Introduction to Longevity and Fasting

Welcome to another episode of the Exponential Longevity Summit. I'm your host, Doctor Jeffrey Gladden, and we're here discussing how we leveraging AI to outlive disease and live young for a lifetime.

And today, I'm joined by a real preeminent figure in the longevity space, doctor Valter Longo. He's the Edmund Jones Professor of Gerontology and the director of the USC Longevity Institute.

And that's a pretty good credential there. And Walter. So welcome to the show. Oh, thanks. Thanks for asking me. Yeah. So I'm I'm just curious. You're famous for fasting, and, maybe you could bring us up to speed.

You know, we hear a lot about fasting. We hear a lot about intermittent fasting. We hear a lot about, some of the negative effects of eating one meal a day.

There've been some studies that have outlined that sort of thing. And then some of the benefits of the five day fast mimicking diet. There's products out there, like Vimeo that sort of mimic fasting without fasting.

I'm just curious to get your take on the field at this point in time, you really sort of have started a real, movement, if you will, in terms of people fasting for longevity and ways to do it.

But I'd be curious to get your take on some of those things. Yes. So I always say, first of all, that fasting is that means everything and nothing like kind of like eating, right?

Is eating good for you? And so I think that for fasting to finally make it into the medical domain, we have to standardize it. And make sure that it's done.

It's personalized and done, you know, in a certain way, that has been clinically proven to be effective.

Daily Fasting Windows and Meal Timing

So with that said, I think that we've been saying for a long time, for example, the time through the eating. So the the length of time in which we eat every day, we always say, 12 hours.

A lot of other people say 16 and that we say 12 hours because of the, the extensive data, breakfast keeping. Right. So, you know, and this has been going on for 30 years.

So for a long time we've known that people that skip breakfast do very poorly worth it. Right. And so some of my colleagues argued, well, yes, but that's because the breakfast keepers, have a lot of problems and they may have bad behavior.

And even if you adjust for these, that you're not going to, see that they have a bad behavior. But I always say, well, even if that's the case, why doesn't it it if a 16 hours is so powerful, why does an at least, you know, counterbalance the bad behavior, right?

Why don't we see it go back to neutral versus instead? What we see is people that skip breakfast live shorter with more cardiovascular disease. These people tend over and over.

Meaning it's it's an association is it's not, causation. But, you know, certainly it's a bad association to have. Yeah. So then ours seems to be, very good.

Not as good. I mean, Sachin Pandey and others have looked at that. Probably not as good as 16 hours, but so far,

I always say I've never seen a negative paper.

You know, this is why you shouldn't do 12 hours of fasting and 12 hours of feeding. And now some people, you know, make fun of it and say, wow, that's just normal eating what it used to be.

Normally it's not anymore. Now. Panda, looked at it, and I think the average was about 15 hours of, food intake, per day. In the people that he studied in the US.

So, yeah. So that's one right then and then, I think the other one, that I recommend is we have to skip something like I do, for weight purposes, keep lunch or have, a small lunch and, you know, and then weigh and maybe have a snack around, you know, in the afternoon.

That way you sort of have an in between day, fasting that helps you, you know, reduce the calories. And there is really I've never seen any negative data about that either.

It doesn't mean that, you know, one day we couldn't have have it, but. So far, I've seen, no negatives on that. And certainly, we have foundation clinics, follow a lot of people.

And, and this that seems to work for, for a lot of people. Now, the the good news for skipping lunch is most people, work. In fact, I skip lunch, they say Monday to Friday, and then I eat normally on the weekend.

And it makes it easier for me because the work days and and then eventually the brain adapts to this skipping and, you know, so after I did it for about two months, I started 20 years ago, then I was and I stopped being hungry.

And that's what we see with a lot of patients that that we follow. Once you once you get used to it, then it's no longer really an effort to do that. And the third is, of course, is the fast moving thing that I've been the first meeting that, is, is a five day.

We first started, we were only fasting, and we cancer patients, and we realized that most patients, they now want to do what? They're only fasting. The oncologists were not happy with it either.

And so we we were funded by the NIH, to do research on and, fasting, mimicking diets. And so and this is a special composition that was first tested in mice and then in people that has, same effects or similar effects as what, only fasting and, for markers, which we look at and we think those are the, telling of the fasting response.

Fast-Mimicking Diet and Clinical Evidence

So IGF one, IGF one, glucose and ketone bodies, those are the four by the four markers that we look in to go up and to go down. Right. So IGF one IGF binding protein.

Did you say. Yeah IGF one and IGF VP1 which is binding protein one, which is that, mostly an inhibitor of IGF one. Right. Those and what was the FARC meeting that tried to achieve it?

It's a plant based five day, diet. And and now it's been tested in over 30 clinical trials, but mostly by independent universities, and a lot of very powerful effects.

Yeah, yeah, a lot of powerful effects. So, you know, it's interesting. There was a study that I read, some some years ago now. Basically it was a cardiovascular trial that was a, I think run from 1999 to 2014 or whatever.

And there were maybe I'm going to say 15,000 people in it, something like that, 20,000 people. And they were looking at cardiovascular risk relative to eating patterns.

And they found that the people at eight, three meals a day, to your point, actually had the lowest mortality. And the people that eat, one meal a day had an 80% increase in all cause mortality and cardiovascular events. And if you skip lunch, it sounds like you're eating a light lunch.

But if you skip lunch, you know, that had, you know, that had, like, a 20% increase if you skip breakfast, that had like a 40% increase if you skipped dinner, it seemed to have the least impact.

On mortality. But the three meals a day, seem to be, kind of the sweet spot. And and I was thinking about that because we know the benefits of fasting.

And certainly you've proven that. And I want to run this by you, because my take on it is that, you know, we tend to think of eating as being restorative, but but if you're just, you know, eating a lot of calories all at once, it's actually a metabolic stress, right?

It's actually a load on the body to actually, manage all those calories. And, you know, insulin goes up and distributes the calories to the fat cells and everywhere else, right?

So I'm just curious what your take is on on that kind of data. Also, it's pretty dramatic, quite honestly. Yeah. I think that, it's very important to also, I mean, I don't know where this habit of eating three times a day comes from, but I always imagine that it was probably a reason why so many people around the world that, eat this way, right?

Three, three times a day. Yeah. So. And this is why I, I introduced this snack in the afternoon. And so you have really two small meals, you know, one in lunch and one in the afternoon.

And so I think that, you know, that's probably not a bad idea to also think about, the possibility that this is not just by chance that we've we've, come up with this idea of what a breakfast, lunch and dinner and so on.

So many people around the world do this, right. So, yeah, it is possible. I mean, of course, one study, 15,000 people seems like a lot. But, you know, it's a correlation study.

Again, you know, there are of course epidemiology. You can get a lot of results, if you just have one study. Right. So I wouldn't put too much, thoughts into one study, but it's certainly, I think telling.

Right. So but it could also be telling you that people that, you know, skip, a meal, like lunch, often time, are not doing it for health reasons. Right.

And then that's a, that's a probably some of these old studies. Right. People are not skipping lunch. I want to be healthy. I want to skip lunch. I think a lot of times people may skip lunch because maybe, you know, they, they, they are their work.

And they're stressing out for other reasons and they don't have time. Yeah. You know, so yeah. So that that that might be indicate as, as you know, and that's been the argument for the 16 hours.

But, but I think that that's a valid if I didn't see a meta analysis. And on the 16 hour on the skip breakfast keeping, I would be, less convinced that it was bad.

So I think, you know, if we saw a meta analysis on landscaping and that 20% was maintained, you know, and then I would be worried about it. But I think that, if you think about weight gain and, and, and how that could really have a remarkable effect long term in, in maintaining a normal weight.

I would say that the chance that that's going to be a problem, it's going to be minimal. Do you want to talk a little bit about, the composition of the five day fast mimicking diet, the different, elements that are in the kit, so to speak, the prolonged kit and what they are and whether or not they spike blood sugars at all and things like that.

Because I've, I've seen that sometimes I think there's, a rice, base to maybe one of the soups or something like that. I've heard some people say with, with their continuous glucose monitors that their blood sugar has gone up with some things.

And I think you've also developed some other modifications of it that are being used in diabetic trials, if I'm not

mistaken. To look at, really having dramatic impacts on people's insulin resistance and insulin sensitivity and, you know, hemoglobin A1, CS, etc..

So I don't know, do you want to comment a little bit on the composition or the very.

Meal Frequency, Weight Loss, and Metabolic Stress

So I, I, I remember I was talking to one of the former directors at the, FDA and and we were discussing, you know, potential to take this the FDA and I was saying, well, I know why the, FMD works.

And he said, well, no, you don't. Right. You think you do, but you, doc. Right. So, you know, probably pretty good idea. And we have a lot of science behind it.

But he said there it is possible that there is one ingredient in there that if you took it out, all of a sudden a lot of the effects would go away. Right?

So my argument would be after five trials, prediabetes and diabetes in the same rice. So, yeah, there are rice, there's starches in the soups and we did it on purpose.

Right? I did it on purpose because first of all, I did not want this. Your your ketogenic back and forth. Right. I want it I mean, it was like extremely paranoid and say, what if after 20 years of doing this up ketone ketone bodies, very high ketone body is very low.

That caused the problem, right. Even if you do it three times a year. Right. Well I just I don't know I like that is I, I want to be to the I'm going to get it.

I wanted to get it to a point where like this is almost impossible to hurt people. So I think the starches, you know, one of the reason for being in there was to avoid exactly that.

People think, oh, I should get ketone bodies should be very high. I don't want kilobytes to be very high. I won't go up ketogenic state, but I don't want it to your your very high very low.

So that was the reason. And then we started running trials and and and looking at experiments and lots of experience in mice. And it turned out that that way seemed to work the best.

Right. And now we have remarkable data and diabetes. University of Heidelberg University Layton, now University of Rome, has done a trial. And and we done a trial in 2017.

So prediabetes, diabetes, it works remarkably well. So people think that a spike is necessarily a bad idea, but maybe not. Right. Maybe the spike, we don't know.

But maybe the spike is was preventing muscle loss. So now trial number 3 or 4, we don't see any muscle loss. And whereas, you know, we allow a GLP one in a lot of different therapies, you see extensive muscle loss.

So is it possible that, in fact that that those spikes are increasing insulin sensitization like remarkable. I mean, if you look at the leading trial you see about late in Heidelberg, I think Heidelberg showed a 1.3, 1.4 drop of A1 C after six seconds, then something similar, but either a monkey drop or, medication drop or both.

Right. So now this is causing not only to drop the one C there was Heidelberg. Right. So with all drug it was diabetes patient taking any type of drug.

And this show, you know, 70% of the patients reducing medication. And on top of it, a 1.4 drop in agency. Right? I would say that's pretty hard to beat. Right.

It's very hard to beat. Yeah. Yeah. So a you know, going back to the FDA guy, I was a little on, right. Because you

only yeah, I will agree. If this was done once a week I will agree to dangerous.

You know. But it's this done, you know, six times a year for a diabetic or, you know, 12 times a year, and then eventually, only three times a year for maintenance in the future.

Fast-Mimicking Diet Composition and Blood Sugar Effects

Let the spikes be because it's working extremely well the way it is now, because some people now start complaining and say, well, you know, I don't like the spike if is a spike.

And then podcasters and people get in there not knowing very much about it and, and you know, so yeah, people start complaining. And then I think the company also did a version that had less spikes.

That seems to be as effective by now. You know, we'll see. We'll see. Now, I mean, there there hasn't been I mean, of course, this is tested a lot less than, than, than the other one.

So I would say the other one work, the original one works. Yeah. You one probably it's going to work, but could it work a little bit less. Well I don't know. Yeah. Well that's a good point.

You bring up that maybe having some exposure to glucose or some rise in blood sugar, you know, it's kind of priming the pump for the body to work in a kind of more physiologic way.

Right. You're not removing the stimulus altogether, so to speak. Well, yes, we know that sugar also converges with amino acid in tau. Right. Then tau is the very center of, you know, muscle synthesis.

Right. So yeah, I mean, of course we don't have time to look at every possibility and everything. We know that it works and it'd be nice to have time to look into it, but that could certainly be right that that it's helping leucine to know that amino acids have enough of a trigger of tau signaling to, you know, have these cycles of, of muscle synthesis.

Yeah. That's right, because insulin itself activates, I'm sure, just so the audience understands, it's not just IGF one or growth hormone or testosterone.

It's actually insulin is is an M tau activator. Right. So it may be part of the magic of maintaining muscle, muscle mass when you're fasting. And just so the audience understands, we're talking about the prolonged five day fast mimicking diet the company has prolonged, prolonged.

So you brought up the idea of GLP ones, and everybody's talking about ozempic in terms of appetite and GLP one and GIP, combination agonists and things like that.

We we have been, we, we use them a little bit, but we're, we're kind of not huge fans of people just jumping on these drugs and taking them for extended periods of time because we're actually seeing what we do, body compositions, that people are losing muscle mass and they're losing weight, but they seem to be preferentially losing muscle over fat.

And that's really. How they do it in Jama, bone bone density loss. Right. Bone density also just was published. Right? I just saw that as well. And so, you know, I think, you know, if you're listening to this and you're thinking about fasting, you're thinking about losing weight, we can you know, we're not opposed to using a GLP one, a low dose to kind of jumpstart somebody into the cycle.

But I'll tell you, the thing that we actually do the most is actually start with a five day fast mimicking diet, because that seems to be the thing that resets the taste buds, resets the gut biome, which, as you know, your gut biome is actually driving your appetite on some level, right?

If you got a lot of sugar loving bacteria down there, they're going to crave sugar and that signal is going to get to

your brain. So I think there's a lot of a lot of sense in starting if you're if you're looking for a weight loss plan, I think starting with a five day fast mimicking diet is almost like the ideal way to do it, as opposed to jump into a GLP one.

So I don't know what your thoughts are on that, but. What my thoughts are that that we I love that when, some years ago, it was a Wall Street Journal article and they say, and as a bonus, you get the weight loss right?

Yeah. Great. Because it was basically saying, look, this is not for weight loss. This is to go after lots of system and dysfunctionality in there. And, and different cells are now being damaged.

They're accumulating. So there's a lot of drunk and as you mentioned earlier, right, that we we eat all the time and, and so in, in that if we go back thousands of years, we most humans had an opportunity to eat a lot in a certain period of the year.

Right. And, and then insulin went up and say a lot of sugar, a lot of fruit and insulin went up. And now you store fat because the others coming in in the other season, whether it's, you know, the dry season or whatever, the winter, you're not going to eat that.

All right. And, and, but now we remove that. And this is why, you know, it's so important to hold back something that has always been part of, of human life, but put it back in a way that is very controlled, because you can go from one problem to even a bigger problem, like you mentioned earlier, and then you skip this and skip that.

And what if now this is contributing, as we know, to cardiovascular disease, you know, if you do 60 hours of fasting every day.

GLP-1 Drugs, Muscle Loss, and Weight Loss Strategy

Yeah. So I think that the the job of the fasting making that is not is is really reset things. And now, you know, in mice we've shown reprograming in pancreatic beta cells.

You know, we now we've shown reprogram we've shown stem cell activation in, in the intestine, stem cell activation in the brain. And now we're about to publish for the kidneys.

We're starting to see the same evidence in people, right, in clinical trials. So that's really what the FMD is about. But the bonus is that the, visceral fat loss with our muscle and and bone density, loss of no muscle loss, no bone density loss and just visceral fat.

So it, that's that's what it's there for. And, of course, you know, a lot of people may want to use it for weight loss. Great. But, yeah, that's not his purpose here.

And now for the two and a half years of median, biological age reduction. Right. That's what we just published. The thing is reducing biological age. Epigenetic age. Right.

So, yeah, it's it's very, you. Know, this was an epigenetic. This was the Morgan Levine, method, bio age developed. Yale. I like him more. And why do I like it more than epigenetic?

Also, although we're also collaborating with Steve over and we're going to do epigenetic, but I like it more because it's based on measurements that are highly, highly standardized and, you know, well-established in the clinic.

Right. That a onesie or cholesterol or total cholesterol, blood pressure. So it's not likely that a clinic is going to get that wrong. And then she took that those simple 7 to 10 markers.

She like that in enhanced database. And then she gets a correlation with, you know, mortality, chance of mortality in the next however many years. So I like that and not because epigenetic and I work but but I think because, it's hard to imagine a clinic getting more than a couple of these markers wrong.

Multiple things. Yeah. Yeah. I mean, one of the things that that we see is that, you know, we actually see people's glucose tolerance tests improve significantly.

So we do two hour glucose tolerance tests on all of our clients because we find insulin resistance where people have a normal hemoglobin. Anyone see a normal fasting blood sugar.

And yet you you do a stress test on the pancreas and oh my gosh they're diabetic for, you know, an hour or two hours and their insulin levels go up from 6 to 80 and, you know, stay elevated at two hours.

So there's clearly insulin resistance there that's typically is missed by people. But what we see is when they do the five day fast mimicking diet, that you start to reverse that insulin resistance, even though they're not diabetic, they have early insulin resistance, which is a big driver of many things, right?

Whether it's thickening of the arteries, senescence, cell formation, aging itself, I mean, all kinds of problems. Right. So, it's been fun to kind of look at it through that lens and see the impact, even on people that aren't necessarily diabetic, but are kind of flirting with insulin resistance, which maybe they don't even know about, but they're getting better also.

So that's pretty pretty fun to see. Yeah, absolutely. This is why it works out so very well. And in our clinical trial with the pre diabetics. And so probably acting and the mechanisms of insulin resistance, which as I was saying earlier, always been there for a purpose.

Right. So diabetes is, was probably there for a purpose to store the fat and, and yeah. So obviously there is a trigger to bring back the insulin sensitization.

And that trigger might have to do with, precise length.

Regeneration, Beta Cells, and Future Collaboration

And this is very important also because people then start thinking, oh, maybe I got two weeks right. Fasting and and but, but then the literature will suggest if you go too long, this is why this is FMD for five days seem to be the the ideal length.

Because if you go too long, you know, there's New England paper from so many years ago showing that eventually you get into a hyper metabolic state, low energy expenditure state.

So you get into a thrifty mode, right? Because now the body says, well, I've been fasting for too long of a time. Maybe I should reduce energy expenditure.

And that's energy expenditure adjusted per body weight is not absolute energy. So now you lost weight and adjusted for the lower weight you're burning less fat, which really condemns you to break it, to regain all the fat.

Right. So is a lot of there is a lot of science behind this. And I think that people, should be much more careful in the way this is approaching. Yeah.

On the other end of the spectrum, too, I'll just mention this, is that we've seen beta cell function improve for people that are diabetic. Like you, they do these series of fast, and then they come back and we'll do to our glucose tolerance test.

Maybe we did one early on and they couldn't barely produce insulin very well. Right. Because it's like the beta cells are shot. Right. So it's like okay well you're diabetic. Well what we see is the beta cells actually coming back now to able to produce.

And so so not only are you improving insulin sensitivity, but you're also kind of rehabbing the beta cells with this to be able to produce insulin, which is you know.

And this is what we published in 2016 in cell for mice. Right. So and we published both for the type two diabetes model and the type one diabetes model and the type one diabetes model.

If you look at the betas, at the pancreatic cells, you see a lot of non alpha non beta cells generated right temporarily. And then you're feed. Then they turn into beta cells.

And and if you look at the the profile of expression you see lots of first of all you see two Yamanaka factors that are it turned out. And then you see a lot of embryonic developmental genes that are involved in pancreatic generation.

Right. Including the the key transcription factor called neurogenic entry. So neurogenic three, which when you're born has the job of helping build the pancreas, is now turned.

That and if you look at the non fasting tissue that all of right. There's 100 different genes involved in embryonic development. All of. And then you do the FMD.

And many of em are turned down including two Yamanaka factors. And then you're feed. And not all of them are still but they want to re feeding you still see many of these right.

So yeah, I'm so. Glad to hear that you're seeing this in patients. And I hope that if you've seen a lot of patient, maybe we can we can do, a, you know now IRB clinical protocol and do a clinical.

Yeah. Love to do that. We'd love to do that with you. Yeah. I think it's it's really exciting. It's interesting just that when you fast like that you know we talk about what stimulated will on to produce stimulated cells are kind of cleaning themselves out.

But now you're actually activating your regenerative capabilities. Right. So the body's you know, progenitor cells and stem cells are being, you know, reactivated in a way that is now repairing the body.

So by doing this five day fast mimicking, diet, you're not only, you know, stimulating autophagy and resetting the gut biome and taste buds and insulin resistance, you're actually regenerating your body on some level.

And that's that's an exciting thing. So this has to be demonstrated for people. But I have to say we have a trial in Italy, and children with type one diabetes that's, very slow.

But also, we've been talking to a doctor or another doctor in the US, and he's seen for type one diabetes. Similar results that you're seeing. Right. So it'd be great to unite forces and then put together a protocol and let's test it out. Right.

Because, I know Harvard was very interested in that trial, but they never they never got it going. So. So I think it'd be good to, it'd be good to do it.

Yeah. Yeah. I'd love to add just on a final note for the audience, it's not that we're anti GLP ones because they do play a role. And there's some nice data on improved cardiovascular risk and decreasing heart attacks and things like that for people with diabetes.

So it's not that we're trashing GLP ones. I think we're just saying that be very cautious when you think about them for quote unquote weight loss, because they're not really what you think they are.

So, Valter, really such a pleasure to have you on, as a guest, really fun and conversation and. Yeah, let's definitely, jump off line and collaborate on this.

I'd love to. So it sounds good. Thanks a lot.