Episode 11 – Aging across the animal kingdom: lessons for humanity?

Guest: Peter Stenvinkel, MD, PhD

Peter Kotanko
Welcome to the Renal Research Institute's Frontiers in Kidney Medicine and Biology, where we share knowledge, and advancements in kidney research with the world. In today's episode we discuss the principles of aging, and we will talk about what we can learn from the animal kingdom in order to identify novel opportunities to slow down the aging process in humans. My guest today is Dr. Peter Stenvinkel, professor of renal medicine at Karolinska Institute in Stockholm, Sweden. Dr. Stenvinkel has published more than 600 articles and videos on various aspects of inflammation, wasting(?), and metabolism in chronic kidney disease. So, hi, it's a great pleasure, Peter, that we have an opportunity to talk today about aging. And I mean, I don't know about you, but when I looked this morning into the mirror, I saw my wrinkles, and said "Oh gosh, I'm really aging!" So, this begs the question, of course. Peter, why do we actually age?

Peter Stenvinkel
Well, actually, Peter, humans are living longer than ever before and in fact, human children in high income countries can now expect to live more than 100 years. And the natural conclusion is that both the miracles of modern medicine and public health initiatives have helped us to live much longer than before. But maybe now, we all will not extend further because I just realized, reading about the literature here that life expectancy has now stopped to increase that was confirmed in UK, and maybe also in other countries. We are now seeing that the gains we have seen are slowing worldwide and of course take COVID-19 pandemic will also contribute to this.

Peter Kotanko
I'm wondering, Peter, has actually the maximum lifespan of humans changed over the millennia? I mean, we know that people have got, I think the oldest, around 120 years. But in the past, say 100 years 500 years ago, say did people also get that old? I mean, I'm not talking about the average lifespan at birth of course, but the maximum lifespan. Has there been a change?

Peter Stenvinkel
Not really. What we know because, of course these data are very hard to scientifically prove, and the human being that we have the longest documented living, that is a French woman Jeanne Calment, and she was born in the late 1800s and she was living 122.5 years which is an amazing lifespan. But we don't really know further back than Jeanne Calment if there's been a longer lifespan than she have had. So the senescence, or biological aging, is supposed to the deteration of functional characteristics. And the causes of aging are present throughout our entire lifespan, and there is no going back. So this senescent change we see increase the risk of pathologies, morbidity and mortality, and that's why we sooner or later we, we die. But if he could stop senescence by for some medical reasons, the majority of us will reach 100 years old.

Peter Kotanko
This is this is a very interesting outlook. I mean, I'm also wondering, Peter, do you think it's really nature or is it nurture that that defines the lifespan, or a combination of both? What's your thoughts around that?

Peter Stenvinkel
Well, I would believe that it is both of them. There is a much discussion among researchers about the mechanisms that contribute to the aging process. It is widely accepted that damage to genetic materials, cells, and tissues that accumulate as we get older, which cannot be repaired by the body, or that's the cause of factors for the functional decline associated with old age. But what causes this damage on the molecular level, and why it can't be repaired in the old organism, that is much less clear. There is a potential for to repair in the younger species but not in old organisms, and that is one of the major research questions that we really need to solve now.

Peter Kotanko
For me, it was always fascinating to see that mammals age at a different rate. So small mammals usually live shorter than large animals. Is there, is this actually known why that's the case? Interesting enough, I mean, I've also read that the number of heartbeats per lifetime in a mouse seem to be the same as in an elephant. So I'm, I'm always wondering there should be or must be some more profound underlying biological principles. What are your thoughts on that?

Peter Stenvinkel
I find it so amazing that the lifespan a bit varies so much between animals. It can range from only a few hours in may flies, and we have Icelandic clams with documented age more than 500 years. And actually there are some primitive animals like sea animals and the freshwater polyp called the Hydra that does not age at all. And we also have other amazing observations. For example, The Greenland shark that can live up to 400 years and reaches sexual maturity at the age of 150 years. So there are many different features that are related to age in the animal kingdom. And of course, we can learn a lot from these observations. We know that the bigger animals they live much longer. The scaling exponent for the relationship between lifespan and body mass is between point .15 and .3. And as you mentioned, the number of heartbeats is also something that is related to age. We know that there is a quite a strong inverse correlation between the lifespan and the heartbeat. For example, in long living whales, there is a heartbeat of the 20-30 beats per minute. It's interesting that humans fit very poorly into this regression line, because we live compared to a long life but we also have quite high heart rate. Among 80 or 90 beats per minute. Other important features that is related to aging in the animal kingdom is related to loss of telomere length is very strongly related to aging. We know that reactive oxygen species is low in long lived compared to short lived animals. Long lived animals have less endogenous antioxidants and much less mitochondrial reactive oxygen species and short lived ones. And we also have a really recent observation, that is not yet published showing a strong relation between the number of somatic mutations in the animal kingdom and lifespan. And for us nephrologists theatre. I think it's just a fascinating observation that phosphate levels is so strongly related to lifespan in the animal kingdom. So the higher the phosphate levels, the shorter that the lifespan. And there are numerous studies showing that phosphate actually

promote aging processes.

Peter Kotanko
I mean, given you have done most interesting research in a variety of animals, I remember your studies in the hibernating bears, for example. I guess you were one of the few nephrologist who ever would crawl into a bear cave. Was this kind of research always related to aging, or did you did you pursue other questions?

Peter Stenvinkel
Well, the original reason for my interest in hibernating bears was, there was a ranger in Yosemite National Park that once told me that hibernating bears do not pee for four to five months during the hibernation period. And for a nephrologist that is just amazing that the creature can sleep for such a long period without eating, drinking, not peeing and waking up in the spring without losing much muscle mass, without getting osteoporosis, without signs of inflammation, or vascular disease. And this was the main reason I got interested in this, and then collaborating with their researchers and psychologist and veterinarians. I realized that there is so much to learn from ingenious solutions in the animal kingdom, and the hibernating bears is just an excellent example of how the creature can avoid a burden of lifestyle diseases that we see in the us humans. They get extremely fat during the late autumn in preparation for hibernation, but this is an obesity that is associated with less insulin resistance which I find is amazing. And we just recently discovered also that they have seem to develop an natural immunization process that protects them against atherosclerosis.

Peter Kotanko
So this is a really fascinating, because this would be a sort of an anti aging mechanism. So, I don't know because you said it hasn't been published yet. If you can say a few words about that. Otherwise we wait for your paper.

Peter Stenvinkel
Well, we have in this paper that is now published. We looked at the oxidation of cholesterol and they seem like they have developed antibodies that decrease the risk of oxidation of cholesterol and there is an enormous difference in these levels of these antibodies during the summer active period, and the hibernating period. But of course we need to understand why they develop these amazing high levels of antibodies during the hibernation.

Peter Kotanko
I mentioned at the very beginning when looking into the mirror of course everyone who ages will see wrinkles. Which brings me to the question Peter, do organs actually at the different rate? I mean, can I tell from the wrinkles in the skin something about the age of the liver, or the bones, or the kidneys, and is there a relationship or some differential organ specific aging rate?

Peter Stenvinkel
Well that is an extremely interesting question and in communicating chronic risks there is an increasing use of a metaphor that can be termed "effective age" or the age of a healthy person who has the same risk profile as the individual that you would like to evaluate. There are some

discussion about the real age, heart age, lung age, kidney age and so on. And I think as a nephrologist, we actually see that patients with chronic kidney disease they have difference in the rate of organ aging. We are all aware of this perfect storm for accelerated vascular aging we see in our patients, and of course this must be a number of different risk factors including hypertension, low grade inflammation, disrupted mineral metabolism, oxidative stress, lack of vitamin K, and somatic mutations, which is an area my research group is now more or less interested in. But without having much evidence in the literature I would say that organs do age at different rates, but the reason for this we don't really know yet.

Peter Kotanko
Yeah, because this, I think would be an important area for instance to understand what prevents aging in one organ versus another. And I just tried to think clinically and I wonder if you share that view, that you sometimes get the impression that patients with congestive heart failure have an accelerated aging, or patients with chronic inflammation, chronic inflammatory diseases, even without kidney disease. Which brings me actually to the question I mean, what's the role of inflammation in the aging process? I mean, we covered we covered genetic reasons or indicators, like shortening of telomeres links, but could it be that chronic ongoing inflammation is the overarching theme when it comes to to aging?

Peter Stenvinkel
Yes, that is my belief. And of course inflammation is acting together with it's partner in crime, oxidative stress. They are always linked together and there is a kind of an evil, vicious circle of inflammation/oxidative stress that often goes together with hypoxia, and mitochondrial dysfunction. They're very closely related you will see them more or less disturbed in most burden of lifestyle diseases that we know tend to aggregate as we get older, and of course our patients with chronic kidney disease they also often have multimorbidity, get heart failure, diabetes, obesity, congestive heart failure, Alzheimer's, you name it. And inflammation is of course the common denominator of all these burden of lifestyle diseases. We also see and they this may be an important link that there is depression of the expression of the transcription factor MRF to in these diseases. Another feature which I find extremely interesting is the gut microbiota because inflammation, and burden of lifestyle diseases, all seems to be associated with the disturbed microbial composition and the leakage in the gut that may contribute to inflammation. And I think here we can actually learn a lot from the animal kingdom because animals that tend to live longer, they have developed ingenious mechanisms that that counter inflammation, oxidative stress, and gut dysbiosis.

Peter Kotanko
So I think that one of the animals you were particularly interested in is the naked mole rat, as as one of those animals that seemed to be almost resistant against inflammation. Is there something that we as humans can from certain animals? How they defy, aging or decelerate the aging process, what would be the kind of lessons for us as humans?

Peter Stenvinke
Well, there's a lot we can learn, and together with a gerontologist, Paul Shiels in Glasgow, a couple of years ago, we really searched in literature to understand what characterized long lived

animals. And that is animals that live much longer than would be anticipated for their age. And here of course, naked mole rats, they stand out because they have the size of an ordinary laboratory, mice or rat, but they live up to 35 years. And they don't develop any signs of vascular aging. They are almost resistant against cancer. And there is now a lot of new pieces in the puzzle that we have learned from these naked mole rats, especially regarding their protection against inflammation. And they have a markedly increased expression of NRF two, which opposes the transcriptional upregulation of pro inflammatory side cytokine genes. They seem to have a highly efficient mitochondrial function, and also superior maintenance of protein homeostasis. Because as we get older our proteins are molduated, they are affected, for example, by carbon malation(?), glycation, which you'll see in diabetic patients. But then the protein homeostasis is really maintained until very high age in this naked mole rats. So there's a lot we can learn from the naked mole rats.

Peter Kotanko
So, low caloric nutrition actually has been shown to expand lifespan I think in in mouse models within other rodent models, and other animals. Do you think that this is one of the lessons that we could all learn to use a low calorie diet as a means to decelerate aging?

Peter Stenvinkel
And yes, you're completely right that compared to control animals caloric restriction, extended lifespan by about 50% and that is found in a large range of different mammals all the way up to primates. And so the reduction of the metabolic rate it has been hypothesized that caloric restriction could extend lifespan by decreasing the rate of free radical damage. So I would guess that caloric restriction also would be operative in humans, but a problem with this strategy is that caloric restriction may have adverse effects and of course, it will reduce the quality of life in humans. You will need extremely long term studies in order to prove this and I think it will be very hard to find the humans that would accept and markedly calorie restrict their diet for many, many years. So therefore, I think an alternative approach to arrest aging, which I will find much more interesting, is to find and use drugs that have caloric restriction mimetic effects. Which are former ecological agents that, we already know many of them, could recapitulate(?) the main biochemical properties, of caloric restriction, which is then of course the global reduction of protein acetylation and the induction of atrophy(?).

Peter Kotanko
So, when one would use such kind of products in a trial, you need of course markers of aging, to show differences in the various groups. So other current lead well established markers that would react in the short term to changes in the aging process.

Peter Stenvinkel
While there are a number of surrogate markers of aging, we don't have a golden standard yet. Of course, we have the surrogate markers for vascular aging that have been used for many years such as endothelial dysfunction and pulse wave velocity. There are a number of metabolic markers that have been used to assess biological age or aging processes. But so far there have been really in no acceptance of a golden standard. I personally think that that DNA methylation markers, the epigenetic clocks is so far the best way to study changes in aging accelerations.

For example, to find a marker of biological age. But unfortunately, these are extremely cumbersome and expensive techniques that doesn't really allow us to do other studies with non-nutritional or pharmacological interventions. But we are in my research group at Karolinska, we are currently trying to evaluate biological aging in patients with chronic kidney disease to see how it relates to risks and outcome.

Peter Kotanko
Yeah, very interesting. So, we are certainly looking forward to the results of your research. I think you, were certainly for me, the first one who kind of would connect global warming to potential to aging processes and it was really fascinating for me to see you making this connection. Actually, this connection might be new to many of our audience members. So, I may ask you, just to enlarge a little bit on that. How is climate change in your mind related to aging?

Peter Stenvinkel
Yes, so we are exposed to the exposome something that affects aging processes, and there is in the intermediate inflammatory phenotype, the one I described before including persistent inflammation, oxidative stress, mitochondrial dysfunction, tissue hypoxia. That is, we know stimulated by many of the well known risk factors, sedentary lifestyle and additional factors etc. But there is now more and more evidence, unfortunately, showing that also our external media will stimulate this intermediate phenotypes with inflammation, and I'm particularly thinking of global warming. Air pollution, and loss of biodiversity may also affect this, and we have in so many different disciplines now had reports that show that burden of lifestyle diseases that accumulate with age will be triggered by the the changes in the environment that we now see. A report from Brazil a couple of months ago actually shows that there is a dramatic increase in the prevalence of chronic kidney disease that is directly related to heat waves in Brazil. We have since many years been known that agriculture workers, often young men in Central America working in extremely warm conditions, have an increased risk for chronic kidney disease. And this is something that we see in so many different fields now. And there's an emerging discipline, the planetary health that we're trying to connect all the dots and see how these changes in our environment will affect burden of lifestyle diseases. So today, I just read a really interesting study from in nature, evaluating changes in food consumption in China. We know that there is no other country in the world where the meat consumption, the red meat consumption, increased so much as it has done in China. And we know that meat consumption and meat production is something that actually have an high environmental impact on the carbon dioxide footprint. And they calculated that if the Chinese would actually follow the rules or the guidelines set up in China's eating habits, their rules, that this would have a major impact on air pollution. So there are intricate links that we have not really been aware of. And there are studies also showing that global warming will affect the gut microbiota, we know that air pollution will affect the gut microbiota composition. There are so many emerging trends that could affect this whole cluster of burden of lifestyle diseases that we need to understand much better.

Peter Kotanko
I mean, I'm wondering, as humans, we can shield ourselves to some extent, say about against warming, by using more air condition and changing clothes, etc. I'm wondering if animals that

can not protect themselves as good against climate change, and live of course a much shorter lifespan, if certain animals would be actually appropriate areas of research to look at what climate change indeed causes in terms of physiology and the pathophysiology.

Peter Stenvinkel
Yes, it's a very good question, and there is my favorite animal. Now when trying to understand what we can learn from animal kingdoms are the bats. These are ingenious animals that have developed so many interesting mechanisms during evolution to protect themselves that we actually can learn a lot from now. And this is of course, now during the pandemic, and the bats they have a very robust interference system and this helped them to resist virus infections. You know that bat immune defenses drive the evolution of false(?) to transmitting viruses we have seen many examples of this not only COVID but also Ebola virus. But the bats are protected against the harmful effects of their own prolific viruses, but other species such as we humans are not and to understand why the bats have developed this ingenious system, we should understand that bats is actually the only mammal that we know that have learned to fly. So they are capable of true and sustained flight. And flying comes at an expense, and that is an enormous increase in the metabolic rate. It's actually increased 15 to 16 holes during flights, and this is compared to only two for the increase in metabolic rate in birds. So if you have an increased metabolic rate that will promote cellular DNA damage, they need a positive selection to have an an interior milieu of low inflammation, which lead will lead to an extremely tolerant immune response. And then of course risk for virus infections, but at the same time they have this extremely robust interference system. So bats seem to have found out how to protect themselves against virus infections and this has a huge relevance for us humans because we know that the main province with COVID-19 is hyper inflammatory syndrome and in combination with poor interferon response. So there are new studies that have shown that bats have targeted the inflammasome pathway at multiple levels which mitigate immune mediated tissue damage, and at the same time they have an markedly increased expression of the transcription factor MRF2. And this may also be one reason why bats leave about four times longer than animals with a similar size. So that they are really really interesting for us to understand how to we should deal with future pandemics, which again, I think is just a sign of the poor, planetary health.

Peter Kotanko
I mean, listening to you, Peter, I have to say it's just, we may need to rethink in a way how we approach these questions just to see to look so carefully into what solutions has the mammalian kingdom found, actually, instead of, for example, using animals predominantly for, say, testing drugs, but just to to really take a look at the animals in their natural habitat in see what lessons can be learned from them. And I think this is one of the, to me, at least one of those take home messages from our from our conversation here. Now, I see that we are approaching the end of it. Peter, may ask you just to summarize in a few sentences, messages about aging that are really important to you.

Peter Stenvinkel
Well, to me, I really found out after studying the literature here that aging is extremely complicated. We have adopted different hallmarks that contribute to the aging processes and

we need a lot of studies here to find out which are of importance. And also I think we have been so focused on lifespan but what we should really address is health span. And we need to increase the health span because this long period in patients with burn a lifestyle diseases for 10, 20, 30 years when they have chronic kidney diseases, the difference between lifespan and health span is extremely troublesome not only for the patient perceive but also for our society. It's extremely expensive to have these long periods of chronic diseases. So what we should focus on is not to increase lifespan, we should increase the health span and try to shorten this very costly period. And here, I am convinced that we have so much to learn from ingenious solutions that have been developed in the in the animal kingdom. That they have, different species have developed protective mechanisms for form almost all of these burden of lifestyle diseases that we are now having so much trouble with. So instead of destroying and using in nature we should actually learn from nature, because there are I'm sure many different solutions out there that we just need to find out if we treat nature in a good and positive way. So I think that to kind of summarized what I believe in this area

Peter Kotanko
Thank you, Peter, you made a strong point, a very good point, that that also emphasizes that maybe we have to rethink our relationship to nature to the environment in a way that will allow us actually to really learn from them and from their millions of years of evolution and from those ingenious solution that evolution had helped mammals, and other animals that they develop. So I would want to thank you, Peter, really a lot for this conversation. It was wonderful. It was inspiring to me, and I hope also for our audience. So thank you again and I'm very much looking forward to to future results of your research and also of research of other colleagues in this area. Thank you.

Peter Stenvinkel
Thank you. Bye bye, Peter.

Peter Kotanko
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