Slow Down the Aging Process: Telomere Biology in Age-Management Medicine

Dr. Kent Holtorf interviewing **Dr. Joseph Raffaele M.D.**

Dr. Kent Holtorf:

Hello. This is Dr. Kent Holtorf with another episode of The Peptide Summit. Today we have the luxury of having Dr. Raffaele on, and he's going to be talking about the role of telomere biology in age management medicine.

Dr. Kent Holtorf:

Dr. Raffaele, thank you so much for being on and taking the time. I know you're a busy guy, extending people's lives, and so it's great to have you. I'm looking forward to learning a lot about longevity and ways to do that.

Dr. Joseph Raffaele:

Well, thank you Dr. Holtorf. I'm happy to be on and happy to talk about one of my major passions in life, which is keeping people healthy and doing what they love to do as long as possible.

Dr. Kent Holtorf:

I love the fact, and we'll get into this, how you don't just do this. You show the people and document that they are actually younger.

Dr. Joseph Raffaele:

Yeah. I mean, we measure ... One of my major focuses is to measure the aging process in people at baseline to see what their strong systems are because we are all a mixture of weak systems and strong systems and you have to focus on the weaker ones and try to shore up the stronger ones. We really want to sort of know, once we start therapies, whether they're effective. It all started back in, I think, it was 2001 when Bob Butler, I don't know if you remember him, he was the founder of the National Institutes of Aging, convened a roundtable and I had been practicing what was going into the rubric of anti-aging medicine at that time, hormone replacement

therapy, testosterone for men, and then growth hormone replacement therapy, and patients were doing well, feeling well. At the same time, the NIA was looking at studies, looking at biomarkers of aging to see whether there was any way to measure whether or not these therapies were being effective and he invited me to a roundtable with a number of relatively illustrious gerontologists and it was sort of like being invited as a sacrificial lamb to this thing where they were going to tell me, "Why are you doing this stuff? You're killing these patients."

Dr. Joseph Raffaele:

What came out of it really was, it wasn't quite as bad as that but when he said, "Look, you're a smart guy, Joe. What you're doing seems to be helping your patients, they feel well, but how do you know if you're actually ... You're calling yourself an anti-aging doctor. How do you know if you're actually altering the aging process," and a little light went off in my head. I'd been doing this for about four years and I thought I was doing pretty good stuff for my patients, but that started me on this journey of looking at the literature for what was available to measure how people age and whether or not we could see whether these things that we were doing for them are actually altering their aging process in either a good or a bad way and that's been one of my passions since then and I thank Bob, who has since passed away, for getting me started on that because it's a fascinating tool.

Dr. Joseph Raffaele:

There's so much literature out there about it in one of the areas, and later, probably about close to-

Dr. Kent Holtorf:

Yeah, I can't see standard medicine moving very fast in this area. I think it's about acute. But just a little formal stuff about Dr. Raffaele. He received his B.A. in philosophy, very nice, from Princeton, no doubt. His M.D. from Drexler University Medical Center. He trained at the The New York Hospital/Cornell University Medical Center and was formerly a clinical assistant professor of medicine at Dartmouth Medical School while he practiced at the Hitchcock Clinic. He's a member of the Endocrine Society, is board certified in internal medicine, and is a diplomat of the American Board of AntiAging Medicine.

Dr. Kent Holtorf:

Are you an endocrinologist or no?

Dr. Joseph Raffaele:

No. I do a lot of endocrinology, but I'm not an endocrinologist.

Dr. Kent Holtorf:

Yeah. Yeah. I'm a member of the Society, but I stopped going to their conferences because it's the same stuff over and over. It's just like they're arguing the same points that they were fifteen years ago.

Dr. Joseph Raffaele:

I would agree with you. I went from between 1995 and 2015. I went to virtually every major meeting, every annual meeting, but I think that ... And there's a lot of good science that takes place there, but they're stuck in not thinking about optimization but about disease and that's really not what we're about. Biological variables are continuous. Testosterone of 301 is not different from a testosterone of 299. Your cut off is 300.

Dr. Kent Holtorf:

Yeah. They're still arguing what the TSH normal should be, even though with all its flaws. I went because the top guy in terms of thyroid replacement and pregnancy was there and I said, "I can't find a study that says that T3 crosses the placenta." He goes, "I don't know. Do you know?" Which we know it does, because we have people on straight T3 that have great babies, but anyways.

Dr. Kent Holtorf:

Some more about Dr. Raffaele. In 1997, he co-founded the PhysioAge Medical Group, where he exclusively practices age management medicine with a focus on personalized hormone optimization, physiological age assessment. In 2007, he co-founded the PhysioAge systems, a web-based biomarker data collection and reporting system now used by age management functional medicine practices around the world to assess, monitor, and communicate to patients effectiveness of their treatment. So we'll get into that about really testing people's age, not just giving them this, "Oh, it's good for you." You can take ten thousand supplements that people say are good for you.

Dr. Kent Holtorf:

Since 2009, he's been involved in clinical telomerase biology research. He's published three studies on the effect of oral telomerase activators on normal aging adults. He has lectured nationally and internationally on the clinical application of telomerase biology. In 2015, he founded the Raffaele Medical Group and blogs written about telomerase biology and hormone

optimization and biomarkers of aging on raffaelmedical.com. R-A-F-F-A-E-L-E-M-E-D-I-C-A-L.com and PhysioAge.com, P-H-Y-S-I-O-A-G-E.com.

Dr. Kent Holtorf:

Well, again, welcome and can we kind of get into the meat here and pick your brain and share with our viewers and physicians and some of the intelligent lay public about all the stuff that you know and that you've been doing? So you've been practicing for like 25 years, kind of like me. It goes by so fast.

Dr. Joseph Raffaele:

It really does.

Dr. Kent Holtorf:

It's crazy. So you've been doing ... You've been focused on this age management stuff the whole time, or?

Dr. Joseph Raffaele:

Yeah. I mean ... Well, no. For five years, I practiced ... I've been practicing for thirty years, actually. For five years I practiced internal medicine, as you mentioned, in the Hitchcock system up in New Hampshire when I moved up there right after residency and sort of got my doctor legs taking care of acute MIs and pneumonia and all the things you do in a primary care/internal medicine practice while I was also on assistant clinical faculty. At the end of the five years, I had kind of aging parents. My parents were a little older when they had me so they were starting to age significantly and I sort of wondered what I could do to help them to age better and that started me thinking that, "You know what? This isn't really the thing to do, is putting bandaids on all these things, waiting for the diseases to occur," so that really made me sort of open up a practice, moved back down to New York City and opened up a practice looking at how to slow down the aging process and keep people as healthy as long as possible.

Dr. Kent Holtorf:

Interesting. And just a side note. Have you found sometimes that these elite athletes who you think are the ultimate in health and they actually turn out to have higher biological ages than normal?

Dr. Joseph Raffaele:

Yeah, I see that. Absolutely. I mean, there is ... I hear about these people that do things like a

marathon a week or a marathon a week in like every state and they do fifty in a row, in fifty weeks. I'm like that's just not good for you. There are people who have some genetics that can get them through that but that's, in the end, just too much of a stress on the body and you see that kind of stuff. Exercise is great for you, to the extent that you got to allow yourself to recover. There's damage during the exercise and then recovery builds you back stronger. If you're breaking yourself down all the time, and this gets back into really into telomere biology where your stem cells have to replenish those degenerated tissues and if they're been asking to divide at a much higher rate because the damage is occurring at a higher rate, then at a certain point, telomeres get too short and they can't do it anymore.

Dr. Joseph Raffaele:

I think that it's ... I absolutely see that kind of stuff. A guy will come in and while his cardio age, a way we measure their central arterial pressure and give them an age for how healthy the elasticity of their arteries is, might be great something like their immune function or their telomere length won't be as good because they're putting a lot of stress on their body with training. And it varies. Some people have, and we'll talk about the inheritability of telomeres, some people have a lot more reserve. They have more money in the bank and they can get away with that, and other don't, and there's a wide variability in what you inherit in terms of your telomere length. So giving them that kind of information is really actionable.

Dr. Kent Holtorf:

Yeah. I imagine it's almost harder to have them reduce their exercise than people to get them to exercise.

Dr. Kent Holtorf:

So it does, it seems like ... It makes sense that they become like a chronic illness, if it's just constantly under stress and breaking down.

Dr. Joseph Raffaele:

Yeah, absolutely.

Dr. Kent Holtorf:

So in terms of telomere biology, how long have you been really ... You've published on that and what's your thought on telomere versus other methods. I know you used a lot of things, which is the way to go and that's the way we assess a sick patient [inaudible 00:10:28], we love to get a ton

of labs and it paints a picture. No one marker can just lead you astray. "Oh you're fine. This is good." I can totally see that and I can see where your software program could be a big benefit, too.

Dr. Joseph Raffaele:

Yeah, so it really ... When I first started looking at biomarkers and I think when the NIA and other people, gerontologists, started looking, they were looking for a single biomarker that could encompass the aging process en toto and sort of predict who was going to die younger or older based on this biomarker and in fact, the NIA, after ten years of looking for that in identical strains of mice, said they couldn't find one like that and I think they were just setting the bar too high. Since then, what you see is the newest kid on the block coming out and then they say, "Well, okay. It's telomere biology so you want to measure telomere length," and then the epigenetic age people come in and they say, "No, this is more correlated with age and so telomere biology doesn't make any difference," and then you see the proteome people coming in or the microbiome people coming in and the truth is they all give information that's important and is useful, as you say, in painting a picture of what's going on.

Dr. Joseph Raffaele:

I think what's really happening is that we're understanding, for aging in particular, that systems biology is what has to be applied and that means looking at multiple markers in multiple systems from many different angles and then applying deep learning, artificial intelligence, to it to try to really understand what's happening and to think that a single biomarker is going to tell you what's going to happen and who's going to have ... Who's going to die at a certain time much less what state of health they're going to be in between now and then is, I think, kind of silly really when you think about how complex the human body is and how it ages.

Dr. Joseph Raffaele:

I got introduced ... We were all doing hormone optimization, we had the big pickup of the Women's Health Initiative that then actually was very good for my practice because all the misinformation out there, so I was helping women sort of navigate that for a long time.

Dr. Kent Holtorf:

That was the biggest disaster, poorly designed-

Dr. Joseph Raffaele:

Yeah, it cost ... I think there's estimate that it caused fifty thousands deaths of women from

cardiovascular disease for not being put on hormone replacement therapy. It was, and it even lingers today, which is just insane because it's been -

Dr. Kent Holtorf:

We hear it all the time [crosstalk 00:12:53] looking at breast cancer.

Dr. Joseph Raffaele:

Exactly. So where was I going with it? So I just started to get into telomere biology when I was introduced to it by Noel Patton, the founder of T.A. Sciences. He came to my practice and said, "What would it take for you to sort of recommend this to your patients?" I said, "Look, I'm an evidence based doctor. I have these biomarkers of aging. The biology is fascinating and I think the telomeres subsequently have" ... They're one of the four major hallmarks of aging. There's nine of them and it's one of the top four. So I said, "Look, if you're willing to have patients come through and get all the biomarkers, we'll track them for a year and see what happens with them," and that's what we did and that was the beginning of the first publication that we had for T.A. Sciences and the effect of the telomerase activator, TA-65.

Dr. Joseph Raffaele:

So that got me started in looking at the biomarkers, seeing what one agent that has pleiotropic effects, because it affects stem cells and the immune system, what that has on the rest of the body and so I got started down the path that way.

Dr. Kent Holtorf:

Nice. Nice. And so you mentioned kind of nine hallmarks of aging. Can you talk more about that?

Dr. Joseph Raffaele:

Yeah. So that ... I think aging, the aging field, has been ... I think at one point, there was papers published that there's maybe 200 different theories of aging. I don't know if you remember Warren Dean was one of the fathers of this back in the late 80s, early 90s, and everyone was trying to figure out what exactly was going on with the aging process. Is there a single underlying aging process? In 2013, I believe, there was a paper published by Lopez-Otin and Maria Blasco and other people that are major figures in the field which had been predated a little bit by [Aubrey Degray's 00:14:59] paper about hallmarks of aging as well, but I think that the field now, the sort of gerontology field, agrees that there are sort of nine major hallmarks of aging : genomic instability, telomere attrition, epigenetic aging-

Dr. Kent Holtorf:

Can you go slower on that?

Dr. Joseph Raffaele:

Okay, yeah. So the nine ... Maybe we go through all of them right now. The top four ... The first one is genomic instability. That is ... We all know what happens. The genome gets attacked by free radicals and copying is ... There's ten thousand hits per day to the DNA in every cell and that's Denham Harman's sort of free radical theory of aging kind of thing.

Dr. Joseph Raffaele:

Then there is telomere attrition, because telomeres are what allow cells to divide. We know ... Remember the Hayflick Limit? There is telomere attrition occurs because the cells can't continuously divide forever. Up until 1961, most biologists believed that cells could divide indefinitely in vitro and in the body and Dr. Hayflick showed that no, that's not the case. Those little cells flipping in the medium into the Petri dishes that they were doing these things in, that's why they were able to continue propagating. So eventually they figured out that the clock for this Hayflick Limit was the telomere. So telomere attrition is a key component.

Dr. Joseph Raffaele:

Epigenetic alterations are the next one, which occurs when the DNA methylation changes and then the access to DNA changes, so your gene expression changes. Michael Fossil, who is one of the smarter guys that I know, is one of the preeminent telomere biologists, likes to talk about the fact that the genes in your nose are the same as the genes in your toes, but what makes a toe a toe and a nose a nose? It's gene expression and so obviously gene expression changes during development, but the same gene expression takes place, changes during aging. Steve Horvath has shown in his elegant series of studies that in fact it's so tightly, when you look at it, certain CPGs is so tightly correlated with age that you can use it in forensics almost to figure out what the age is.

Dr. Kent Holtorf:

That is a very interesting point. It's because you do have the same genes everywhere, but all the different parts are doing different things and basically epigenetics and that's where a lot of peptides will show. They'll turn on 45 genes and turn off 26 genes that they know of, and a lot of things work very ... Flavonoids, you know, they love. But keep going.

Dr. Joseph Raffaele:

Yeah, I mean, so that's I think ... The same thing that takes place during development takes place in aging and so there's an aging ... A youthful gene expression and there's a more aged and then there's an old gene expression and that shows that there is malleability to the aging process if you can turn it back. And there was a early study, a recent study, looking at turning back the epigenetic clock with growth hormone, DHEA, and metformin, the TRIM trial. So I think that ... obviously, gene expression is a major hallmark for aging.

Dr. Kent Holtorf:

Question for you just about growth hormones. Anti aging people use growth hormone, shown to help ... No study has shown that giving growth hormone causes cancer, which everyone brings up, but the longest lived people seem to have low IGF1. How do you reconcile that?

Dr. Joseph Raffaele:

Yeah, that's a very complex area. I think that if you talk to, and those are very good points. There's a little bit of a trade off between function and performance and potentially aging and some of these ... The old, old that they study and it shows some of them have lower IGF1, I don't necessarily don't want to be like that when I'm that age. I mean, I think that the animal models that they look at where IGF1 and growth hormone is way over-expressed, these transgenic mice, we know what happens when you have way too much growth hormone. That's acromegaly. Those people don't live long. They get big hearts, big jaws, they have other issues. So we don't want that. The real study that-

Dr. Kent Holtorf:

No one's rich enough to have that happen to them.

Dr. Joseph Raffaele:

Right. Exactly. You need a lot of growth hormone to have that, and you don't want that. But then they do look at these studies in the mouse models and they say that IGF1 turns up, is a pro-aging form. It's also a pro-performance. We know that higher levels of IGF1 are associated with better levels of cognition, so the question is, in the aging adult is keeping growth hormone and IGF1 levels in the more youthful physiologic range in the aggregate beneficial? There's no study that speaks to that. The NIA did short term studies, and there wasn't any increased risk of cancer.

You're not going to see that in a year long study. There was some improvement in lean body mass, but there wasn't long enough to know whether overall it's going to affect the aging process.

Dr. Joseph Raffaele:

One of the reasons growth hormone is approved for long term therapy in growth hormone deficient adults is because of the two to three fold increase risk of cardiovascular disease that you have if you are ... If you have a very low IGF1 for a long time. So the growth hormone story and IGF1 story in aging is just another sort of evidence that you have to look at the whole picture. You have to look at-

Dr. Kent Holtorf:

And plus, look at all the studies in sick patients and aging when you look at even involution of the thymus. Everyone has hypothalamic pituitary dysfunction so really in the modern world, toxins, pesticides, stress, chronic infections, all the gut dysbiosis, is going to suppress that. We have now kids coming in at 25 and their testosterone level is like 200, which is that of a 90 year old. Growth hormone is super low, so how can that be healthy?

Dr. Joseph Raffaele:

It's not. If you look at them, and I've been treating patients with growth hormone for, like I said, 25 years, and you have to look at each patient individually and you have to say, "Look, okay, if your IGF1 is below 150 and you're having trouble with abdominal fat even though you're exercising, giving growth hormone fixes the abdominal fat, brings the IGF1 up," then you set into motion a whole bunch of beneficial things. The insulin resistance reduces. So it's gotten a lot of hype, both in the negative and in the positive and the truth is it's just another one of the hormones that's important. Not everybody needs it. Some people do, some people don't, and that's the way I practice.

Dr. Kent Holtorf:

The problem, too, is you look at reference ranges. So they'll take 95% of the people, take testosterone for instance. It's like you have decade ago ranges were higher and decade before that they were higher, so now it's like they let, especially with growth hormone, the lower limit of normal is like a person seems like they're going to be dead, and it's crazy.

Dr. Joseph Raffaele:

Yeah, so to sort of bring it back to telomeres, growth hormone is important because what it does in muscles. It stimulates muscle satellite cells which are the stem cells in muscles to divide, which

then can be worked on by testosterone to get bigger for ... If you have hyperplasia and hypertrophy. But if you're stimulating the muscle stem cells to divide more rapidly with growth hormone, you got to make sure they got telomeres that can do that. So that's what I think that telomere biology dovetails very nicely with hormone optimization and knowing whether or not someone has adequate telomere reserve to be able to take the increased stimulation for cell division that the hormones give you is important. I haven't done this study, but a hypothesis is that perhaps some of the risk, which in aggregate is either none or very, very little of increased risk of breast cancer, may be localized in those woman who have very short telomeres, because very short telomeres are unequivocally associated with increased risk of cancer of many different kinds, epithelial cancers.

Dr. Joseph Raffaele:

So that's why I, now, when I measure telomere length in all my patients and I want to know what's happening because if the telomere lengths get too short, the cells then they get genomic instability and they become much more likely to become cancerous cells.

Dr. Kent Holtorf:

Interesting. BPC157 actually increases growth hormone receptors in the cell. Now in terms of telomeres, what's more important, the average length or the percent of short telomeres? Can you discuss that?

Dr. Joseph Raffaele:

Yeah, that's a great question. The vast majority of the data on telomere length and health and disease is using mean telomere length. So that's still a useful measure for looking at where somebody is. But it is pretty well established that it is the critically shortest telomere within the cell that causes the cell to become senescent or to go into apoptosis and into crisis. You have ... It can be two or three short telomeres within the cell that causes that and we know that telomeres preferentially goes and tries to lengthen telomeres that are shorter. In the actual biology of telomere length, it is the critically short ones.

Dr. Joseph Raffaele:

You have to remember when we're measuring telomere length in blood, we're measuring telomere length in the white blood cells and depending on the technology, PBM or if you're using the technology that I use, we can break it down to the granulocytes and lymphocytes. That's a surrogate marker for what's going on in other tissues and there's concordance between what's happening in the white blood cells and what's happening in other tissues that's been studied, but you want to look at the data which shows that ... I think that looking at the average telomere

length does help you know whether or not a person's at risk and also whether or not the telomerase activator is working. There isn't a really good commercially available short telomere assay. LifeLength does have ... They give a 20%, but that's really more correlated with the mean telomere length than it is with the critically short telomere lengths which are under three kilobases.

Dr. Joseph Raffaele:

Just to give you sort of an idea, for your listeners, telomere length by what we call flow FISH is usually somewhere between eight and twelve kilobases, or eight thousand to twelve thousand base pairs in length at birth, and then you rapidly lose some during the growth phase, and then after that it's 0.05 kilobases or 50 base pairs per year. So that is kind of just sort of an idea about where you are with telomere length when you're measuring.

Dr. Kent Holtorf:

And you kind of answered the question. I was going to ask you, you're checking telomeres in white cells. What's going on with whatever, think of all the different cells in the brain, heart, whatever. They tend to correlate, is that ... Have there been studies on that?

Dr. Joseph Raffaele:

Limited studies, not as extensive as you'd like, but as you can imagine it's not easy to get biopsies of liver and lung and brain, but the studies that have been done show that there is pretty good concordance. The reason for that is because one of the major determinates of your telomere length in all your tissues is what you inherited from your parents, and so that's about 70%. That's a very highly inheritable trait, which we call a telotype. So when it comes to telomeres, lifestyle is very important and everything else you're doing, but you really want to choose your parents wisely. That's really what happens there.

Dr. Joseph Raffaele:

The difference between eight kilobases and twelve kilobases of telomere length inheritance is about equivalent to the amount of loss that occurs between young adulthood and death. So if you start at eight, you're pretty far along as compared to somebody who starts out at twelve. And that's why people have quibbled about whether or not telomere length is a useful biomarker of aging, because a seventy year old can have the same telomere length as a forty year old and so why is that useful? Well, it's useful because we still know that once you get down to a certain telomere length, all hell breaks loose and that's below five kilobases so it's a matter of what you inherited and then what's your attrition length because you can't change what you inherited but you can change the attrition length. And that's why telomere length is so interesting is that pretty

much every healthy behavior from lifestyle to exercise to diet to supplements, et cetera has been shown to slow down telomere length loss. And pretty much everything that you do is bad, smoking, being overweight, not exercising, all those things are associated with shorter telomere and so it's kind of an integrator of many different of what we call allostatic load on the body.

Dr. Joseph Raffaele:

So if you're doing all the good things that are healthy, you might have a slower attrition but if you start out with really short telomeres, it's still going to be a problem. You could have a healthy person, and I have people that do everything right and I see that, because I track them over time, they're not using telomere length at a very but they didn't start out with very good telomere lengths and so they have to be more careful. Don't smoke. It's very behavior modifying, as well. When you tell somebody that, "Your telomeres, you're forty and they're more like a fifty or sixty year old," then they're more likely to be more proactive about healthy behaviors because they know that their 401k, I like to call it the biological 401k or their biological IRA, is just not as full for their retirement for health aging as they get older.

Dr. Kent Holtorf:

And does sleep affect telomere length?

Dr. Joseph Raffaele:

Yup, it does. The same way in which ... I mean, I would say it's not a good biomarker of aging if sleeping doesn't affect it, so epigenetic aging, DNA methylation has shown to be highly affected by poor sleep because that's when your body gets into reparative state and fixes things. It's definitely associated-

Dr. Kent Holtorf:

I'm like, "Do as I say and not as I do," and I know I stayed up all night to get projects done. That's when I work well, and I feel like it's aging me and studies on night shift workers and telomere, is there anything like that?

Dr. Joseph Raffaele:

Yeah, they're shorter and also night shift and of course it would make sense that night shift workers have increased risk of cardiovascular disease and cancer and it's probably not solely because of their telomere length, but there's other things that occur. Vitamin D is associated with telomere and so if you're a night shift worker, you're probably not getting as much Vitamin D and

your Vitamin D level's low. It's really a very good integrator of many different things but also with the caveat that it depends on what you inherited. One telomere length measurement gives you some information, particularly if it's very short and also if it's very long, but what really gives you information is serial measurement over time.

Dr. Kent Holtorf:

You want to see where you're going.

Dr. Joseph Raffaele:

Yeah. Where you're going.

Dr. Kent Holtorf:

So how much of an increase can you see with TA-65 over what period of time or with other interventions, with some of your major things, say it's the number one thing. I guess it matters what also people are doing, like what's the worst thing they're doing, but like let's say we give someone TA-65. When do you recheck and what type of response have you seen?

Dr. Joseph Raffaele:

Yeah, so let me start with the clinical studies that we have. In the cohort study that I mentioned, we didn't see an actual increase in telomere length, but we saw also some improvements in immune system function and reductions in senescent T cells which we think had to do with perhaps decreasing the number of shorter telomeres within the cell, but that spurred the company on to do a randomized control trial looking at the effect of TA-65 in CMV positive patients and we found that there was a 533 base pair increase after a year of TA-65, so that's a pretty big one. Now, that was using the technology where the average telomere length is about 40% longer using that technology, so we have to take that 533 and make it more like about 300 base pairs, or 0.3, which is still quite significant increase and it was highly statistically significant in comparison to placebo which lost telomere length which of course you would consider. So we do have randomized control trial data showing that there is an increase in telomere length with TA-65 at the doses that are normally used, 250 IUs to 500 IUs.

Dr. Joseph Raffaele:

In my practice, I have seen patients have actual increase in telomere length over time, going up as much as half a kilobase, or 500 base pairs, over a couple of years. What I see most often is that the loss stops and you get ... I myself have had telomere length of about 6.4 kilobases for the last 13 years, which is I would expect over that time period to have lost about 0.8 kilobases and gone

down to below five. If you can maintain telomere length, as I said it's when they get critically short that it's a problem, then that really is quite good. It's just like a coronary calcium score. You don't want to have a coronary calcium score too high, but if it stays at 200 or 400, you're unlikely to have a coronary event [crosstalk 00:33:59]

Dr. Kent Holtorf:

And do they do CMV infected patients, kind of speed up the aging, the telomere loss, so you can get a better ... So they can do a shorter study and not wait twenty years?

Dr. Joseph Raffaele:

Yeah, so the reason ... CMV is a whole nother fascinating thing that there's whole conferences that are convened on CMV. Just for everybody that knows, CMV is Herpes virus 5 and immunocompetent individuals, most doctors are like, "It's not going to do anything to you. Don't worry about it," and about 60% of the U.S. population is CMV sero positive and it goes up 1% per year starting at ten years of age, so by the time we're in the eighth or ninth decade, it's virtually 90% to 100% CMV positivity.

Dr. Kent Holtorf:

That's doesn't mean active, right?

Dr. Joseph Raffaele:

Well, so that's the interesting thing. As with all herpes viruses, they sit latent. It's the gift that keeps on giving. It doesn't ever go away. To the extent that there are reactivations, there's a problem. So when you get a cold sore that comes out, that's Herpes virus 1, you feel systemically kind of crummy. It's not just the cold sore, because there's a whole reactivation of it, and that makes your immune system have to rev up to then make it latent again. That causes your white cells to have to divide more, your lymphocytes to have to divide more, and that shortens your telomeres.

Dr. Joseph Raffaele:

Same thing happens with CMV except when those reactivations occur, there's no real symptoms. You might feel a little crummy, you may be a little something, but most people don't have any idea that they're having a reactivation. If that occurs over and over and over again, that accelerates telomere loss, increases the accumulation of senescent T cells which we know are bad for you because they secrete what's called the senescence associated secretory phenotype, all these

inflammatory markers like IL6, TNF alpha. They reduce their production of interferon gamma to fight off viruses. So it increases and causes this state of what we call inflamagging.

Dr. Joseph Raffaele:

So CMV, even in an immuno-competent adult, causes over time an acceleration an aging of your immune system and we think most other tissues in your body as well. There might have been some benefit to it in our ancestral environment because it allowed us to potentially have a more robust immune response to pathogens and nobody lived long enough to have the adverse effects, something called antagonistic pleiotropy where something is good for you when you're young but may have other adverse effects when you get older. That's true of CMV.

Dr. Joseph Raffaele:

We chose CMV for that trial because there isn't more acceleration of loss of telomere length in them and because we saw in our cohort that a lot of benefit was in the individuals that were CMV positive within that cohort.

Dr. Joseph Raffaele:

So subsequently there is a trial that is pending right now, submitted to OBM Geriatrics to look at the effect of TA-65 of senescent T cells and that's in both CMV positive and CMV negative that we see a beneficial effect whether you're CMV positive or CMV negative.

Dr. Kent Holtorf:

Yeah, because I rarely see anyone, and ... what tests these? Can you see IGG and they don't make even a reactivate. IGM is not a new infection and the PCRs from standard labs are so insensitive. It's like HHV6, Montoya showed a little bit of a good study where the reference range is like one to twenty but really a positive is like twelve hundred because that doesn't mean it's reactivated but it's more likely the higher it is. Is that what they did, or do they do a PCR, or what do they do?

Dr. Joseph Raffaele:

For looking at?

Dr. Kent Holtorf:

The CMV.

Dr. Joseph Raffaele:

No, it's just whether you're CMV positive or negative.

Dr. Kent Holtorf:

Okay.

Dr. Joseph Raffaele:

We didn't look at the titer. What you're talking about is the titers and yes, those actually in CMV, the higher titer you have, the more you have senescent T cells because there's more reactivations taking place. I think that CMV is not unique but is probably the most immuno-competent in terms of stressing your immune system but pretty much anything that causes you to have to mount a response, intracellular pathogens like Lyme and the [inaudible 00:38:28] and the things that you're mentioning, I have patients that come in that are being treated by Lyme doctors for chronic Lyme and their telomeres are shorter and what's interesting is there's something called the lymphocyte, the granulocyte telomere length gap. So granulocytes, which are neutrophils, come from the bone marrow, circulate for a day and then are gone. The telomeres ... They don't divide again and telomeres don't get any shorter. They are a good reflection of your bone marrow stem cell telomere length and your inherited telomere length.

Dr. Joseph Raffaele:

The lymphocytes, however, as you know, fight off ... They're released from bone marrow and then fight off the infection, the tumor that they need to fight off and then memory cells are left behind and if they're challenged again then they come out again and that's what's happening with CMV, that's what's happening with other herpes viruses and that's what happening with other chronic infections. So any time you have a chronic infection that is asking the immune system to keep it at bay, you are going to cause telomere attrition and in fact a nice study was done looking at the number of herpes viruses that you have in addition to CMV. From one through four, EBV, HSV2, HHV6 which I think is a big immune stressor and I know you work with that in chronic fatigue, the more they have the much shorter, the much faster the telomere attrition is. So there's a slope that's relatively shallow, about the 0.05 kilobases, for one herpes virus infection. It gets steeper for two, even steeper for four, and four it's very steep. So it's like a 50% steeper slope.

Dr. Joseph Raffaele:

You want to try to avoid these things, so I tell patients, "The way we're treating COVID right now, you should try to keep other pathogens away from you. When you're young and you're trying to teach your immune system, maybe getting a few things to help tolerance, but when you're older, you want to stay away from these things."

Dr. Kent Holtorf:

Yeah, and even like HHV1, herpes virus 1, okay you got a cold sore, but they find it travels up the nerves into the brain and associated with Alzheimer's. So these things are not benign, you know?

Dr. Joseph Raffaele:

They are not. That's a nice series of studies that I think is just starting to get the recognition that it should get, that HSV1, or human herpes virus 1, is a bad actor for risking of Alzheimer's disease.

Dr. Kent Holtorf:

Yeah, everyone's chronically infected and I think it's so much higher than twenty years ago. Now I can't go to a party where, "I'm so sick or my brother's so sick or family." We didn't hear that twenty years ago. Everyone has this chronic illnesses that standard medicine just doesn't know what to do with and everyone's immune system is shot.

Dr. Joseph Raffaele:

Yeah, and that's where some of the peptide therapies that you talk about, thymosin 1 Alpha and that kind of stuff, and I think even potential growth hormone, which can rejuvenate the thymus in some smaller studies. The focus, when you're talking about these chronic immune stressors, should be on the host, on shoring up their defenses through immune system rejuvenation and then through maintaining telomere lengths so the cells can continue to divide because once they become senescent they can't do their job and not only can they not do their job, I kind of liken them to an old watchdog which not only doesn't go after the burglar but bites the owner and snarling all the time, causing problems. So I think that keeping your immune system youthful is I think, not only for fighting off infections and cancers, but also for chronic degenerative diseases like osteoporosis, cardiovascular disease and Alzheimer's because of the reduction in inflammation.

Dr. Joseph Raffaele:

I follow C-reactive protein in everybody, IL6 in everybody. People that have a lot of inflammation-

Dr. Kent Holtorf:

You have a good lab for IL6?

Dr. Joseph Raffaele:

Yeah. I mean, Quest does a good job. LabCorp, they have a good assay for that.

Dr. Kent Holtorf:

We find that ... I think it matters the draw station, how they hold it and a lot of these key tasks, they'll come out zero-

Dr. Joseph Raffaele:

Oh, really?

Dr. Kent Holtorf:

And they hold them, they're supposed to be frozen or whatever immediately and they're sitting out. We find that's a big problem, but yeah, FDA is coming after Thymosin Alpha-1 because people are using it for COVID and studies are great on COVID and it's reversing COVID but God forbid, they don't want that and so they're coming after it.

Dr. Joseph Raffaele:

Yeah. Well, you can't make those problems, that's the problem, without going through the trials. But we know, treating patients, and we're allowed to do off-label stuff, that things works. That's how medicine progresses, through doctors treating patients and you have to look at the risk/benefit equation. What's the risk/benefit equation here? We know it's highly in favor of benefit because the risk is so low.

Dr. Kent Holtorf:

Yeah, yeah. That's the same thing with COVID. Why aren't we giving everyone Vitamin D and zinc and Vitamin C and flavonoid, even Ivermectin, even hydroxychloroquine. Oh no, the black helicopters are coming after me. We don't even need the vaccine. No one should be dying from COVID. The hospitals aren't giving people anything. A study just showing people on ventilator, they gave them half Vitamin D, 5% mortality. The other half without it, 50%. There's no downside.

Dr. Joseph Raffaele:

Yeah, and that all speaks to ... Look, I just did a talk for the Institute of Functional Medicine on the biorome, telomere biology and the effect, what you need to do is to shore up the host because COVID has shown us that the age association of COVID is so strong that it's the aging process and the debilitated host that's the problem and the cytokine storm coming the senescent associated secretory phenotype, but the fact that it happens to younger people is the really interesting thing and what markers of risk are there? I believe that, and other authors that are in telomere biology,

that probably these people have short telomeres. These younger people that are getting really sick, they have either short telomeres or they have much higher accumulation of senescent T cells and it may be that that's what's putting them at risk. Now we don't have the data fro that, but we're looking for it.

Dr. Kent Holtorf:

I bet you're right on that.

Dr. Joseph Raffaele:

Physiology works out.

Dr. Kent Holtorf:

I would bet a lot that you're correct. Is there a racial difference in telomere length?

Dr. Joseph Raffaele:

There is in ... African Americans have slightly longer telomeres, but that's the only major one, but then on top of that there is the senescent T cell stuff comes in because there's a higher incidence in CMV in non-white ethnic populations in the United States and so that stresses the inheritance that they got and over time, I think their risk increases.

Dr. Kent Holtorf:

It becomes so difficult to ... So many of these people. "Oh, these people are this," but why is the real reason, you know?

Dr. Kent Holtorf:

So there's other things like DNA methylation, proteomics. What's your thoughts on those?

Dr. Joseph Raffaele:

So just going back to the biomarkers, the hallmarks of aging, the mitochondrial dysfunction. It's all linked. What I found fascinating when a paper came out in 2011 which looked at the effect of short telomeres on mitochondrial biogenesis and mitochondrial efficiency and it's through that master regulators that PCG1 Alpha and Beta, they are turned down when telomeres get short so that you get less mitochondrial biogenesis. So keeping the telomeres longer helps your mitochondrial and vice verse because having efficient mitochondria decreases reactive oxygen species which then don't attack telomeres as much. So diving cells lose about 100 base pairs per year, but then while you're dividing, if you have a lot of oxidative stress ... Telomere, which I didn't

say for the audience, is TTA GGG. TTA GGG. It's a repeat of those six nucleotides. The GGG is very susceptible to free radical damage. You maybe use in your practice, or have heard of, the DNA damage test which looks at 8 hydroxy 2 deoxyguanosine in the urine, that's those base pairs getting repaired because they've been attacked in the DNA and end up in your urine as a good measure of it.

Dr. Joseph Raffaele:

It's all ... What I like about where the field has gone is we now have a sort of a unified ... The equivalent in physics of a unified field theory in aging where we're really starting to put all the pieces together. It's not just this or just that. It's like the free radical damage affects telomeres. That affects epigenetic DNA methylation and then we're just learning. It's all coming together and it's a really fascinating field.

Dr. Joseph Raffaele:

Then we have other hallmarks of aging. Cellular senescence, stem cell exhaustion, and the list goes on of all these things that you look at as the major things and I actually ... In my practice, I target the hallmarks of aging. I look at ways to measure them. We have DNA methylation, we have telomere length, we have ways to look at DNA damage, we can look at senescent T cells, and I focus my therapies on certain things like flavonols can have a beneficial effect, hormone replacement therapy can have another kind of effect, to try to make your hallmarks of aging as healthy as possible and then put it all together. That's at the molecular level.

Dr. Joseph Raffaele:

Then you look at things like arterial stiffness, pulmonary function. These are tried and true biomarkers that are hard end points for mortality and cardiovascular disease. Most people don't know that FEV1 ... They know it's associated with age, but they don't know that it predicts mortality 25 years later from all causes, not just pulmonary and respiratory causes. If you have a lower FEV1 relative to others in your age group. So looking at all these different biomarkers, we get a feeling for what's happening to the aging process and things like TA-65 which helps keep telomeres longer has affects in pretty much every system. I haven't talked about cardiovascular disease. There's a trial going on right now in the UK looking at the effect of TA-65 on senescent T cells in people who have had a MI and whether or not through reducing senescent T cells and the inflammatory response of key regulatory cells, will we have a reduction in repeat MIs, because we think that, and there's very good data showing that short telomeres are associated with cardiovascular disease as well.

Dr. Joseph Raffaele:

So that's what I like about it, is that you're fixing many things when you're fixing the telomere length. We all know the power of hormones. I mean, postmenopausal woman comes in and you fix her hormones and she feels 100% different and very gratifying kind of medicine.

Dr. Kent Holtorf:

Oh, I'm sure you can, and I don't want to offend anyone, but a woman who's not on estrogen, you can pick them out like-

Dr. Joseph Raffaele:

Yeah, I've been doing it for 25 years and I have patients that have been going along and they tell me, "My girlfriends are saying they're looking different and feeling different," from me, but then you want to make sure that their telomere lengths aren't getting shorter so you want to optimize all aspects of the aging process.

Dr. Kent Holtorf:

That's great. And you have a test, can test for mitochondrial dysfunction?

Dr. Joseph Raffaele:

I don't really have a great one right now. I think that your View2Max might be a beneficial one to a certain extent, but a lot of that is built in in genetics. I've been looking for one, and if anybody-

Dr. Kent Holtorf:

Yeah, I've been looking for a long time. There was the MitoSwab, but I don't think it ... Yeah.

Dr. Joseph Raffaele:

It's pretty hard.

Dr. Kent Holtorf:

Yeah. Well, we'll check people's basal metabolic rate, which correlates they don't have mitochondrial function, but so many diseases are associated with mitochondrial dysfunction.

Dr. Joseph Raffaele:

Sure. Sure.

Dr. Kent Holtorf:

Most everything. Aging especially. Then let's see. What was my other? Oh, EMFs. Do you know anything about EMFs and telomeres?

Dr. Joseph Raffaele:

You know, I don't. I've looked for data on that and off the top of my head right now, I can't tell you that I found anything, but one would think that there's ... I mean, look. Low level EMF could be beneficial, potentially, as some people would use therapeutically. Let me get my screen opened up again. I don't have any-

Dr. Kent Holtorf:

Yeah. The problem is showing ... I started looking into it, very skeptical, like, "Oh, it's got to be safe," and dramatic increase in IL6 and they activate the calcium voltage gated channels, but calcium-

Dr. Joseph Raffaele:

This is in vivo, in vitro, though, right?

Dr. Kent Holtorf:

Both, and then also ... One study they put just a cellphone in a middle of a box of rats for nine days and then they sacrifice them. They got hippocampal degeneration. It's crazy. I'm worried. The more you dig into it, the more you're like, "Oh, my God," but that's a whole other topic.

Dr. Kent Holtorf:

What are some pearls? What are your favorite treatments? I know TA-65, of course. Other things? What are your top five things?

Dr. Joseph Raffaele:

I mean, for me in my practice, I do a lot of hormone optimization. I don't think that people without sort of more optimal hormones are going to enjoy life as much as people that do have optimal hormone levels. I mean, I do use TA-65 a lot. I have a whole pack of supplements that I think ... The omega-3 fatty acids I think are very, very important. There's a lot more coming out on that, particularly in Alzheimer's disease and then the plasmalogens, which you may have seen some of that work that's been done where by you're looking at APOE genotype and risk being abrogated or almost completely mitigated by having good plasmalogen levels. So I try to ... I saw your Boston Heart up there in the corner. I do the Boston Heat Essential Fatty Acid Analysis and I have

everybody, when I get their omega-6 index in optimal range, so I use them ... If they don't get it through fish, I get it through the fish oil.

Dr. Kent Holtorf:

And the plasmalogens, I have some here. All I can say is that I've also heard they just get broken down in the gut.

Dr. Joseph Raffaele:

So plasmalogens do, but what you're seeing there is a precursor then that makes it through the gut and is used to plasmalogens. At least that's how it's been explained to me.

Dr. Joseph Raffaele:

I've done my first baseline, and I have to do the follow up ones to see whether or not it's effective, but I'm just ... That's an area just in general, fatty acids, I think, and plasmalogens are an area that I think is really up and coming for data supporting optimizing those levels for healthy aging and disease prevention.

Dr. Joseph Raffaele:

I would say ... We talked about senescence of the immune system. For people that can't necessarily send their stuff to UCLA where I send it for looking at naïve T cells and senescent T cells which are specific markers, CD95 and CD28. If you have a CD4 to CD8 ratio, which is available at Quest or LabCorp or any lab that does lymphocyte subset panel, if it's less than one there's a good body of data that shows, particularly in older individuals, those who are 80 and above and then even 60 and above, that they're starting to collect more senescent T cells because the denominator is the CD8s and it's the suppressor of cytotoxic T cells that get senescent, not necessarily the helper cells as much.

Dr. Joseph Raffaele:

So the top stays fairly stable, the CD4, but you get this accumulation. They don't die and go away and it's not because you have a healthy suppressor cells, you have an accumulation of them and if that gets below one, then you really want to look at ... I would then measure the telomere length in that patient and if they're not doing everything that you can do from a lifestyle standpoint, then do it. Quit smoking. Make sure, because they're at significant increased risk of disease and mortality when that ratio gets inverted. It's normally around two to two and a half, and when it gets below one, things get really pretty bad.

Dr. Kent Holtorf:

Yeah, because I'm thinking of a Lyme patient. You see their CD8s drop much more than their CD4s.

Dr. Joseph Raffaele:

Drop? No, it's ... The total CDA population?

Dr. Kent Holtorf:

Yeah.

Dr. Joseph Raffaele:

I'm not sure about ... That I kind of ... You sure? I'm not sure about that, because what would happen I would think is that you would increase the number of senescent T cells because the Lyme is trying to be fought off by that, and the patients that I have come in, I see ... I have a number of them, they have large accumulations of senescent T cells. Just to give you an idea, you typically have zero senescent T cells when you're born. Then they thought that you used to accumulate them with just the aging process, but it's really whether ... It's really your viral load and particularly CMV, that causes that and also other. We talked about other immune stressors.

Dr. Joseph Raffaele:

So I have patients that are in their sixties that have twenty, thirty senescent T cells on a measurement and then I have patients who have eight hundred and that's like 75% to 80% of their CD8 department is senescent and secreting all sorts of inflammatory-

Dr. Kent Holtorf:

And what kind of test do you use for that?

Dr. Joseph Raffaele:

Yes. So that's the CD28 negative is the senescent T cell that you can get at UCLA and you can get it through PhysioAge. You got to physioage.com and become a licencee. You can get it through that, or T.A. Sciences also offers that at tasciences.com to get the test through UCLA as well. But as I said, the one that can go through insurance and is less expensive is to just look at the CD4 to CD8 ratio and if it's under one, then you almost assuredly have a high accumulation of senescent T cells.

Dr. Kent Holtorf:

And how about CD16?

Dr. Joseph Raffaele:

You mean ... There's not a CD16. There's CD19, which is the B cell.

Dr. Kent Holtorf:

I remember, because I haven't done my labs in a long time and mine was just so slow when I was sick.

Dr. Joseph Raffaele:

Well, CD56, CD16 you're talking about for the natural killer cells. That's what you're talking about.

Dr. Kent Holtorf:

Yeah. Those numbers, CD56 or CD57, but anyways, it's one I also ... some of the immunosuppressants suppress for autoimmunity, but they tend to be really low in some patients. It's weird, it's a subset of patients.

Dr. Joseph Raffaele:

Yeah, I don't measure that one. We look at the natural killer cells, which is the CD56, CD16 positive and then we look at the CD4, CD8.

Dr. Kent Holtorf:

And did you measure function?

Dr. Joseph Raffaele:

No. It's the lymphocyte subsets because there's a very large body of data showing the association between those and autoimmune disorders and viral load, mortality. Functional assays would be interesting. There haven't been as many studies with those, but you get very good information in just looking at the markers on the-

Dr. Kent Holtorf:

And for instance, like natural killer cell function, it's a hallmark of chronic fatigue syndrome and Lyme, that are about 70% are low in natural killer cell function. About 30% are low in natural killer

cell number, so a lot of them [inaudible 00:59:27] and that's not working. The problem is that Quest does the function, and Quest is so difficult to deal with, they're all messed up. LabCorp, much easier to deal with, but I don't know. Their tests, a couple of their key tests that we like, Quest does a better job, but overall, Quest is a pain in the ass.

Dr. Joseph Raffaele:

Yeah, they've been going through a lot the last two years in trying to become a true national lab and they're just not there right yet.

Dr. Kent Holtorf:

Yeah. Yeah, I'd love to see someone else come online. Let's see. You wrote a number of papers on the TA-65, so imagine that's a core treatment. So hormones. You do thyroid, by the way? Do you?

Dr. Joseph Raffaele:

Oh, yeah. Yeah. Thyroids ... I mean, what you were talking about with getting women pregnant with T3, it's very gratifying when their fertility doctor is telling them, "Your thyroid tests are normal," and they've done three rounds and you get their T3 above 3.8 and all of a sudden they're pregnant. So I do a fair amount with thyroid. I find it to be-

Dr. Kent Holtorf:

Yeah. And that's like I spent most of my medical career convincing people that TSH is not reliable because all these sick patients, they get suppressed hypothalamic, pituitary, thyroid access and they're not making TSH but that's just the way. It's an easy test and a bit controversial. So I've been working on an assay that will show that, but working on it for fifteen years and I get to a certain point and something happens. So now I'm going to some big guys and see if I can get that done. Kind of prove that all these people with normal TSHs and they come in and normal TSH and we check their basal metabolic rate and it's super low and they're basically relaxation phase or their reflex is super low and their pulse is 50 and they're gaining weight like crazy and then you give them some thyroid and it suppresses TSH, it's like, "Oh, they're hypothyroid." Oh, they can't get out bed. Their pulse is 48 and they're freezing cold. Anyways, another thing. I mentioned thyroid has a lot so you can increase mitochondrial function and does so many things.

Dr. Joseph Raffaele:

Yeah, absolutely. I mean, it's just ... It needs to be optimized as well. Thyroid analogs have been looked at to lower cholesterol. I mean, we all know that cholesterol when you're hypothyroid and

patients that have good thyroid function, their cholesterol can come down quite significantly, so yeah, I mean-

Dr. Kent Holtorf:

Yeah, take the safest way and ... Or the Star Report. Largest study ever done on antidepressants showed that T3 was a better antidepressants than antidepressant with less side effect, but it didn't make the abstract because they didn't pay for part of the study.

Dr. Joseph Raffaele:

You have to deal with that in our field.

Dr. Kent Holtorf:

There's so much bias. That's basically driving me crazy.

Dr. Kent Holtorf:

But yeah, your whole program sounds very interesting and looking at all these things is, I think, the key to so many ways of approaching so many illnesses and I think that's the problem with modern medicine is you get sent to gastroenterologist for this, you get neurologist and you don't go until something's really bad and people say, "Oh, I can't. Out of network. Da da da." And how much is it worth to not be in a nursing home for twenty years? Living longer, being longer with your kids and your grandkids and having a better quality of life? You can't put a price on that, and when I had Lyme and was bed bound, I would trade everything for ... Just take everything. I just want to be healthy because you can't ... Doesn't matter how much money you have when you don't have your health and so I think you're doing some amazing work and helping so many people because we take it for granted that we're healthy until we're not and shit happens, you know?

Dr. Joseph Raffaele:

Yeah, and the key thing that I drive home is that you can measure how healthy you are and you may not be as healthy as you think you are even though you feel good because a lot of this stuff smolders at a subclinical level until it breaks through. The idea is to pick it up ten to fifteen years before then and that's why we look at-

Dr. Kent Holtorf:

Yeah, when you can do something about it.

Dr. Joseph Raffaele:

Yeah. Exactly. There's old phrases that at first a disease is easy to cure but difficult to diagnose, but as time passes it becomes easy to diagnoses but difficult to cure. That's Niccolò Machiavelli, and he was right.

Dr. Kent Holtorf:

That's a good summary right there. I think this is fascinating stuff. I think you're doing great work, and I think the way showing people all these different markers, I think, is just huge. You're very, obviously, evidence based and as patients, you're proving to the patient this therapy works not just, "Hey, take this."

Dr. Kent Holtorf:

Oh, one question I wanted to ask you. What's your thoughts on statins?

Dr. Joseph Raffaele:

You know, I think that statins, interestingly ... The world is kind of, it's gotten really divided. There are pretty that are pro-statin and people that are anti-statin.

Dr. Kent Holtorf:

Everything becomes like a political argument.

Dr. Joseph Raffaele:

Yeah, exactly. I think that statins, my quick take on it is that in certain correct populations, they save lives. There's strong data for that. They're overprescribed in people that don't need and most people tolerate them, but a lot of people don't tolerate them. Interestingly, statins are a mild telomerase activator and maybe one of the reasons that they're effective by turning on telomerase and lengthening telomeres. That's part of the work that's being done by [inaudible 01:05:49] out in the UK and the same one that's running that trial that I talked about with telomere biology. I think that the problem is that cardiologists and internists sort of don't give patients the chance and say, "Look, you can get your cholesterol down if you make these changes in your diet and get exercise and do all these things," and I have patients who have cholesterol of 300 because everything else is working well. They got clean coronaries and they're 75 years old. So that person doesn't need a statin. The person with a cholesterol of 200 with a coronary calcium of a thousand, I think you're probably ... It's malpractice to not give them a statin at that point if

they're not doing everything else because of the anti-inflammation. Probably doesn't have that much to do with the cholesterol.

Dr. Kent Holtorf:

Yeah, I think the whole cholesterol theory of heart disease is getting its legs knocked out over and over and it isn't inflammatory but also it's a mitochondrial inhibitor.

Dr. Joseph Raffaele:

Right. Yeah. And so that's the problem. Exactly. So I think there's a better way to do it in certain patients-

Dr. Kent Holtorf:

For instance, the study came out and showed basically it seems the ideal patient, diabetic patients with heart disease, it showed an increase in mortality. Okay, it doesn't work for these people and I think any time you try to give it to everyone, they want to put it in the water, that's when you get into trouble.

Dr. Joseph Raffaele:

That was the big problem. I mean, the polypill back in the day when they wanted to put a beta blocker, a statin, an ACE inhibitor, aspirin and I think one other thing in a pill, that's the opposite of personalized medicine. You would probably get an overall beneficial effect on mortality, but you'd have a lot of people being treated that don't need to be treated. You'd have side effects. NF1 is really where medicine is going because we're all very different in many different ways and unless you're exactly like the average person in that large clinical trial, the data may not be applicable to you.

Dr. Kent Holtorf:

Yeah. Yeah. And it's totally true. I tell patients, "Look, we go by the studies." But you're not a study, you're a person and they usually take people that have don't anything else, so they're a rare breed to find those people and so we're doing studies and I'm thinking, "How do you find a healthy person," and everyone's exposed to toxins, pesticides, plastics, stress, all this stuff and BPA and all the pollutants, chronic infections. I don't know if there's healthy people out there to do a control on, but yeah.

Dr. Kent Holtorf:

Hey, fascinating stuff. I think this is great. I think you're doing such a great service and happy to

help get the word out. I'm going to give you a buzz later on this week and see if I can get your software. I'd love to-

Dr. Joseph Raffaele:

Okay, sure. Yeah. I'll be around. Absolutely. Great talking to you. Thanks for having me on.

Dr. Kent Holtorf:

Great. Thank you so much.

Dr. Joseph Raffaele:

All right. Take care.

Dr. Kent Holtorf:

Have a great day.