not become diabetic?

Dale Bredesen, MD:

As with all of these complex chronic illnesses, there is a set of things, but you can have a huge impact by reducing your intake of simple carbohydrates, by optimizing your microbiome, by making sure that you don't have a leaky gut. Of course, Virta has had very good results, as you know, with ketogenic diets.

Dale Bredesen, MD:

So ketogenic diets, and we recommend a plant-based ketogenic diet, not a bacon-based ketogenic diet. But having the ketogenic diet helps you to improve your insulin sensitivity. Literally, you're burning fats instead of, as you know better than anyone, you're burning fats now instead of burning the simple carbohydrates.

Georgia Ede, MD:

There are strategies to reduce insulin resistance that are very simple but they're not necessarily easy. They're simple because insulin resistance is primarily about eating processed foods, refined carbohydrates and vegetable oil. So, if you can eat whole foods, real food, meat, seafood, poultry, fruits, vegetables, eggs, foods that any kid would recognize, if you do that it would be very unlikely that you would develop insulin resistance. People who already insulin resistance may need to eat a low carbohydrate diet to really protect that delicate insulin signaling system and prevent insulin resistance from worsening.

Georgia Ede, MD:

So don't wait until your fasting blood sugar is high. By the time your fasting blood sugar is too high, you've already got diabetes and then you're way out here, in a really high risk for Alzheimer's and all kinds of other diseases, like heart disease. What you want is, you want to find out whether or not you have high insulin levels, and most doctors don't test for that.

Georgia Ede, MD:

There are simple things that people can do to find out whether or not they've insulin resistance. One of those simple things is to just look at how big they are around the middle, a lot of extra belly fat is often a sign of insulin resistance.

Georgia Ede, MD:

For people who are interested in lowering chronic inflammation, which is a really good goal to have because inflammation is a driving force behind most of the diseases we are afraid of getting. The number one thing is to avoid all of the processed foods, the refined carbohydrates and the seed oils.

Sarah Gottfried, MD:

There's a number of different ways to take care of your insulin-glucose relationship. One of the most important is exercise.

Sarah Gottfried, MD:

So the idea here is that there's an equation. So the food that you eat can raise your blood sugar. Stress can raise your blood sugar. And we know that exercise can help you manage your blood sugar. So what exercise does is it makes your muscles hungry for glucose. So I actually think that if we get back to the definition of health and wellness, it is absolutely essential that you're exercising regularly, that you've got a lot of physical movement, so that you're making your muscles hungry for glucose.

- Leo Galland, MD: The first step in avoiding the kind of chronic inflammation that is associated with weight gain, diabetes and Alzheimer's disease is to be physically active and to eat a really healthy, well-balanced diet.
- Valter Longo, PhD: Fasting we've actually shown in both the mice in a diabetes studies, and in humans in a clinical trial, fasting sensitizes the cells of the body to insulin so it's an insulin sensitizer.
- David Perlmutter, MD: Fasting is a promising tool that we have to fight insulin resistance. It helps our cells by restoring insulin sensitivity and making it easier for cells to use glucose as fuel. Because of these benefits, I recommend exploring fasting as a way to improve your blood sugar and insulin levels as well as optimizing your overall health.
- David Perlmutter, MD: But keep in mind, engaging in a fasting program should be done under the guidance of a healthcare practitioner.
- David Perlmutter, MD: We are so grateful to our guest experts for sharing their incredible knowledge with us regarding how diabetes relates to Alzheimer's disease.
- David Perlmutter, MD: To recap some of this key information, we see that when we eat a diet that's high in refined carbohydrates and sugar, insulin struggles to keep up and begins to have difficulty transporting sugar into our cells. This leads to higher levels of insulin and blood sugar in the body, creating a condition called insulin resistance. Over time, this progresses further and further until we develop full blown diabetes. type 2 diabetes is a powerful risk factor for inflammation and is very much linked to risk for Alzheimer's disease. It's incredibly important then that we prevent this insulin blood sugar issue as well as reduce inflammation by eating a diet that's lower in sugar and refined carbohydrates. This will help protect the health of our bodies and our brains.
- David Perlmutter, MD: Here are some practical ways to make these changes today:
- Dramatically reduce your intake of simple sugar and refined carbohydrates.
 - Optimize your microbiome. We'll learn more about this in episode seven.

- Consume a lower carb or ketogenic diet that is focused on ample amounts of plant foods and fiber.
- Exercise regularly.
- Consider fasting.
- Get good quality sleep.

These are simple but nonetheless powerful steps to help prevent you from developing type 2 diabetes and help improve and manage your blood sugar even if you already have type 2 diabetes. As you form new habits, you can then include more of these concepts over time and again there's no need to feel overwhelmed.

David Ludwig, MD:

The path to chronic disease starts depressingly early in life. There is evidence that even young children with obesity already have the beginnings of fatty plaques in their arteries, so it's never too young to start with a disease-preventing lifestyle. And at the same time, it's virtually never too late. The body has tremendous recuperative potential, if given a chance. It may take more work and more diligence once a disease has developed, but I've seen as a clinician advanced cases of type 2 diabetes go into remission with major lifestyle changes, sustainable changes. We need more research, but we're entering a very exciting era, where we will have new tools to prevent and treat chronic diseases without just relying on drugs and surgery.

Anna Cabeca, DO, FACOG:

I've seen the reversal of diabetes, the reversal of cognitive decline through making these changes, making these strategic changes such as the intermittent fasting, going keto green, and incorporating incredibly beneficial stress management techniques...

David Perlmutter, MD:

Whether or not you develop type 2 diabetes is largely up to you.

David Perlmutter, MD:

If you have type 2 diabetes, there are absolutely things you can do right now to improve your blood sugar and insulin and even potentially put your diabetes into remission. When we understand that this disease more than doubles your risk for developing Alzheimer's we see how critically important this idea really is. You can start implementing the changes we discussed in this episode right away, thereby improving the health of your brain and helping reduce your risk for Alzheimer's.

David Perlmutter, MD:

In this episode we learned about diet as it relates to blood sugar. In our next episode we're going to take a deeper dive into



the importance of our food choices showing you how to eat right for your brain. Diet may very well be the single most important factor when it comes to the health of our brains and preventing Alzheimer's disease.

David Perlmutter, MD:

I'll see you in our next episode, Eating to Prevent Alzheimer's.