



ALZHEIMER'S

THE SCIENCE OF PREVENTION

Episode 2: Untangling Alzheimer's



David Perlmutter, MD:

In episode one, we learned what Alzheimer's is. What is going on in the brain of an Alzheimer's patient, and the economic and emotional toll that the disease is taking on our society? In this episode, we will learn about the current standard of care for Alzheimer's, the changes in the brain that accompany the development of this disease, and why our medical establishment has struggled to develop meaningful treatments. We will then focus on the need to develop a comprehensive plan for Alzheimer's prevention.

I'm Dr. David Perlmutter, and this is Alzheimer's - The Science of Prevention.

David Perlmutter, MD:

Let's review the important risk factors for Alzheimer's and the tests that help determine your risk for this disease.

David Perlmutter, MD:

We will also find out how patients are diagnosed with Alzheimer's, review the standard of care and treatment options, cover the natural progression of Alzheimer's, and gain an understanding as to why mainstream medicine is reluctant to embrace the notion that Alzheimer's is by and large a preventable disease. When it comes to risk for Alzheimer's disease, there are several things to consider, and one of the main risk factors is diabetes. If you have Type II diabetes, your risk for developing Alzheimer's more than doubles.

David Perlmutter, MD:

Another important statistic is that women are more likely to get Alzheimer's in comparison to men by a ratio of two to one. We also know that being overweight significantly increases the risk for Alzheimer's as well.

Max Lugavere:

Everybody is at risk for Alzheimer's disease. If you make it to the age of 85 today, you have a 50% chance of being diagnosed with Alzheimer's disease. So if you want to know whether or not one day you will become demented, it's a coin toss. And to me, that's tragic and also infuriating because when you look at what's on the line, it's really our cognitive capital. It's who we are. There are certain genetic markers, alleles that put you at increased risk for developing Alzheimer's disease, about one in four people carry those genes. But you can develop Alzheimer's disease, whether or not you have that gene.

Lisa Mosconi, PhD:

Alzheimer's risk is higher for some people and lower for other people. The major risk factors for Alzheimer's are age. So anybody who's older than 65 is by default at higher risk of

Alzheimer's as compared to younger people. Female sex is the second most significant risk factor for Alzheimer's disease.

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.

Lisa Mosconi, PhD:

So for people who are overweight, but do not have diabetes, a potential mechanism that could trigger Alzheimer's is through inflammation. There are many studies showing a connection between low grade chronic inflammation, and an increased risk of Alzheimer's later on in life.

Max Lugavere:

We're all at risk. And aside from just Alzheimer's disease, age related cognitive decline is something that many people experience. And it's increasingly occurring at a younger age. About one in seven younger people today complain of memory problems.

Dale Bredeisen, MD:

There are a whole set of things, of course, that contribute to Alzheimer's disease, but high among those and high priority items include insulin resistance and obesity, and ultimately type 2 diabetes, and before that, pre-diabetes. These are all important risk factors for cognitive decline.

David Perlmutter, MD:

There's a notion that Alzheimer's is pretty much a consequence of aging, and yet we're seeing that rates of Alzheimer's are increasing much more rapidly than the aging of our population. What's going on?

Jeffrey Bland, PhD:

Yes. You know, it's been often asked what is the singular most significant risk factor to disease? And that's a complicated question, but it's pretty well now understood among all the students of this field, that the singular most important risk factor is age. Your age in birthdays. So then people say, "Well, hold on just a minute. Why is that? What's going on?" And when you start to dig deeper into that, what you find out is actually not your age in birthdays. It's what's called your biological age. And now we have metrics that can be used to measure biological age. And the most interesting metric to me. It's the measurement of the amount of damage that your immune system has undergone over the course of your process of living.

Ayesha Sherzai, MD:

Women are affected by Alzheimer's disease disproportionately than men. One in six women are at risk of developing



Alzheimer's disease during their lifetime as opposed to one in 11 men. Two-thirds of all Alzheimer's disease living right now are women. And as it happens, most caregivers, two-thirds of caregivers are women as well. So women are at the center of this disease. Now, there have been some hypotheses of how hormones actually play a role in the development of Alzheimer's disease and bringing health in general. Women actually metabolize lipids and fats in a different way compared to men. Glucose dysregulation affects women in a different way.

Ayesha Sherzai, MD:

The timing of menopause and when women actually start taking hormones is a big risk factor for Alzheimer's disease as well. Now there are some studies that look at factors around pregnancy for women that put them at a higher risk of developing dementia and Alzheimer's disease later on.

Dean Sherzai, MD, PhD:

When this disease starts affecting your family, it doesn't affect just the patient. It affects the family members that have to stay home. The family members that have to deal with their emotional and behavioral aspects of it. The pharmaceutical aspects of it. All these things start affecting the entire family and overwhelming them. And indirect evidence of that is that the caregiver, there's evidence that the caregivers die actually 60% faster than the patients. Just imagine the amount of stress that would lead to that. And other factor is that the partner of those who have dementia, I have a 600% increased risk of developing dementia as well. Obviously, that's not genetic. That has to do with shared risk factors.

David Perlmutter, MD:

Now there are several important laboratory tests that you can get to help determine your level of risk for Alzheimer's disease. Certainly, there are genetic tests, but I would indicate that genetic testing should always be done with the counsel of a healthcare provider. Other important tests include fasting blood sugar and fasting insulin level, as well. As we've mentioned earlier, inflammation plays a very important role in the genesis of Alzheimer's disease. C-reactive protein is a powerful marker of inflammation and should be included as one of the laboratory risk markers for Alzheimer's disease. These are important, because they give you behind-the-scenes information in terms of determining your risk from a genetic perspective, a metabolic perspective, and even a perspective that focuses on inflammation.



- David Perlmutter, MD: Beyond genetic testing, what other typically available laboratory studies might somebody wanna know about at their doctor's office that might be helpful in terms of information?
- Jeffrey Bland, PhD: Start looking at inflammatory markers, because we know there's a very significant connection between inflammation and neuronal death and conditions like Alzheimer's'. We would look at blood sugar relationships because we know that dysglycemia or high blood sugar, or elevated insulin levels are another marker for later stage, cellular apoptosis or damage.
- Jeffrey Bland, PhD: We might look at things that are related to various kinds of immune complexes and things that we can now measure, antibodies in the blood, that might relate to an autoimmune type of response where the body is responding to itself as a foreign invader. So those are kind of analytes or tests that one can have at a routine medical test, to put a portfolio together I think, as to how we as an individual, not our brothers or sisters or parents, but how we as an individual are responding to our environment, and on that we can use those as markers for tracking our performance going forward.
- David Perlmutter, MD: An Alzheimer's diagnosis is typically multi-faceted, and requires an experienced clinician to interpret a variety of data. These data include neuropsychological testing results, bloodwork, and even sophisticated brain imaging studies.
- Kirk Erickson, PhD: Alzheimer's disease is diagnosed typically through a team of professionals. It requires a fairly comprehensive neuropsychological assessment. A battery of cognitive, memory, executive function types of tests that get delivered, scored and assessed by professionals that are experienced in interpreting these data.
- Kirk Erickson, PhD: Then based on those scores and based on all the medical information, a diagnosis can be made.
- Lisa Mosconi, PhD: So Alzheimer's disease is usually diagnosed based on the presence of very specific clinical symptoms and cognitive symptoms as well. And first and foremost memory loss, I would say is to defining signature of Alzheimer's when people cannot remember names or lose their belongings, they forget keys. Forgetting keys is a big deal. What experts say is that if you just forget keys that could be aging but if you forget what keys are for, then we really have a problem. And that's a discord. A

strong distinction. Many patients report complaints not just the memory, but also attention in language. So an increasing difficulty in being able to carry out the conversation. Remembering words, remembering names, and also for women specifically, there's often a sense that you can't multitask. Women are usually pretty good at multitasking and so not being able to juggle as many things as they used to be able to is usually quite the red alert.

David Perlmutter, MD:

Once a diagnosis of Alzheimer's has been made, therapy usually begins immediately. Unfortunately, the current standard of care calls for intervention that may manage some symptoms but don't appear to be meaningful in terms of impacting the disease process itself. These drugs with names like Aricept and Namenda might decrease some symptoms, but they do not cure or even slow the disease progression. Some research has actually suggested that these drugs may make the disease worsen more quickly.

Amy Berger, MS, CNS:

The standard of care for Alzheimer's disease is that there is no standard of care. The standard of care for this illness is, "get your affairs in order, and good luck." It's really unconscionable and terrifying to receive an Alzheimer's diagnosis. There are some drugs on the market. There are some pharmaceutical drugs intended to address some of what's believed to be going wrong in the brain. Most of them are either completely ineffectual, or they, at best they can slow the progression. They can slow the decline, they can't stop it, they can't reverse it.

David Perlmutter, MD:

I'm sure there are people who would say, "Why should I pay attention to an Alzheimer's prevention program? After all, there are Alzheimer's drugs out there." What can you tell us about how effective those drugs are?

Dale Bredeesen, MD:

Of course, there have been a lot of study on Alzheimer's drugs, and in fact, some have been rejected even after looking very promising that actually made the disease worse instead of better. The effects of the current Alzheimer's drugs is minimal, and in fact recently, a publication has appeared that showed that people who were on these actually, over time, did worse than those who were not on them.

David Perlmutter, MD:

Do you mean the actual people using the so-called Alzheimer's drugs actually declined more aggressively than if they weren't taking the medication?

Dale Bredeesen, MD:

That's correct. The people who were on the drugs had worse outcomes. It was pointed out in the paper that that may not be related to the drugs. This may be something separate. It may be, for example, that the doctors recognized, for some reason, that that group was doing poorly, and therefore they started the drugs, and the other ones, they didn't start the drugs because they weren't doing as poorly.

Dale Bredeesen, MD:

It's not yet known, but it's a concern, and it's something we need to be aware of. The bottom line is, it's clear that these are not a significant improvement, and it's clear that they don't help you with the long term outcome, so you don't have a disease-modifying effect from these drugs. The best you do is a bump up, and then you go right back to declining again. This is one of the big differences. When you're actually getting at the root causes of the illness, in fact that's when you get a sustained improvement in cognition.

Dean Sherzai, MD, PhD:

So when Ayesha and I first met, and we were working at UCSD, patient, after patient, after patient would come in and get the diagnosis of Alzheimer's, and they would get some papers to be sent to a nursing home or to some information as far as the pathway that they're about to lead and what they're expected to see. And the medications that were given were simple things like Aricept and Exelon or Namenda, and they got a sense of hope, but not realizing that none of these medicines, or any of the pharmaceutical companies behind them ever make the claim that these drugs slow down the disease or abate the disease. None of them.

Dean Sherzai, MD, PhD:

They're just symptomatic drugs that lasts for a few years. But the curve of the disease continues. So it's almost like a ruse. We give false hope and in fact, the majority of patients aren't told of it by the fact that these drugs are not meant to slow the disease. Or if they're told, they're told in such soft manner that because they want to hope, that they assumed that it does that. It doesn't. None of the drugs we have does anything to slow the disease.

Max Lugavere:

We know when we look at research that polypharmacy and the overprescription of these drugs, especially in the elderly and the frail contributes to early mortality. So I think we really need to take a step back and ask ourselves really whether or not the drugs that we're doling out almost as if our healthcare system is this grand Pez dispenser for these drugs that really are not all



that efficacious, is in the true interest of the patient. It's sad that the language of medicine at this point has been co opted by Pharma. And I don't think that Pharma is all bad, no way. But it really has put a stranglehold on medicine and the way that we tend to view healthcare.

Lisa Mosconi, PhD:

The standard treatment for Alzheimer's is based on pharmaceuticals. So once a patient receives a diagnosis of Alzheimer's disease, then treatment usually involves Acetylcholinesterase inhibitor like Donepezil or Aricept or Memantine which is a glutamatergic drug.

Lisa Mosconi, PhD:

These drugs are called symptomatic drugs, because they relieve the symptoms of Alzheimer's for some time, but they are not a cure for Alzheimer's. They cannot stop disease progression. So they work for a certain number of years but then eventually do don't work anymore.

Lisa Mosconi, PhD:

Now they're called disease modifying drugs or vaccines for Alzheimer's disease that then I engineered to literally remove Alzheimer's plaques from the brain. And these drugs are successful in removing the plaques from their brains, but they do not reverse cognitive impairment or dementia.

David Perlmutter, MD:

Now, you may have heard of something called amyloid, a protein which is found at high levels in the brains of some people with Alzheimer's disease, and because of this connection, some have hypothesized that the amyloid may in fact cause Alzheimer's. This has led researchers to try to develop various types of treatment to either remove or stop the production of amyloid in the brain. Unfortunately, those therapies have been very disappointing. And it turns out that trying to fix Alzheimer's by targeting one specific problem may not be the best way to approach this complex disease.

David Perlmutter, MD:

Why has a pharmaceutical cure been so elusive?

Dale Bredesen, MD:

Yeah. We're asking one drug to patch 36 holes essentially. We always make the analogy that imagine that you have a roof with 36 holes. We use that number just because we initially identified 36 different members of the mechanism that leads, ultimately, to this imbalance that we call Alzheimer's Disease. If you try to patch 36 holes with one little patch, it's a great patch for one hole.

Dale Bredeesen, MD:

I think in the future, the drugs will be very important in combination with personalized programs. But the idea of taking one, and then trying to do all these different things, change your inflammatory status, change your insulin resistance, change your nutrient levels, change your hormonal levels, change your trophic levels, change your toxin and detoxification. These things are major systemic changes, and to do all of that with one drug, it really doesn't make sense.

David Perlmutter, MD:

With the understanding that available therapies are limited, we all need to take steps necessary to keep cognitive function intact.

David Perlmutter, MD:

Alzheimer's does not show up overnight. Rather, there is a slow progression from normal cognitive function to ultimately manifesting Alzheimer's disease. Typically, this begins with what's called "subjective cognitive impairment." That moves to mild cognitive impairment, or what we call MCI.

Lisa Mosconi, PhD:

So Alzheimer's disease doesn't just turn on in your brain. There's a slow progression phase that really goes from normal cognition to some subjective cognitive impairment. So people really becoming aware that there's been a cognitive change and for some people that leads to a diagnosis of mild cognitive impairment. Mild cognitive impairment is somewhat tricky diagnostic entity. It's somewhere in between normal aging and Alzheimer's disease or dementia. So it's basically it's a high risk condition for Alzheimer's disease, but it does not mean that a person with a diagnosis of MCI, mild cognitive impairment will necessarily decline further to an Alzheimer's diagnosis.

Max Lugavere:

Mild cognitive impairment, is a condition that's a prodrome of Alzheimer's disease. It's thought to be a form of pre dementia.

Max Lugavere:

And not all cases of mild cognitive impairment convert to Alzheimer's disease. So it's thought to be this really precious window of opportunity where we can intervene and determine whether or not that person ... maybe either delay or prevent that person from ever converting to more severe forms of cognitive impairment. Well, the neurology guidelines were just updated to include exercise as an intervention that could potentially improve cognition in those patients. And that's an incredible thing because there actually are no FDA approved pharmaceutical interventions to treat mild cognitive impairment.

David Perlmutter, MD:

Truth be known, there remains a great deal of reluctance in mainstream medicine to embrace the notion that Alzheimer's may well be preventable, and I think there are several reasons for this. One reason might be that you can't patent, sell, or write a prescription for the various lifestyle interventions that can play a role in Alzheimer's prevention. In addition, these ideas aren't taught in medical school, and therefore, they aren't widely understood by mainstream medicine, and this makes it harder for Alzheimer's prevention to be incorporated into the traditional healthcare system.

David Perlmutter, MD:

Why is mainstream medicine so darned reluctant to embrace the notion that, to a significant degree, Alzheimer's is preventable?

Dale Bredeesen, MD:

I think that's a very good question. Why has there been such resistance to this? When we're saying something that is deviating from what has been taught to us in medical school, that "Hey, we're going to go get a monotherapy, a single drug, and that's the way to go, and don't worry about all these other factors," it's hard to change the inertia that's there.

Dale Bredeesen, MD:

People want to adhere to these old ideals, these old ideas of, "Let's get a drug and that's the way we deal with every disease." With complex chronic illnesses, whether you're talking about Alzheimer's, whether you're talking about Parkinson's, whether you're talking about type 2 diabetes, they have multiple factors, and when that is taught in medical school, I think that we will make a major step forward.

Amy Berger, MS, CNS:

There's so much pushback against the mere notion that Alzheimer's can be prevented and I think it's because, and understandably so, it can be very difficult for a medical professional, for a neurologist to even entertain the possibility that something as complex and mysterious as Alzheimer's can be prevented. It's almost unbelievable that you can prevent it, but I think a growing body of research is showing that it probably is possible.

David Perlmutter, MD:

Why is there such a pushback from mainstream medicine to embrace what it is that you're talking about that Alzheimer's may in fact be somewhat preventable?



Mark Hyman, MD:

Well, I think it's changing. I think there's huge shifts in thinking that there are things we can do to prevent Alzheimer's in the mainstream literature like the FINGER trial which looked at exercise and diet and lifestyle issues, managing stress, sleep and cardio, metabolic risk factors led to an improvement in cognition in people who are declining and a stopping of Alzheimer's disease. This is radical so there is data that's showing this as possible though we still have the traditional healthcare system and traditional neurologist focused on the wrong end of the stick, which is trying to deal with the end result of all these insults in the brain, which is the plaques and the tangles that we know are involved with Alzheimer's, but they're driven from something else it's upstream. And I think that it is very hard for people to get out of that paradigm of looking for a single drug, for a single disease to treat a single target like amyloid.

Mark Hyman, MD:

And that has failed massively. We've spent \$2 billion over 400 studies. They've massively failed to show any benefit and many drug companies are now bailing on the agenda of trying to discover the cure for Alzheimer's.

David Perlmutter, MD:

Understanding that we really don't have any meaningful treatment options for Alzheimer's disease, makes prevention all the more important. Fortunately, as we will explore in this series, we do know how to help reduce our risk, and potentially prevent this disease in the first place.

Ayesha Sherzai, MD:

There's so many things that people can do to prevent Alzheimer's disease. We actually have an acronym, NEURO. Self-serving because I'm a neurologist. But NEURO stands for Nutrition, Exercise, Unwind or stress management. R is for restorative sleep, not just the type of sleep where you close your eyes and go to bed, but the type of sleep that allows you to go in each and every stage of sleep because they're very important for brain health. And O is for optimizing cognitive activity. And it's not one of them at one time, it's all of them comprehensively and in a very multifaceted way all the time and as early as possible.

Sarah Gottfried, MD:

Is it a pleiotropic approach, where it's not a pill for this particular ill, but rather an integrated approach that takes into consideration the food that you eat, the hormone imbalances, the exercise you're getting, the connections that you have, the meditation and other forms of stress resilience that you're

developing? So this integrated approach, I definitely believe can reduce the risk of Alzheimer's.

Mark Hyman, MD:

Number one, our diet is super inflammatory in America and the rest of the world, lack of exercise is inflammatory, stress is inflammatory, not sleeping is inflammatory. Being nutritionally deficient is inflammatory. Having toxins is inflammatory, having bad gut microbiome is inflammatory. These are all things that are modifiable risks. So we can change those things, which then will lead to reductions in inflammation and healing and repair of the brain.

Dean Sherzai, MD, PhD:

We have profound amount of information, not just a few papers. Thousands of papers over the last decades, that lifestyle, including nutrition and exercise by themselves, slow the disease down or actually stop you from ever getting the disease if started earlier by as much as 50% when it comes to nutrition, and 48% as it comes to exercise.

Max Lugavere:

We can really bolster, buttress these processes in our brain by eating the right foods, by exercising, by improving your sleep, by finding a way to cope with stress.

David Perlmutter, MD:

We are so grateful to our guest experts for sharing their incredible depth of knowledge about this devastating disease. In this episode, we learned that we cannot depend on pharmaceutical interventions to cure Alzheimer's or even meaningfully treat it. Prevention is the most prudent course of action. Now let's review three key points we've covered in this episode:

David Perlmutter, MD:

- Alzheimer's is an incredibly disabling and progressive disease for which we have no meaningful treatment whatsoever.
- The best research suggests that many of the risk factors for Alzheimer's are within our control.
- You could start making changes today to potentially reduce your risk of developing Alzheimer's disease.
- There are many practical ways to approach Alzheimer's prevention, and we'll be covering these tools we have in our Alzheimer's prevention toolkits in detail in further episodes. But some areas as straightforward as simply changing your diet, getting better sleep, and starting a stress reduction plan are

really important. And don't worry. We'll show you exactly how to make these changes as we move forward.

Max Lugavere:

All roads are pointing to prevention when it comes to Alzheimer's disease. Like many of the other chronic diseases that we're seeing burdening society today, these don't bubble up overnight. When you have a heart attack and show up at the emergency room, or a stroke, the conditions that fertilized that event didn't begin the night before you having that cardiovascular event. And so too with the brain. These are problems that take almost a lifetime worth of simmering before they emerge as cognitive problems.

Max Lugavere:

Healthcare is not something that you're going to receive at your pharmacy. It's something that you procure for yourself when you are pushing your shopping cart through the supermarket. That point in the day where you're able to summon your willpower to avert the aisles where all those packaged processed foods lie in wait and stay around the perimeter, that's really where you are procuring health care for you and for your loved ones. It's when you're deciding whether or not you're going to head to the gym. Anytime of day that you decided to make it to the gym, that's the right time. You don't even need to go to the gym. You can work out in your home with body weight exercises. That's to me, what health and wellness is about.

Sarah Gottfried, MD:

What we know when it comes to your sense of health and wellness, we know that 99% actually comes down to you. I want you to feel really empowered to step into the grace of really architecting the best health and wellness for yourself.

Ayesha Sherzai, MD:

One of the most impactful things that I've learned about prevention of Alzheimer's disease is that you can affect your brain, any moment, every single day of your life. Every decision you make in your waking hours and in your sleeping hours, affects your brain. Everything you do either makes your brain or breaks your brain. I think that's a very powerful message. I think it gives a lot of people hope too because all Alzheimer's is a synonym for a devastating condition. But when people know that their actions determine brain health, it's very empowering.

David Perlmutter, MD:

It's very clear that you're calling out this fallacy of wanting to off-load our medical and health decisions and outcomes to doctors.



Michael Merzenich, PhD:

I think that in an ideal world, the doctor would be continually monitoring what's happening in the brain health of every individual and there are instances in which they must intervene, ... but there's a tremendous amount of positive work that can be done by the average citizen working on their own, to their own advantage. And they shouldn't wait for the doctor to tell them. It's a sad thing but in the current state of things, lots of doctors will never tell them. So, you worry yourself about your brain health and get busy at keeping it in good stead. And by all means, try to engage your doctor as a source of advice to you but, meanwhile, take charge. You are that captain of that ship.

David Perlmutter, MD:

I hope that you feel excited to learn how to improve your brain health. It's never too late or too early to start caring for your brain. You have the power to take control of your health destiny.

In our next episode, we're going to take a closer look at some of the most effective tools to help prevent Alzheimer's disease. And I can't wait to share this information with you. I'll see you in our next episode, The Alzheimer's Prevention Toolkit.