The Telomere Factor: Why DNA Isn’t The Only Key To Aging Transcript

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Introduction to Longevity and Dr. Raphael

This is Doctor Talks, real talk from real doctors on the issues that matter to you most. Welcome, everybody, to this edition of the Exponential Longevity Summit.

I'm your host, Dr. Jeffrey Gladden. And here we are, as always, discussing leveraging AI to outlive disease and live young for a lifetime. And today I'm joined by a gentleman I have a lot of respect for, Dr.

Joseph Raphael. He's been in the longevity space for many years. When I first started getting into the longevity space back in 2012, he was already there and has been instrumental, I think, in bringing a lot of things forward with regards to the importance of telomeres and the immune system and immunosenscence.

So Joseph, it's great to welcome you to the show. Thank you, Dr. Glenn. It's great to have to be on your show and talk about stuff that's near and dear to my heart.

Yes, I have been in the field a long time. We won't tell anybody how long. Yeah, okay. Well, actually, that's a bragging right. So yeah, how long have you been in the field?

started practicing longevity medicine, which was back then called anti aging medicine in 1998. Okay, okay. Good for you. So that's 26 years. So good for you.

So tell us, tell us a little bit, you know, when I got into went through my own health crisis in the 2000s and then transitioned out of interventional cardiology into what's become gladden longevity.

One of the first things that I was reading about was really the impact of telomeres on longevity and health.

Telomeres vs. Epigenetic Clocks

And then there were some papers that came out that talked about, well, maybe telomere length isn't all that important because it's not as reliable of an indicator for chronological or biological clock as maybe DNA methylation.

And I always looked at that with a little bit of a jaundiced eye, because I think short telomeres are always a problem when they show up. So I was just curious, what's your what's your take on the telomere story today?

Yeah, well, I think you characterized it very well. You know, when they first came out, it was the new kid on the block, you know, when it became commercially available, and people were talking about how you was your molecular clock, your ticking clock.

Every time the cells divide, the kilomeres get shorter and get short enough the cells stop dividing and then a lot of the aging process starts to accelerate.

If you take the kilomeres as a way to predict chronological age, they are nowhere near as good as the first generation epigenetic clocks, the Horvath clock, the original one.

That's because those clocks were trained on chronological age. You don't really want something that's perfectly predicting chronological age because, well, we already have chronological age.

Just a little bit about biomarkers for your audience, if you haven't talked about it that much. A biomarker that has a score of zero or value of zero doesn't correlate with age at all, the parameter you're looking at.

One that has one of one is 100% correlation with it. That's close to the epigenetic clocks, which can be as high as 0.98, 0.97. What you want is one that has a correlation in the maybe 0.5 to 0.8 range where there is difference on both sides because that captures the biological difference in aging between individuals.

So you really don't want a perfect clock. And two numbers are somewhere around 0.5 or so. But now the epigenetic clocks are all moving away from the original first generation of our bath clock.

And instead of training them on chronological age, they're training them on things like immune cell subsets, they're training on telomere length, they're training them on blood pressure, like Morgan Levine's clock, which is called pheno age is trained on nine routine chemistry and CBC and CRP markers that can predict biological age pretty well, but also predicts mortality.

And so, but the, you know, the prediction R squared has come down quite significantly when you do that, but then they become much more biologically useful.

And I agree with you about telomeres. I mean, when Carol Greider once said she was one of the co-laureates for the Nobel Prize in 2009, along with Elizabeth Blackburn, that telomere lengths don't mean anything clinically because you can be 40 and have the telomere lengths of a 70-year-old or 70 and have a telomere length of a 40-year-old, I would ask Dr.

Greider, if you had to choose, which telomere length would you rather have, out of a 70-year-old or a 40-year-old? Right. I dare say she would say that before you.

It's an interesting point. It's an interesting point because the audience should understand that telomeres which are these end caps on the chromosomes that are every time a cell divides basically some of those base pairs are clipped off and The idea is that when the telomere gets short enough, then it sort of signals the cell to become senescent or to be old or to stop dividing.

And then from there, it can go into being an inflammatory cell, a senescence associated secretory phenotype, which basically is putting out all these cytokines that basically accelerates aging, right?

So we know that the telomere shortening has an impact. It's also interesting when telomeres shorten, they have another impact on another hallmark of aging, which is your mitochondrial function gets shut down.

So we know that telomeres and your immune system gets senescent, right? So we know that telomeres are important But it's this question of when DNA methylation clocks came around, all of a sudden, everybody just abandoned telomeres as if they're no longer important.

And to your point, which telomere length would you rather have? I think they're still important. I think they're still you don't mean something. And when people are born, people are born just like they have a different physical height.

Telomeres, Immune Aging, and Senescent Cells

They can have different telomere lengths. So some people are more gifted or less gifted. But then we know that people that have severe limitations in their telomere lengths, progeria being a classic disease, those people age much more quickly.

Really in their 20s, they developed the kind of age-related diseases people have in their 70s. So this telomere equation, I've always felt has been an important thing.

We've continued to test it kind of right along. So I know you've kind of done that as well. Tell us a little bit about the interplay between telomeres and the immune system, because immunosensence, you know, is really one of the key, I think, drivers in terms of why people die.

In other words, this is when your immune system can no longer respond to a new threat. Let's say it's COVID or a

cancer cell that shows up or whatever it might be.

Yeah, so I just want to make a couple of points. You made some good points. I want to elaborate on them just a little bit. First of all, telomere length is highly heritable.

It's about 70% heritable. So, you know, as they say, choose your parents wisely when it comes to telomere length, because it is one of the, you know, it's not like Huntington's disease, quite heritable.

The other point that I want to make about telomere length is that telomere length itself, because of that high heritability component, where you can, you know, I have patients that come in, the average telomere, let's just give some other factors, average telomere length at a young adult is somewhere between 8,000 and 12,000 kilobases, you know, averaging somewhere around, sorry, between Yeah, around there, around 8,000. So from birth to young adulthood.

But there's a range of about four kilobases so that when you're 20, you could have the telomere length of a six-year-old just from what you inherited versus somebody who inherited longer telomeres.

This is not such a great biomarker for predicting chronological age. But what it is, and then we talk about species lifespan, mice have very long telomeres, organisms that live much less than we do, much fewer years than we do have longer telomeres.

But if you look at telomere attrition rate, how fast you're losing telomeres, a very nice paper by Maria Blasco looked at that in nine species and found that telomere length attrition rate correlates very highly with species lifespan.

And that's what I tell you. Yes, a single telomere length measurement will tell you sort of what you got genetically inherited and then also what all the things that happened to you that made your telomere length get shorter up until your current telomere length that was measured.

But it is really what happens going forward that you want to look at. And so what I do is I track it longitudinally. I want to make sure that you don't lose telomere length at as fast a rate as you might, or even potentially add telomere length on.

And in that regard, I think it's a very good aging, if you look at kilomer length, attrition loss over time, which is about 50 base pairs per year or 0.05 kilobases per year in subjects.

Yeah. You know, what's interesting is we do the same thing in our practice. We measure it and continue to follow it so we can see if people have accelerated aging telemirically or whether or not we're actually sort of reversing the aging process for them sort of telemirically again.

And I think it's useful. And for us, what's interesting is it does relate with immune system senescence. I think you've seen that. You want to know more about that?

So let me talk about that. I mean, remember, we're measuring telomere length in white blood cells, right? and the immune system is white blood cells. I mean the cellular portion of it aside from lymph nodes etc.

So when you're looking at someone's telomere length, now there is a correlation between telomere length in white blood cells and in other organ tissues just to make that clear so that it's not like it's completely different but the reason one of the reasons is a correlation between immune system health and aging and telomere length is because When your telomere length of your white blood cells get too short, particularly your lymphocytes, that is when the cells become senescent, as you mentioned over the longer divide, but aren't sitting there quietly being sort of, you know, they don't die, they don't get taken care of like apoptosis.

what they do is they sit there and secrete a lot of inflammatory cytokines that you're talking about that then increases the potential of their neighbors to become senescent as well.

Now the thing about the immune system is it's one of its main jobs. We all know its job is to fight off infection and tumor, to create the cleaning up of dead and degenerating cells in all organs.

So the immune system is sort of the queen really, of the aging. We're king, depending on what point of view you want to take on it. I'm not going to be sexist about it.

Measuring Immune Status and Telomerase Activation

And a very interesting paper looked at it very, very starkly, which was they knocked out a gene in white blood cells called XRCC that is involved in DNA repair, but only in the immune system, not in the rest of the tissues in these mouse models.

What they found was that Even though it was just the immune system that had the gene knocked out for DNA repair, the rest of the organism aged much more rapidly, even though they had normal DNA repair in it, because the immune system wasn't there to do its job.

And so that's a very stark example of how the immune system really orchestrates the aging process. Just just so the audience understands this, then I'm going to I'm going to echo that back to you for a second.

Correct me if I'm wrong. But, you know, when when when you develop senescent cells in any tissue, right, whether it's your muscle or your heart muscle or the liver or wherever.

It's really the job of the immune system to go into natural killer cells to go in there and actually remove those senescent cells. And that keeps a balance.

And one of the things that happens as people age is they accumulate a higher percentage of cells being senescent and in that secretory state. So that's kind of accelerating.

And so you have this buildup of these cells and then you have this decrease ability of the immune system to remove them. And you can sort of start to see how this is really accelerating the aging process.

So having the healthy immune system becomes absolutely critical. And, you know, in our practice, we've been able to use a test from UCL. I believe you use the same thing and maybe some others as well.

But this test from UCLA that basically will characterize the status of the immune system. I call it an anatomical look at the immune system functional assessment, but it's the anatomical look.

And then really, if we've had success like this, and I'm sure you have too, but it's exciting because if you give people telomerase-activating agents, which is the enzyme that can re-lengthen telomeres, you can actually see these immune systems go from senescent to not being senescent.

And that's super exciting to me. Yeah, so that UCLA panel is a panel that we developed initially back in 2007 when we did the initial report that went through my practice, looking at the effect of the polymerase activator that you're mentioning, TA65, on healthy aging individuals.

And it consists of that T cells, naive T cells, and particularly cells as measured from a cellular level as whether they're expressing this marker CD28 or not expressing CD28.

I assume you're talking about the same one. That's right. Yeah. And so yeah, what you can see is, and what we published in subsequent paper, a randomized control trial, is that when you turn on telomerase, you get a reduction in senescent T cells.

at about 10% in that study. But I see in my practice that if you go on for a year, two years, you can have some patients where you have as much as 50% reduction in their senescent cells as defined by lack of expression of that CD28.

And that's not just sort of like gray hair. That molecule is what allows the cells to briskly proliferate and fight off whatever infection tumor or molecular snippet it's uniquely designed to fight off.

in a very robust way. If you don't have that, you can't. And in fact, when you don't have that, you also have less solomerase activation, there's altered metabolism of the cell, and then it starts to produce that inflammatory secretory phenotype called the set.

We have seen, yes, the reduction in those and actually an increase in the naive T cells, the ones that have not found the molecular snippets they're supposed to fight off and are available to fight off new infections and tumors.

But by doing that, which is really pretty rejuvenating, I think. Oh, exactly. Yeah, we've seen the exact thing. So if you're listening to this and you're wondering what we're talking about, you know, many of you have heard about DNA methylation tests and you can check that in the urine, you can check it in the blood.

The people at TrueAge have developed a protocol that looks at a number of different parameters related to DNA methylation ages. They now have a symphony age where they can go in and give you a DNA methylation age for about 11 different organ systems, which is useful.

And they can also give you a rate of aging. All of that's very useful. But I think you'd be remiss to not actually measure your telomeres and actually understand where are you in this game of telomere shortening and also understand what's the status of your immune system, right?

The DNA methylation testing will estimate it in the past, although it's not on their current report, but we found that actually measured it. We got better results than what was estimated from the DNA pattern.

So if you're thinking, how do I optimize this part of my longevity strategy? Yes, do the DNA methylation, but don't think that that's the only thing that you need.

I still think you really need to know what your telomeres stand and where your immune system stands. Yeah, I 100% agree with you. I think that DNA methylation is a really exciting technology.

And I think moving away from the first generation clocks to the second and even the third generation clocks is really a very good move forward clinically.

But predicting telomere length or immune cell subsets, which actually be submitted, we share data with two diagnostics from our practice in the UCLA test to help them come up with those predictions.

They're good, but I think seeing what I see in my practice, the effect, and I haven't tracked it as closely as their T cell substance that they're predicting, but I think you're right.

You want to actually measure the flow cytometry, which is what this UCLA panel is, to see the actual subsets themselves. And then telomere length, of course, while they can predict it, and I have talked to Ryan Smith, I think it is really interesting that they can predict, and they can be pretty close in their predictions.

And there is this idea that predicting, the way it predicts better some of the outcomes that might be related to telomere length, I think that still needs some more some more science to kind of solidify that claim.

Lifestyle, Stress, and Telomere Attrition

But I want to get back to just one point today, which is a very good point about people with really short telomeres, the short telomere syndromes, what they call telomere biology disorders, TBDs.

Progeria is one of them. But I think it's a really good example of why when people say, you know, your telomeres aren't that important for you, if you have one of these telomere biology disorders, you either lack, you can lack 50% of your telomerase activity because of a genetic mutation that you inherited from your parent.

And even with just 50% loss of that activity, your telomeres are much shorter at birth and they get shorter much faster. And the second and third generation of people that have had that mutation, they don't make it past 10 or 12 years old because of the lack of enough reserve for their telomeres.

The first generation, they often die of pulmonary fibrosis or bone marrow dysfunction, aplastic anemia. But in fact, the next generation, they've inherited short telomeres from them, and they have only 50% telomerase, they get shorter telomeres, and the disease is called genetic anticipation, where the disease gets earlier and worse and different in its presentation with each generation.

After the third generation, they don't make it out of the uterus. you know when somebody says you feel like doesn't matter that's I show them that yeah in fact is really what you're saying right it's compounded through the through the generation so to speak right so each generation gets it worse than the other yeah no and we haven't taken care of folks like that but but we know it's out there and it's another I think really strong is how important telomeres are, right?

You don't want to get into that particular situation with your own telomeres and being short. Do you want to talk a little bit about some of the lifestyle choices that shorten telomeres for people and maybe some of the impact of COVID, just so people are aware of some of that?

Sure, what I love about is until in your length as a measurement is that everything that we know that is good for you from a lifestyle, diet, exercise, even drug therapy standpoint.

is associated in many studies, there's thousands of studies now on telomere length association with multiple parameters, is associated with telomeres.

It's not necessarily that exercising and eating a healthy diet, getting enough sunlight to get vitamin D or taking vitamin D is going to lengthen your telomeres, but you're going to have a slower attrition rate, which again, remember, that's what's associated with lifespan of species.

Conversely, everything that we know is associated with bad habits like smoking, being sedentary, being overweight, being overly stressed is associated with more rapid telomere length.

And there's molecular mechanisms for that. For instance, stress. Why does stress cause your telomeres to get shorter? Well, cortisol, which is increased in stress, is a telomerase inhibitor.

It turns down the enzyme somewhat. So you get less telomere length for telomerase activity because you have more cortisol. So really a great integrator of multiple things that you're doing to get an idea about, like I like to say, all the slings and arrows that your body has had to withstand over the years.

That's what is integrated in telomere length. I should say something about telomere length measurement. There are a number of companies that use them.

There are an reasonable job, but the company I like to use is called Repeat Diagnostics because they measure both your lymphocyte telomere length and your granulocyte telomere length.

Granulocyte is the cell that goes on to become a neutrophil, and it is released from the bone marrow, circulates for a day, and then doesn't divide again.

So that is a good proxy for your. So one of the things that is interesting about this is that when are having those bad lifestyle choices, smoking, sedentary lifestyle, high insulin, you know, insulin resistance, things of that nature, you're actually increasing inflammation and oxidative stress.

And when senescent cells kick in, they also, with this secretory phase, increase in oxidative stress. And it's possible to actually measure the DNA damage that's being done by that oxidative stress.

We have markers for that in the blood work that we do through Genova, actually, and whether or not telomeres are being attacked, if you will, by this inflated stress.

So to Dr. Rafael's point, the fact that you're inhibiting telomerase. So now you can't re lengthen them. But so you're accelerating their demise through this inflammation and oxidative stress.

And that becomes a really critical part of the story. So the other We know that meditation and learning to meditate and really gaining perspective on life to work.

COVID, Long Haul Effects, and Final Takeaways

You're not really struggling over the details, but your kind of rest at peace and kind of a higher psycho spiritual space really takes a lot of pressure off.

your bionic decreases inflammation. It's associated with increased telomerase activity, increased telomere length. It also is associated with improved DNA methylation age.

So that kind of psychospiritual approach, we focus so much on the biochemical approach, but that's sort of understanding that that psychospiritual space is so critical.

It will move the meter on many, many, many different metrics of measuring the aging process. And I think if you'll take this to heart, we've been impressed with the ability of re-lengthening telomeres to revive the immune system.

We've used TA65 to do that. There are other things out there like TAM818, which can also have an impact on this. You can look into these things, but I think a good start would be to do a DNA methylation test and at the same do a telomere test and do a UCLA test to look at your immune system.

This would be a nice triad of testing that you could do to kind of put this together for yourself. So Dr. Rafael had a little bit of a technical difficulty and departed the show here a minute ago.

But I just wanted to give you that sort of synopsis and summary. I will say this, too, about COVID and with regards to long haul COVID. And that is that what we notice is that there's two things going on here.

One, people that had short telomeres were ones that ended up in the ICU and died. In other words, it was also indicative of the fact that their immune systems couldn't modulate themselves properly.

They ended up with excess inflammation that couldn't be calmed by a normal immune system. And then the flip side of it is that people that got COVID and survived it, also shorten their telomeres.

And you should understand that telomere lengths are dynamic. They go up and down. It's not just a linear line. Like as you go through life, they're always going to get shorter.

For example, if you go through a stressful period, your telomeres may get shorter. You get into a very abundant period or a different mindset, your telomeres will re-lengthen.

Someone carries a child and is pregnant, her telomeres will shorten and she'll age. and then afterwards she'll regain telomere length. So these dynamic and part of the people that have long-haul COVID and sort of persistent immune issues, one of the things to look at there is what the length of their telomeres are.

Maybe that's a piece that also needs to be addressed as well as addressing their decreased energy production through mitochondrial interventions. So I just wanted to Let you know that telomeres, even though people think that, well, it's all about DNA methylation, it's really not.

Telomere length is alive and well. It should be looked at. They should be taken care of. And I think when you do that, you're going to find that you really do a lot to optimize your longevity and your potential for a lifetime.

Thank you for tuning in to Doctor Talks. We hope today's episode has enlightened and inspired you on your path to optimal health. Each day is a new opportunity to make choices that empower your well-being.

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