

TRANSCRIPT

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WEBINAR
Weight, Metabolism, and Aging:
The Science Behind Fasting and Keto
featuring

John Newman, MD, PhD
Keto and Healthspan
expert

Satchin Panda, PhD
Circadian Rhythm and Aging
expert

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american federation
for aging research

Prevention

Sarah Smith(SS):

Hello, everyone. I'm so happy that you could all join us today for '*Weight, Metabolism, and Aging: The Science behind Fasting and Keto.*' This promises to be a compelling and constructive discussion. I am Sarah Smith, the Editor-in-Chief of Prevention, and I will be talking to our terrific experts today and taking your questions for them too, later. Before I introduce them, though, let me tell you how fascinating it is to dive into the science of aging here in our 'Live Better, Longer' series, put on by the American Federation for Aging Research along with Prevention. If you love knowing, not just for what people think is good for you, but why, we are here to explore those things. AFAR is a real leader in making sure there is science happening in our world. Science that is poised to change our lives. And Prevention, where I work, has been a wellness leader for decades, and we are very proud of our association with AFAR and our mutual commitment to bringing the latest research to all of you. So today, to talk about weight, metabolism, and aging, I am pleased to welcome Dr. John Newman, of the Buck Institute for Research on Aging, and the Division of Geriatrics at the University of California, San Francisco. And also Dr. Satchin Panda, of the Salk Institute for Biological Studies, and the author of "*The Circadian Code*". So, hello, doctors.

Dr. Satchin Panda (SP):

Hello. Glad to be here.

Dr. John Newman (JN):

Hi, Sarah. Happy to be here.

SS:

Great. Thank you both. You know I'd love to start by asking you both if you could tell us about your area of expertise, but also how you got interested in it. Why do you think it's so fascinating. Dr. Newman, could you start us off?

JN:

Sure. So I'm a geriatrician, and I'm a basic scientist who studies the mechanisms of aging. And that's how I got into ketone bodies. The audience, the folks of you listening, who are interested in AFAR, probably feel the same way I do. I still have this child-like enthusiasm of, 'Wow, we can actually understand the biological mechanisms of aging, at like a cellular-molecular level.' Understand them and even manipulate them. And I still feel that sense of wonder. The geriatrician in me is really excited about using this understanding, the mechanisms of why we age, to understand the complex problems of older adults. And that's what I focus on in my basic science and my clinical translational science. Where ketones fit in is, as many of the audience know, there are really tight links between metabolism and aging. And we can talk a little bit about the history of that, but one of those links is that many of the molecular mechanisms that we study that affect what we see as aging are controlled by metabolism. And one of those links that links metabolism to aging, we think, are ketone bodies, and we'll talk a lot more about that.

SS:

We will. Thank you. Thank you for giving us that great intro-overview. Dr. Panda, how about you? Can you tell us about your area and what's so interesting about it?

SP:

I work on circadian rhythms and when people hear the words 'Circadian Rhythms' they usually think about sleep and wakefulness, where every day or the night, our brain has to get into sleep. Seven to eight hours of sleep to repair, reset and rejuvenate. And that's great for the mental health. But the same time, over the last 20 years, my research also revealed that almost every organ in our body, just like our brain, has its circadian clock. And the function of the clock is to make sure that every cell is healthy and is repaired, and is rejuvenated almost on a daily basis. At the same time, we also made a discovery that just like our brain needs sleep and wakefulness for a robust circadian clock, a healthy clock, the rest of our body needs daily eating and fasting to take care of the clocks in all of our organs. Whether it's heart, gut, liver, muscle, you name it. So, then we got interested in this concept called time restriction, which is now popular in intermittent fasting. What we find is if people and animals eat consistently every day between eight to ten, or maximum 12 hours, that helps the entire body to reset, rejuvenate, and repair itself on a daily basis so that we can age slower, and we can prevent, reverse, manage, wide range of diseases and conditions, starting from overweight obesity, diabetes, high blood pressure, high cholesterol, and even cancer and dementia. So, this is a very rapidly growing of research and I am super excited to see that one simple daily habit that anyone, anywhere in the world can do can have such a multi-solving benefit on entire health.

SS:

Thank you so much. Well, I'm really looking forward to diving into both of these areas, but even before we do that, I thought it might be helpful if we address, even just a little bit, the issue that might have brought a lot of people here in the first place today. Which is why is weight loss harder as we age, and why is it worth thinking about beyond the 'Eat less, Exercise more' advice, you know, that people throw around all the time.

SP:

Yes, so John you want to go first?

JN:

Sure. I guess first, just to acknowledge, Yeah it is harder to maintain your weight as we get older, I am certainly in that group already. And there's a lot of reasons for that. As Satchin will dive into too. You know, as we get older, what we eat may change, but also how we live changes. And our bodies are changing, underneath all of that. So we tend to get less active, we tend to move around less, but also as we age our body's metabolism, and this is sort of a cliché but I think we understand it more and more at a deeper level now, our body's metabolism does change. How we use energy changes, we need less energy in part because of the same, our bodies are using less energy to do the repair and rejuvenation processes that we all have, and so it gets harder to maintain our weight. Or maybe another way of turning that around is we have to constantly adjust how we live in order to maintain our weight, in order to fit our body's needs. But changes in metabolism are about more than weight too. And this will tie back to why am I studying ketone bodies for problems of aging and of older adults. Many of the most important problems that older adults face, and dementia certainly is a big one, but other problems of the aging brain too, like delirium, which I spend a lot of time studying. Part of why they happen to older adults are because of these changes in metabolism, because the body has a harder time ramping up its energy production when it needs to. When you're sick, when your brain needs more energy to cope with unfolded proteins in Alzheimer's disease or whatnot. So, on the one hand, one way that many people experience this is trouble maintaining weight, but there is another angle to that, that these metabolic changes it's so important to understand them because they also affect these diseases of aging that we're trying to figure out how to prevent and how to treat better.

SP:

Yes, John, thank you for giving that primer on with aging the metabolism changes. This is a very new and exciting area. And I must remind all the audience that if you dial back to 1910 or 1920 the life expectancy in this country was only 45 to 50 years at best. So that means only in the last 50 years, the vast majority of us can live beyond the years of 40, 45, for at least three, four decades. And this also gives us a chance and challenge for the scientific community because for the first time in human history we are living a greater number of years in the post-reproductive phase. So, for women it's post-menopausal years, and for men you can say lower testosterone, that kind of phase. So we are still learning... But from the circadian point of view what we also know is as we age, our sleep becomes very fragmented, we wake up too many times, we don't get a good night of sleep, and when we don't get enough sleep our brain cannot decide, makes not good decisions. And in a given day we make nearly more than 200 decisions about what to eat, how much to eat, when to eat, what combination to eat. So we tend to overeat because I our brain is sleep deprived and cannot decide. So that's the biological

aspect of what happens from circadian point of view. Then there are practical considerations. And I will allude to two different things. One is, during our lifetimes we also accumulate a lot of damages, for example, almost anyone, most of you who are above the years of 50 may experience some pain in joints and muscles. So that reduces our mobility, so it's really hard for a 50 or 60 year old to complete a five mile run every other day. Whereas a 20, 25 year old can actually do that. So there is a biomechanical aspect to aging that reduces our mobility so we cannot move more to lose weight. And since we are a bit sleep deprived and we cannot think clearly about what we eat, how much to eat, even though we know that our metabolism has reduced, we cannot adjust. The third thing is, a lot of us, nearly one third to one half of us, are taking some kind of medication to control blood pressure, blood sugar, many other aspects of life, and what we are learning is many of these medications also have adverse side effects. And one of the side effects can be weight gain or food retention. So it becomes even much harder for people who are on some of these medications to try to lose weight. So these are some of the practical aspects of why it becomes difficult to lose weight. But the good news is there's some control, we can change, we can make small changes in our behavior and that will help us to lose some weight. Second is, even if we don't lose weight, we can actually become healthier with no or even little work.

SS:

I love to hear that there's some small things, and practical things that you think will work for people. Can you tell us more about your work around time-restricted eating vs. intermittent fasting. I've heard them used interchangeably. Are they? Is there a difference and, if there is, why is it important for us to know?

SP:

So intermittent fasting is a very broad term. It includes any type of fasting, ranging from fasting for one day in a week, to two days in a week, to even five days in every month or five days in every three months. It's called pre-week fasting, alternate-day fasting. And so all of these concepts were there before we encouraged the term 'time-restricted eating.' The way that time restricted eating research is done, at least in basic science, is slightly different because all the other forms of fasting, their origin lies in calorie restriction or the concept that if you reduce calories for one or several days then you can get some health benefits. In time-restricted eating, in animal experiments, we do not reduce any calories on any of the days. The animals can eat the same number of calories as the animals that have access to food 24/7. The only thing is that they have to eat those calories between eight to ten, or maximum 12 hours every day. By doing that, what we find in basic science and laboratory research is we can prevent, reverse, or manage their chronic conditions and body weight. In a way, if you're thinking of cars, the term "car" covers everything from pickup van to electric car to plugin-hybrid. Similarly you can think of intermittent fasting as a broad term and time restricted eating is just one form of that intermittent fasting. The only difference is you have to do it every day, or at least five to six days in a week, and you have to be consistent with sticking to the same eating window so that your circadian rhythm, just like you have to sleep every day around the same time to have a good night's sleep, unrestricted sleep, similarly, from circadian point of view, you have to eat within eight to 10 or maximum 12 hours to maintain healthy circadian rhythm throughout your body so that it pays back to you in terms of good health and maybe modest weight loss.

SS:

Thank you, that really helps clarify what we are talking about and why it's so important. I'm sure we'll talk more about that commitment in a moment, but while we're sort of clarifying things for people, Dr. Newman, what do you think people might not know about ketones or the ketone diet? Misconceptions or information that you think is worth people really understanding as we continue on talking?

JN:

I think one of the most important things is that ketone bodies are a normal part of our body, and they are there all the time too. So what are ketone bodies? Briefly, I know that most people in the audience are probably experts and would be ready for a Master's class, but for the rest of us, ketone bodies are one of the ways that your body metabolizes fats for fuel. They're little molecules. Your liver makes them. They're sort of like batteries, right? They're a way of converting energy from one form into another so your body can use it. When your body needs to burn fat, that will go to your liver, your liver turns it into ketone bodies, and then the ketone bodies then go to your heart, your muscles, your brain, and your cells use them to produce energy and do whatever your cells need to do. And they do that all the time. Now, normally, we're not making a lot of ketone bodies because we're eating. Satchin has done some incredible research about how modern life, most of us are eating from the moment we open our eyes to the moment we close them at night, and we don't make a lot of ketone bodies when we're eating. When we're fasting, then we start to make a lot more because we're burning our fat. But we do still do it all the time and one of the interesting things that we're learning is that ketone bodies are obviously really important in fasting, and there's something that kind of links the idea of ketogenic diet and intermittent fasting, but they're important all the time for our bodies too. They have important functions in just helping our bodies to get through day-to-day life. Some really interesting work on this was done by Omer Yilmaz at MIT showing how ketone bodies that are made in the intestine, not even in the liver, but just made in the intestine all the time, help to keep stem cells in the intestines working normal. So that's something that I think most people don't know. That ketone bodies are part of normal life and they are important for our bodies normally, especially as we age, and we're learning more and more about them.

SS:

When people become so much more interested in ketones because of the popular keto diet, what's happening in that scenario?

JN:

Where does the keto diet fit in now?

SS:

Yeah, exactly.

JN:

So, the ketogenic diet is a way of sort of tricking your body to make more ketone bodies. Ordinarily, we'll make a lot of ketone bodies when we're fasting, when there's no food around at all. But if you're mostly eating fats, and not eating carbohydrates, not eating sugar or other carbohydrates, your body is relying on fat for fuel and it will turn a lot of those fats into ketone bodies in order to use them. So a ketogenic diet is a way for your body to make a lot ketone bodies without actually fasting. You know,

while eating and while still having lots of energy around, but you're making ketone bodies. It's sort of a way to simulate part of the fasting metabolism. And that's an important point that ties together a lot of what we're talking about today. It still blows my mind what Satchin was saying about what we've learned about fasting and dietary restrictions in the lab is that you can actually eat the same calories, and the science from this is now really, really rigorous, these animals in the lab can eat the same number of calories but if they have a fasting period they do better. They control their weight better, and they're healthier and they live longer. So it's not just about the calories it's actually changing the way your body works. And a big part of that is switching your body into a fasting-like metabolism where you don't have a lot of sugar around instead, you're burning fats. Part of that may be having ketone bodies around.

SS:

Interesting. So, Dr. Panda, I also wanted to bring up this issue of the calories maybe the same, but I think there are some self-styled, you know, 'experts', who might say, "Well, you can eat anything you want, just only eat for six hours or eight hours a day." What do you say to that? What are we talking about in your world, in terms of what you're eating in that time frame?

SP:

So, I want to connect with what John said about ketones because those are really very important points. It's better to dive a little deep into it then we'll come back to your question. And when we think about, say eating, one thing is we use the word 'time-restricted eating' not 'fasting' because a lot of people, yes, there are some people who like the word 'fasting' but then when we do clinical research, we bring people into the clinic and ask, "Can you do fasting?" they would say "No". But if we say, "You can eat whatever you are eating now within eight to 10 hours, can you do it?" Then they would say "Yes, we can do it!" So, it's a semantic point, but it changes how we think.

Coming back to what happens during this eating and fasting cycle. Basic science in endocrinology for the last 50 years has taught us very, very solid science that when we eat something, and in real life situations when we eat something, most of the stuff has some carbohydrate, fat, and protein. But in response to that food, your body is making insulin, and that insulin will store some carbohydrate as fat, it will also store some fat and then use some carbohydrate or glucose as insulin. After our last meal of the day, as we're going to bed, overnight fasting, maybe after six to eight or maybe 10 hours of fasting, then our body will slowly use up most of the glycogen or carbohydrate storage, and then it may begin to break down some fat to make ketone bodies. So, if you're doing an overnight fast, I'd say 16 hours and eating only for eight hours, then the last three to four hours of that fasting your body is already making a good amount of ketones to keep your heart and brain and muscles working.

So now coming back to your question, whether people can eat anything. And now, if we connect these two, then you'd suspect that if I eat too much carbohydrate then maybe my body will take a long time to get rid of or use up all the carbohydrates and then switch on to keto. So that makes sense because if you are storing a lot of carbohydrates, you are beginning with a lot of carbohydrates, then it will take long time, you might not get the benefit of that ketogenesis that happens towards the end, the last two to three hours. So that's why the first step, maybe many self-styled gurus and guys who are coaching you to say that you can eat anything, this is the hook so that you can get in and you can start practicing. And in real life, what we find is once you start practicing, then automatically you may reduce your after-dinner snacks and after-dinner alcohol, and a lot of that is carbohydrates where you are automatically reducing some carbohydrate. And second thing is, carbohydrate, particularly highly processed food and highly-processed carbohydrates, they create an insulin spike and then you have a glucose dip, so you're likely

to feel very hungry after a few hours. So, in real life, it would be very hard if you just eat highly processed food, for example Basmati rice, or something that has a lot of carbohydrates well-processed. It would be really hard to practice intermittent fasting or time-restricted eating, because your hunger drive would be so strong that it would be hard. In laboratory experiments, we do the experiment because we take away all the food from mice so they have no way to go and reach out, but in real life, for humans, we will always find food. It's within five feet. Now, if you're sitting there, just look around in the same room, there's some food. So that's why it's important to make small changes to what you eat. What you can begin with, whatever you're eating, and you'll slowly notice the changes, and then, once you have one discipline of stopping eating at certain time, you can pick up another discipline of reducing your carbohydrate diet intake so that you can get the natural benefit of producing more ketone. And to add to that, just like John said, if we increase your fat, good fat intake, then that again doubles your benefit. So you combine time-restricted eating with low-carbohydrate diet, or the ketogenic diet, then you can reap even more benefit.

SS:

Dr. Newman, could you speak to the issue of the consistency here? Dr. Panda talks about sticking with it in the circadian rhythm aspect of the time-restricted eating, but does that play into how we develop the ketone bodies as well? Is it something that you could do for two days in a week and then stop?

JN:

I can tell you a little bit about how consistency would work with ketone bodies. Of course, I don't use ketogenic diets in my clinical practice, so this is not something that I do as a doctor. But it's an interesting question because a lot of people will ask. So if we think that having ketone bodies around sometimes is good for you, and we can talk more about the science of that, well does that mean you have to be on some regimen for your entire life? And the science so far says maybe, maybe not. For example, I studied ketone bodies in a laboratory and one of the first questions we wanted to answer when we first kind of had this connection between aging, fasting, metabolism and ketone bodies, is would mice that ate a ketogenic diet be healthier as they got older, or live longer? So, we did that experiment a couple of years ago now, and the mice that were eating a ketogenic diet did actually live longer. Another group did it with us, or did a similar experiment at the same time. We did them slightly differently but one of the key ways that we did it differently is that they fed the mice a ketogenic diet all the time, and they lived longer, and their brains were healthier when they were older. We actually only fed them a ketogenic diet some of the time, about half the time, every other week. And this was not really on purpose, this was kind of experimental necessity so that they didn't gain weight. Mice, unlike humans, gain weight on a ketogenic diet. But they weren't eating all the time and yet they still were healthier, they still lived longer, and they still had healthier brains later on. And the really interesting thing we found was that they actually had healthier brains and their memories worked better, even when they even weren't eating the ketogenic diet later on. So, I think there's some hope that ketone bodies, at least the biology that's kind of encapsulated by ketone bodies, might be something that sticks around, might be something that we could work out how to do intermittently, or when needed, and may not necessarily be something that people need to do for the rest of their... all or nothing, for the rest of my life or never. When it comes to ketogenic diet, I can tell you that it is hard to do for just a couple of days, because your body needs to adapt to it, needs to adapt to using all that fat, to making ketone bodies. And that happens over a period of a week or two, or even a little bit longer. So what I've heard from my colleagues is ketogenic diets are easier to do the longer you do it, but the first week, everyone says is the hardest. And this is one reason, as we are starting to think about clinical applications of

ketone bodies and ketogenic diets, to think about how to break it down a little bit. For example, can we give ketone bodies directly, essentially as a drug. So not as part of a ketogenic diet. And that's something that a lot of scientists are interested in, in part for that question.

SS:

Oh, that's so great. You know, I'm really glad you brought up about the brain and the other long term health impacts, because I'm hoping, Dr. Panda, you can speak to that too because it seems to me that, well, many of us want to lose weight and we want to do it in a healthy way, it's so interconnected with overall health. And so, could you speak to time-restricted eating in that sense of how it's affecting our overall health? I think there's some blood pressure, some heart issues, I'm sure you could tell us.

SP:

Yeah. I'll just continue where John left of. Again, you have to do all seven days. What we're seeing is, both in mice and humans, people who can do time-restricting for 10 hours for five days, they're still seeing lot of benefits. So now, going back to humans, although we could not ask mice how they felt, what they feel like when they do time-restricted eating, we're pleasantly surprised when human studies started because in our first study, we asked our participants to do time-restricted eating for 10 hours only for sixteen weeks. Then they lost modest amount of body weight and they came back after one year. So, between 16 weeks and one year there was not contact with them. And they were still doing it. And we asked, "Why are you still doing it?" It was not the weight loss that was driving it. What was surprising was they said they slept much better. And they felt more energetic throughout the day, particularly more energy in the morning, and they felt less hungry at bedtime. So this was kind of our window into looking more deeply and almost all of them who had acid reflux, they also said that their acid reflux got better. So a lot of them got off their acid reflux heartburn medication. So then, in the subsequent stories, what we are finding is almost all times we take studies of this so far, they report much better blood pressure control, whether people are already taking blood pressure medication or not. So that's a great news because nearly one in two adult Americans do have either pre-hypertension or hypertension. And if this habit can reduce blood pressure that's good. And what is more interesting is the reduction in blood pressure did not correlate with the reduction in weight. So that means even people who did not lose weight, just by doing time-restricted eating with their usual diet, they didn't have to change, we didn't ask them to change that, they could still see improvements in both systolic and diastolic blood pressure. Then the third thing that we find is a lot of people who do time restricted eating for several weeks, maybe a few months, they report their back pain and some of their joint pain slightly goes down. That might be due to reduction in systolic inflammation, that's what we're finding in mouse study and now human studies. Then, we also find that people who are pre-diabetic, or are listed as diabetic taking Metformin, and if we combine pre-diabetes and are listed as diabetes, Type 2 diabetes, they are nearly 95 million people, adults in this country, nearly two out of five adults are pre-diabetic or diabetic, they can also control their blood glucose much better. So in that way, this sounds like a multi-solving habit, but at the same time, you might think, "So how can one simple habit change so many things?" But at the same time, just try. If you sleep deprive yourself for five days, almost all of your conditions will worsen. So, similarly if you fix your body circadian rhythm, by the time you're sleeping then we can expect to improve on most of our health conditions. At the same time, I must emphasize there are a lot of studies going on right now to see how many weeks of time-restricting we have to do before you see benefits on blood pressure, versus arrhythmia in heart, versus type two diabetes or GI reflux et cetera. But stay tuned. And this is something that your body is designed to do and we can do.

SS:

That's great to hear. And I'm interested... Yeah, go ahead, Dr. Newman, go ahead before I ask.

JN:

As Satchin said, how could something so simple do so much, I think is a great lead-in to one other thing that people might not know about ketone bodies but which aren't just about ketone bodies and helps to kind of understand the science of all of this. And that is that we talk about how ketone bodies are like batteries, they carry energy from one place to another and they burn through fuel, but that's not all they do. Ketone bodies, and this is really where my lab focus is, ketone bodies have a whole secret life, of other things that they do, that are kind of like drugs. They're molecules that they bind to stuff, they bind to other proteins, they bind to receptors, they turn things on, they turn things off. They even bind to the proteins around which your DNA is wrapped inside yourself. So, they work almost like drugs to affect the way your cells function. To control how your genes are expressed, to control inflammation, to control other aspects of metabolites in your cells. And we're kind of just scratching the surface of what this all means in the big picture. You know how these molecular actions relate to big picture things like brain health or weight loss. But it's clear that this is probably part of the answer to the question of how simple changes can affect so many things. But it's not just ketone bodies, that's the other key thing. We've learned so much about ketone bodies because they're cool, okay? Because they're really interesting, so we've been studying them a lot. But I think that most of what we're learning about how interesting ketone bodies are actually applies to lots of other similar metabolic molecules. And just imagine, if your time-restricted feeding, if you're intermittent fasting, you're changing your body's metabolic state quite a bit from time to time. All of these different metabolites you're changing in your body, and some are going up and some are going down, and they all have all these different things that they do in your cells, affecting your gene expression, binding to things, activating things, and that complexity, I think, is just a symphony of metabolism, helps to explain why things that sound so simple, like fasting, can have such broad biological effects.

SS:

That's fascinating and what I am hearing is that we have a lot of control over our destiny here. You even mentioned, DNA, these things we're talking about are a way we can really take control of our health, which I think is a really great important message. And we're starting to get a lot of questions about, "Actually tell me more about taking control of my health." But before I go to them I want to ask you both one last question that you sort of alluded to both of you is, what else are you excited about that's coming ahead? What else are we learning in these fields that you think people might be interested in hearing about what's coming next. Dr. Panda, maybe, first?

SP:

Yeah, so we are very excited about these two things. One is what kind of conditions people have and how they can do time restricted eating and what benefits it will give them. And second is, another aspect of circadian rhythm, we're finding that almost all of us are taking some medication or supplements and new research is showing that what time you take that medication, whether it's morning or in the evening or bedtime, can completely change how much benefit you get out of this medication. Some might have adverse side effects and by changing the timing you can reduce adverse side effects. You may be taking your medication without seeing a significant drop in your blood pressure and by changing the timing you can see, so that's very exciting. One thing, back to the question, and I never

explained this, what is time-restricted eating, how to do it. Very simple thing, you can self-select a 10 hour window within which you can eat everything, drink everything, except water within a day, and try to stick to it for at least five to six days in a week. For example, if your first bite, or first sip of anything that has calories starts at 7 o'clock in the morning, try to finish all of your eating by five o'clock in the afternoon. And you can go up to 10 hours or 12 hours but never beyond 12 hours. I just wanted to dive in.

SS:

Thank you for clarifying that. Thank you. And Dr. Newman, are there areas of research you're excited that are coming?

JN:

I'm going to come back to the link between metabolism and aging. And something that we're working on now, which I am really excited about is understanding exactly how the ketone machinery in your body changes as you age. And what role that has in making an older brain, for example, susceptible to things like dementia and Alzheimer's disease or delirium. And as we understand that, the hope is that we can turn that into interventions and treatments. For example, delirium, which might be the worst medical thing that most of the audience has never heard of, is a severe, acute, sudden confused state that'll happen to people when they're really sick in the hospital, or especially around a surgery. And part of that involves your brain not being able to ramp up its energy production in response to that stress. So, if we can understand how ketone bodies play a role in helping make some people more resilient to this than others, or helping your brain to cope with that kind of acute need for energy, then that's a whole new pathway of creating therapies for these really serious but very difficult-to-treat conditions of aging. I'm really excited about that.

SS:

Wow, that is fascinating. All right, I'm going to dive into some of the questions that we're getting. Speaking of different ages, are there considerations of time-restricted eating at different ages? For example, is it appropriate for someone in their 80 to do it? Are they going to get the same benefits as someone younger? And this is a question I was wondering too, is it ever too late, does it work at all ages?

SP:

So, I think we're designed to eat, anyone from 10 years old to 100 years old, they can eat everything in a day (except water) within 12 hours. So almost everybody can do. And if you want to get some health benefits maybe you can try to shrink that to 10 hours. Particularly, if you are pre-diabetic or diabetic or Type 1 Diabetic, you are at the risk of hypoglycemia. And if you are taking certain kinds of medications, particularly with Type 2 Diabetes, diabetics who take certain medications, or if you're on insulin then you should consult with your doctor before you do this because in many stories, what we're finding, is you may have to change your medication or reduce your dosage, which is a good thing, to combine it with time-restricted eating. And then if you're pregnant and, of course, you have to talk to your doctor. I cannot say whether a pregnant woman should do it or not because there is not much research in this area. The only thing is I hear once in a while some pregnant person would come and say, "I've been doing it for 12 hours, what's your advice?" And I would say, "Just talk to your doctor." So that's my take-home message. And to make it much easier, if you are thinking about your dental health, anyone from

three years old to 110 years old , if you have teeth than you should brush your teeth every day. So 12 hours of time-restricted eating is just like taking care of your teeth. And if you want to get better benefit, maybe you'll floss, so that's 10 hours of eating. And if you want to go to the dentist and get it cleaned, then maybe you can try eight hours or once in a while, as John mentioned, maybe ketogenic diet once in a while, or reduce your carbohydrates significantly for a month or a few weeks. And that's like going to dentist.

SS:

That was a great analogy. The dentist. We have a number of questions Dr. Panda, about the amount of time. Is there an ideal or best practices on eight, 10, 12 hours that you're choosing to eat.

SP:

Yeah, so what we find is in most clinical studies, if we ask people to eat within an eight hours and fast for 16 hours, they can do it for three to four days and then for other days they go towards 10 hours of eating and 14 hours of fasting. And all of these clinical studies are giving some benefit. What is more important is just think about your lifestyle and see what time you can do. For example some questions are can I do from 8 a.m. to 6 p.m. versus noon till 10 p.m.? The bottom line is whatever window you can do it's better to do that. Instead of eating at a random time. There's some research showing that, all the time that you're eating, if you start say before 10 or 11 o' clock, your first bite of calorie, and then finish early then it might work better than late time that you're eating. There's some biological significance and habit that plat into it. One is, your ideal circadian day should look like you should go to bed sometime in the evening or night, whatever time you go to bed, try to be in bed for eight hours, so that you can get at least seven hours of sleep, which is healthy by most sleep specialists. After waking up, do not eat for 1-2 hours at least because that's when your night hormones are going down and your day hormones are coming up and they don't have good effects on your metabolism when these hormones are changing their guards. And then after your first bite, try to eat everything within the next 10 hours, most people with families or with jobs can manage to do it. And once in a while, if you cannot do it, try to do it for 12 hours. And make sure that your last calorie is 2-3 hours before you go to bed. Because in that way you can get good night of sleep. So now keeping this in mind, eight hours in bed, don't take for 1-2 hours at least in the morning, eat for 10 hours, and your last meal should be 2-3 hours before bedtime. Then you can come up with a window that works for you. Second thing is if you start late, say noon, and you are trying to eat till 10 o' clock, most of our bad habits actually happen in the evening, at night, because that's when we socialize, our guards go down, and then we can drink more alcohol, or may indulge in many unhealthy desserts and other food. So from a practical point of view, if you're very disciplined then it's okay, but if you're not that disciplined then pay attention to reducing your alcohol and reducing your dessert. Because there is no research that says alcohol at any time or too much sugar at any time is good for you. And by doing an early time with your eating you can automatically control your alcohol and dessert.

SS:

That's a good point. Dr. Newman, there's a questions about the fats that people would eat on the ketogenic diet. Is there a downside to this? Does it affect cholesterol? Is that something you can speak to?

JN:

Well, let's talk a little bit about what a ketogenic diet means. I'll say as preamble, I am a doctor but I am not your doctor. And I practice hospital-based geriatrics so I don't use ketogenic diets in a long term nutritional practice. But I could fill you guys in on what I know, a ketogenic diet means eating a small enough amount of carbohydrate so that your body will start making ketone bodies. You have to eat something, so what do you eat? You mostly eat fats and a normal amount of protein. And all the nutritionists that I have heard talk about a well-formulated ketogenic diet emphasize a couple of things. You should eat a normal amount of protein and not overdo it. That actually is really important. Because you can hurt yourself by eating too much protein. If you eat nothing but steaks and bacon and eggs. So normal amount of protein.

JN:

And the fats should mostly be health fats. And we have learnt that there is a difference between less healthy fats and more healthy fats. For example, a Mediterranean style diet that's been shown in clinical trials to help keep your brain healthy, involves healthy fats. Things like fats from fishes, avocados, olive oil, things like that. And that should be the core of a well formulated ketogenic diet. And in fact most of the ketogenic diets that are in clinical trials, for example, in clinical trials to treat Alzheimer's disease, are modified Mediterranean style diets. So, take a look at what a Mediterranean style diet is and that can help you in kind of picking out your food choices. The biggest unknown area with people who want, beyond the ketogenic diet, for a longer term, is this question about heart health. I think it is an unknown. Most diets don't have rigorous long term, years long, decades long data. To know exactly what the effects of different diets are on long-term heart health. And that's certainly true for ketogenic diets too. We know that we get nervous about eating lots of fats, but what if they're good fats? What if they're not saturated fats, not trans fats? What if it's Mediterranean style fats? And your cholesterol definitely changes on a ketogenic diet. I've heard cardiologists talk about if you drill down, some things get what we think of as worse, some things gets what we think of as better. But the bottom line is that it is still an area of active research and controversy, about what is the long term effect of the ketogenic diet on heart health. And you'll hear strong opinions on both sides. So certainly talk to your doctor and do your own research. Especially if heart problems are something that you may be dealing with and you're thinking about trying a ketogenic diet.

SS:

How about gender differences when we're talking about the ketogenic diet and time-restricted eating. Is there a difference for males and females here and how well they work or what we know?

SP:

As for time of eating, at least most of the animal's studies have been done in male mice, the female mice experiments are very limited. But the female mice experiments that are done, those are mostly done on female mice in an experimentally post-menopausal state. Because in humans also we know that after menopause it's really hard for women to lose weight and they are more likely to get many metabolic diseases and that time-restricted eating works both for male and post-menopausal females. Coming back to human studies, interestingly the earliest that time-restricted eating may help people improve their health actually comes from breast cancer studies that women who maintained at least 13 hours of

overnight fast, so that means they were eating for 11 hours, fasting for 13 hours, and had breast cancer once, they had lower risk of getting a relapse in their breast cancer.

SP:

And the same group also published that women who are doing time-restricted eating or overnight fasting for thirteen hours or longer, if they have breast cancer, then the prognosis of the getting cured was much better. So in that way we know that this works for both male and female. Coming to weight loss and blood pressure, and all of those indications, most of these studies included males and females and in all cases we do see health improvements. But at the same time, I must say that these studies are small enough to see, say, whether females lose three percent whereas those males lose four percent, those kind of studies have not been done yet. So those are in response to gender differences.

SS:

Thanks. Dr. Newman, gender differences, have you studied that?

JN:

Everything has gender differences and in multiple cases its horribly under-studied, as Satchin said. I think that ketogenic diets and ketone bodies are no exception. We're actually studying that in the laboratory. Differences between male and female mice and how they respond the ketogenic diets, and how their own bodies ketone systems change as they age. And there are clearly differences. The biggest use of ketogenic diet in human clinical trials so far is in the studying of weight loss and as far as I know those studies have included both men and women, of course, and haven't seen dramatic differences between the sexes, but this is a great question. Everything has gender differences, and in general we need to study them and understand them more.

SS:

That's great. That's a great reminder, the need for research in those areas. Dr. Newman we've got a question also about potassium? If an older adult is taking extra potassium for blood pressure, then maybe it leads to cramps? Is this something that you can speak to about how ketones in the system relate to potassium levels?

JN:

This is a great question, and if you are thinking about trying something, I can tell you my own understanding from my nutritionist and other colleagues who know much more about this practically than I do, one thing I have learned is not to be afraid of a ketogenic diet. It's something that most people could probably try. But also, is something that a lot of people should do with their doctor. In part because it's a different metabolic state for your body. And like any big diet change, a lot of things in your body will change. So if you're taking medications, you should do this together with your doctor and think about how your medication needs might change. One example of that, which is kind of a good thing, is that people who have diabetes who started a ketogenic diet in a clinical trial around weight loss or in clinical practice, often lose a bunch of weight and often lower blood sugars and often actually have to have a plan for reducing their blood sugar medications so that their blood sugars don't go too low. So definitely, if you take medications, talk to your doctor ahead of time. The other reason to talk to your doctor is so that you can get your blood checked after you start a ketogenic diet. Particularly for things

like potassium. Because it can change the way that your body absorbs and excretes some of the salts, like potassium. Everyone should probably do that. Some people needs to take supplements on a ketogenic diet to keep things level. But certainly if you're taking medications that already affect these things, absolutely do this together with your doctor.

SS:

A good reminder, thank you. We have an interesting question about the immune system. The pandemic has shown that aging immune systems, there's risk there. Does fasting and the ketogenic diet affect the immune system?

SP:

Yes, so the circadian rhythm itself is a very strong regulator of the immune system because, experimentally, if we take rats or mice and give them injections, that is, changing their day and night cycle by eight hours, and if we do it for three to four weeks then these rats and mice will become so susceptible to pathogens. That simple pathogens that they could easily tolerate now, those same pathogens, can kill them. That's one aspect. The second is when mice and rats are sleep deprived, even for four or five nights then they can become even susceptible to pathogens including viral infections and flu-like symptoms. So in that way, having a good circadian rhythm is always good for building your resilience against infection. And what we're seeing in time-restricted eating experiments, we do see mice that do time-restricted eating, their immune system gets much stronger so this recently published paper shows that they are also more resilient against infection. So that way, beyond sanitation and vaccinations and social distancing, you can build your resilience by sticking to your regular sleep schedule. Try to be in bed for eight hours, but also try to eat everything within maximum 12 hours. The third thing to keep in mind is right now, a lot of people will get in line to get the vaccine. What is interesting is a study showing that those who slept enough, four to five nights just before getting vaccinated, they produced much better immune response to the vaccine and they get protected for a long time, for vaccines like flu vaccines, not COVID-19 vaccine, of course, and other vaccines against pathogens. So that's one rule. The second is, the results show a lot of studies showing that people who get vaccinated in the first half of the day build their immune response much better and much stronger than people who get vaccinated in the second half of the day. So try to be in line early in the morning. So these are some of the connections between immune system and circadian clock that are practical. The other thing that we find is, in almost all of our mouse studies, and now we are beginning to see that among firefighters who are exposed to a lot of toxins and also have high systemic inflammation, their inflammation goes down if they do time-restricted eating. So it would be very interesting because firefighters are also very prone to different kinds of cancers that are linked to inflammation. So, the long term goal is to see whether time-restricted eating can reduce the cancer risk. As I mentioned, it does reduce the risk of getting breast cancer relapse, or accelerating the cure from breast cancer. So we feel that there are a lot of benefits of time-restricted eating, or eating within 10 hours. Improving their immune system, building that resilience.

SS:

Great. Dr. Newman, is there an immune system connection in your area?

JN:

There may well be. There's certainly a strong connection with aging and metabolism in general. I think the COVID-19 pandemic has, we already knew that, but the pandemic has really driven that home, right? How diabetes is a risk factor for severe COVID-19, even among younger people, and how aging is such a powerful risk factor. And we've also known for so long that older people tend to have a less of a response to vaccines than younger people, and then that's something that's incredibly important right now, to protect our older population with the vaccines. And targeting aging, we hope, is a mechanism to ameliorate that. The listeners have probably heard what is the best example of that so far, Joan Mannick's work with mTOR inhibitors to enhance vaccine response. I know she's studying this in the context of COVID-19 now. Is there a similar role for ketone bodies around modulating these aging-related mechanisms and immune function? There might be. It's very early science and there is a lot of sense out there about anti-inflammatory effects of a ketogenic diet. One of the mechanisms for that may be that ketone bodies directly reduce harmful inflammation, inflammasome activation, on a cellular level. How that molecular mechanism translates to treating an inflammatory condition or maybe enhancing the response to a vaccine, we have yet to work out. The science is early. But I am very interested in that area, I am hopeful we can figure out a way that ketone bodies, or be similar metabolites, might be harnessed to improve the immune response and maybe dampen the unproductive, immune-hypo-activation that you see in a disease like COVID-19. And that might give us more tools to help protect the health of older adults.

SS:

Terrific. Thank you. We are just almost out of time, so as a last question before we go, do either of you have any final word to our audience as they head off into deciding whether they're going to try these weight loss and general health methods. Quickly, Dr. Panda?

SP:

Yeah, so Sarah, I was just going through some of the questions and maybe I could quickly address. A lot of people have this question: Can they drink coffee, what time they should drink coffee, and can they have sugar, can it have half and half? All of that question. The first thing is you're drinking coffee because you want to wake up your brain, so that means you haven't slept enough. So there are three rules to coffee. One is, you can drink coffee, a black coffee before your eating window starts. If you haven't slept enough and your job depends on it, so very early mornings, a lot of you have to go to the job, and we don't want you driving sleepy so it's better to be caffeinated and drive. Second is, if coffee is the only love in your life, yes, go for it. But at the same time, I must emphasize that you should not drink coffee after lunch because coffee can stay in your system for at least six and, for many people, up to 12 hours, so that means it will affect your sleep. And if you have bad sleep, then it can reduce the benefit of time-restricted eating. The other question is how little calories you can eat. I'll just give you some real science. For example, if you drain all of my blood, I am around 140 pounds, then you'll get five grams of sugar. That's all in my blood. So that means, when you have that half and half, that actually has more than one gram of sugar, that will increase my blood sugar, say from 100 to 120. Which is almost like getting diabetic grades. So keep that in mind, if you're going to get your blood sugar test done in the morning, after fasting, if your doctor tells you, then you know that you should be going completely empty stomach. So that's what I mean. That's how we can get the best benefit of this. Last word is if you still have questions on how to do it, we do have a website mycircadianclock.org. You can go and learn a

little bit more about this. There is also an app called "[mycircadianclock](#)" it's a research app (not a commercial app) that will also help you monitor your own circadian rhythm and eating pattern for two weeks and then nudge you, guide you to adapt, time what you're eating. It's free for anyone and we use it only for research.

SS:

Thank you so much for sharing that. Dr. Newman, any final word before we say goodbye to everyone?

JN:

Circling back to the beginning, when it comes to healthy habits, when it comes to maintaining your weight, try different things and find what works for you. Find what fits into your life and find what your body goes with. Different people, it's different things. But whatever you try, the geriatrician in me is going to say, make sure that you move more, make sure that you're more active. However active you are now, be a little more active tomorrow and more active next week. Having an active lifestyle is one of the most important things that you can do to keep every part of you healthy adults you get older.

SS:

Great. That's a terrific message to end on. Thank you so much, Dr. Newman and Dr. Panda, both of you, for all your insight today. And thank all of you in the audience for your terrific questions. Please join us at the end of March for our next 'Live better, longer' webinar: Gaming and your brain. I mean, no matter what kind of games, puzzles, your iPhone games, whatever it is, we're going fill you in on what they're doing to your brain and how you can use them to help stay healthy for life. All right, so thank you again, everyone, enjoy the rest of your day.

SP:

Thank you, have a great circadian day!

JN:

Thanks. Everyone stay safe. Take care.

-End-

