Episode 5 –A fresh look at an old problem: renal anemia
Guest: Roberto Pecoits-Filho, MD, PhD, FACP, FASN

Peter Kotanko
Welcome to the Renal Research Institute's Frontiers in Kidney Medicine and Biology, where we share knowledge and advances in kidney research with the world. It's my great pleasure to welcome today Dr. Pecoits-Filho. Dr. Pecoits-Filho is a senior research scientist at the arbor Research Collaborative for health in Michigan, and a professor of medicine at the Pontifical Catholic University of Parana in Curitiba, Brazil. He is the current chair of the Education Committee of the International Society of nephrology. As a clinician, he has broad activities in internal medicine and nephrology based at the university affiliated hospital where he was Chief of the Department of Internal Medicine between 2010 and 2016, the director of residency program in the fall from 2013 to 2016. Dr. Pecoits-Filho is principal investigator for the Study CKDOPPS, a multinational study on practice parents and outcomes in chronic kidney disease, and he acts as the scientific leader for clinical trials in the Americas with the Georgie clinical. Dr. Pecoits-Filho received his MD and trained in internal medicine nephrology in Curitiba, Brazil, before completing a nephrology research fellowship at the University of Missouri in Columbia, and a PhD from the University of Sao Paolo. He was a visiting scholar for extended periods at the Karolinska Institute in Stockholm, Sweden, in the Georgia Institute in Australia, and he has participated as a principal investigator, regional leader and in steering committees in multinational clinical trials. Dr. Pecoits-Filho served as a member of the Executive Committee of the International Society of Nephrology, the Song initiative and KDIGO.

Welcome and I'm wondering, could you just say a few words about renal anemia, what is it? What's the current thinking of where it comes from? how prevalent is it? And what is the consequence of renal anemia?

Roberto Pecoits-Filho
Yeah, hi, Peter. And well, first of all, thanks so much for inviting me to chat with you today. My pleasure. And also a pleasure to talk about anemia, which is one of the main topics of my research in the in the last several years. But I guess my interest in in the topic comes from observing and treating patients. And I would start by saying that this is one of the one of the problems that affect patients' lives, the way they feel, and their perspective of living well and longer. I think there are two things that anemia does to patients. One is when anemia develops, they feel worse. And that has a profound impact in the way they feel in terms of physical and mental activity. They feel fatigued, they feel tired, they feel dizzy. And, and they get much better when we treat them. The other problem is that in the long term, it seems like you know, anemia, which we monitor by measuring hemoglobin levels, when anemia develops, represent a risk for patients longevity in the long term. And I think that's another thing that, patients want is to live longer and to live well. So that is the main motivation for us as clinicians and researchers to be so interested about this topic. In anemia, obviously, is not a condition that affects only patients with kidney disease, but it's actually very, very common in patients with kidney disease. First of all, it anemia worsens as kidney disease progresses, and kidney disease is a is a disease that has a spectrum from, you know, very mild kidney disease to a very severe one. And at the end of

this spectrum, patients require kidney replacement therapies like dialysis and transplantation. And if we focus on that end of the spectrum, I think that anemia is actually very common, and most patients require active treatment to control anemia. While you know when kidney disease is starting to develop anemia is not that common. And I think the motivation for us to you know, keep studying anemia is the fact that with the current available treatments, we are not really solving the problem for all patients. And I guess this will be my the focus of our discussion today.

Peter Kotanko
Yeah, that's right. But before we go into this just I mean anemia, so the lack of red blood cells and low hemoglobin levels, occurs also in non-kidney patients or subjects, like particularly in I think it's more prevalent in younger women, for example. What is what is the difference between the anemia we observe, say, with iron deficiency, as opposed to the anemia we observed in kidney patients? I believe there are some fundamental differences. And could you could you say a few words about that?

Roberto Pecoits-Filho
Yeah, sure, it is quite different. And the mechanisms behind anemia of kidney disease, they have some peculiar aspects. I think the most important one is the fact that there is a hormone that stimulates the differentiation from stem cells in the bone marrow into circulating red blood cells, which is called erythropoietin. And this hormone is actually produced as actually stimulated by low oxygen levels in the circulation, or low hemoglobin levels. This hormone is produced by the kidneys, it actually has an important function to do that differentiation of precursors of red blood cells into the final mature cells. In patients with decreased kidney function, they lack or they the production of this hormone is significant decrease. That's perhaps one of the reasons why anemia worsens with the increased severity of kidney disease, because the worse the kidney function is, the lower the production of this hormone. Also, yes. The other the other aspect is related to iron metabolism. And patients with kidney disease, usually they show signs of systemic inflammation. And the inflammation which is, is due to several things in patients with kidney disease. For instance, the comorbidities around a lot of kidney disease patients are diabetic patients that have comorbidities like hypertension, like heart failure and other problems. And together with the decreasing the clearance of some molecules that might alter the physiology of the body, that we call the uremic toxins, there is chronic stimuli to the production of an inflammatory response. And one of the consequences of the inflammatory responses is a disruption in the way that we can use iron from our stores. So usually patients with kidney disease, they have iron deficiency. Sometimes they have the iron somewhere stored in the body, but they have a problem using it. And I think those two aspects, at least from a more traditional way of seeing anemia and kidney disease, those two aspects have been identified as the main problems that determine the reduction in hemoglobin levels or anemia, but also has been have been important as motivators and actually targets for interventions or treatments that we use in patients with kidney disease to treat their anemia.

Peter Kotanko
So I think you really pointed out this important role of erythropoietin that's produced in the kidney? And that's stimulated by sensing a low oxygen concentration, or is oxygen saturation in

the kidney? And can you just talk a bit about the use of erythropoietin in the treatment of anemia? I mean, I recall it very, very well. And I think it's some 40 years ago, when erythropoietin was being started to be used for the treatment of anemia in kidney patients. And what was seen were real. I mean, it was like magic, you would give erythropoietin and hemoglobin levels would just shoot up and in so this was certainly an extremely exciting time and, and patients just felt better. And but then there were data that actually treating patients to the extent that their hemoglobin levels would normalize may not be such a good idea. So where does this trade off come in? And one that you want to normalize the level which seemed to be reasonable. On the other hand, it didn't, it turned out to be not beneficial for the patient. So, so what's this fine balance? In that respect?

Roberto Pecoits-Filho
It is a it is a fascinating story, isn't it? And I also have been a nephrologist long enough to have seen the transition. I was a resident, actually, when I saw the first patient being treated with a synthetic erythropoietin late in the 90s. In, and I think I had the same feeling that you had been so impressed about that because, you know, in the past, there were no options, right. So we were just sort of rescuing patients from very severe anemia with transfusions. And then, you know, generate the cycle of patients on feeling better after transfusions. And, and then feeling worse, over time, when the effect of transfusions faded away, and actually seen all the consequences of transfusion in the lives of patients, I mean, a lot transfusions lead to risk of infections. You probably remember the time that we had, you know, so many problems with viral infections in dialysis patients, that hepatitis surges and, and there was there was also a sign that the previous treatment was not adequate. So it was it was really, it was really life changing therapy for patients. And we could really feel that and I think, what came after that is the feeling that you know, with this treatment, you could actually normalize hemoglobin levels and patients will feel better and better as hemoglobin goes up to the levels of people or healthy people. And, and that I think that that that's what brought complexity to the field. The fact that you know, when the urge to eat and the synthetic EPO was used to try to normalize hemoglobin levels, there was a signal of cardiovascular risk in those patients in the trials that really tried to normalize hemoglobin giving erythropoietin synthetic one need to remember that, you know, sometimes, for some patients, the those of erythropoietin that was needed to normalize hemoglobin not to bring hemoglobin to a level that is in the target or even above the target in some of the interventions is, is not very physiologic. It's several fold higher than circulating erythropoietin that people healthy people would have. So, there was a first of all, there was the observation of an increased risk when erythropoietin was given to patients, especially at higher doses. And at the same time, there was a reaction to redefine the targets to a range of hemoglobin, a little bit below the physiological hemoglobin range of healthy people that define the treatment that that sustained until today,

Peter Kotanko
Actually now thinking back I, there was this sort of discussion, medical community, but also industry, what the target level should be. And I think that companies that produce epo? or in some form or others, they may have had an interest to go for actually higher hemoglobin levels on one hand, but then the data that came out that lower levels might be actually beneficial. I don't know if you if you have the same experience than I to see this, this back and forth between

medical community and industry, what the target level should be. And it took quite a while, I would say 20 plus years, right, to settle on where we are now. But so how do you see this, this conversation between medical community patient outcomes and I guess also industry interests in in prescribing more erythropoietin?

Roberto Pecoits-Filho
Yeah. Well, you know, Peter, I think, the idea to normalize hemoglobin was a good one and perhaps a match between, the interest industry strategy, but also a medical question that was relevant. So when the when the trials that show this increased risk and higher hemoglobin levels came out until they came out, I think, I think there was a match between, you know, what the, what patients would like to see, feel better, feel even better? What Doc's would like to have in terms of new information to guide their practice, and also, you know, allow for, let's say, a broader Treatment range maybe reaches more patients and perhaps even higher doses. The problem is that the trials, they provide this answer there was quite clear that there was this risk in the in the higher in the in the more aggressive treated patients. And I think maybe something else that is even more difficult to understand until today is that there was not a very clear benefit from increasing those levels, even from a patient reported outcome level. I mean, we really felt that when, when normalizing hemoglobin, we will we will create, or we will impact patients, symptoms and the way that they feel and there was not very clear from those studies, and I think that's one of the reasons why, today there is no question about limiting the upper level of hemoglobin as a target to you know, something that is below, you know, what a healthy person would, would require to feel to feel better. And, and I think this has been the status quo for many years now. Because we're, we're still trying to do that the same way that we did 20 years ago, giving iron replacement to patients and providing exogenous erythropoietin.

Peter Kotanko
I mean, the thought to replace erythropoietin is very much in line with, with supplementing other missing hormones, like in type one diabetes, or in, in certain specific disorders of growth. And many other examples exist in medicine, of course, but you also mentioned and this is interesting, that erythropoietin that's produced by the kidneys is produced in response to low oxygen levels. And, and I think this has opened up new avenues of treatment. Can you say a few words about how, how is this low oxygen level actually sensed in a way without going too much into the details, of course, because it's a really complicated pathway, and how this can be used actually for new treatment approaches?

Roberto Pecoits-Filho
Right. Yeah. So yeah, so and this is super relevant scientifically, and recognized even by the Nobel Prize, right? So this, this is the discovery of this pathway, that involves hypoxia inducible factor that is involved in sensing oxygen and regulating endogenous erythropoietin production has led to the Nobel Prize of medicine in 2019, which was giving to the three investigators that discovered this and investigated this area, including the first nephrologist, whoever won the Nobel Prize in Physiology medicine, it is a fantastic way of understanding how this is a self-regulated and tight, tightly regulated process. The idea that stabilizing this hypoxia inducible factor has an influence in leading to the endogenous erythropoietin production. And because stabilizers of the hip as we call the hypoxia inducible factor have been developed. In terms of

pharmacology, this is latch the series of studies from preclinical to clinical studies all the way into phase three trials that really look at safety and efficacy of the drug in the population where the drug will be used with the indication of treating anemia. For decades, fantastic story, that it's, it shows the value of the translational research from the bench to the bedside, in a very short period, if you think. I mean, it's, you know, now more than 15 years, perhaps since the discovery of the pathway to the application in a potential new treatment.

Peter Kotanko
And in the end, we'll see, I think, in large, large populations, once this class of drugs becomes available, what the what the impact will be, and maybe, do you think actually, that target levels may need to be redefined for this this class of drugs?

Roberto Pecoits-Filho
It's, that's a million dollar question, right? Are we ever going to be able to do again, well, we did in the early 2000s? And, and try it try again, to bring hemoglobin levels to something that is closer to what healthy people would have. In theory, if the if the initial studies that would have to target the same hemoglobin range that is prioritized by the current evidence based recommendations. If those trials show safety, there is always the chance of trying to design trials to challenge that again. But you know, this is always a very complicated population to study, because they, you know, patients with kidney disease, particularly with more severe kidney disease, and that's when anemia becomes a prevalent problem. They are very fragile. And I think we need to be very careful when challenging, you know, the current therapeutic approaches and do that, you know, in a very, in a very planned in, in trying to keep patient safety in front of all other aspects of, you know, the clinical trial object.

Peter Kotanko
No, I certainly agree. I just wanted to bring this to the table, because it, it certainly goes through my mind what will happen with target ranges with this absolutely new approach. Now, what we didn't touch on is actually something very interesting that, that the lifespan of red blood cells in patients with kidney disease is shorter. So and in you and I get blood cell lifespan would be something like say 110 121 and 30 days something in the ballpark. In patients with kidney disease, on average is reduced, say 60 days, 70 days, 80 days, something in that ballpark? I am wondering, first, what do you think are the reasons for this shortened lifespan and, second, do you see in principle, the totally new therapeutic approach that could aim to increase that lifespan of red blood cells?

Roberto Pecoits-Filho
Well, first of all, Peter, I think this is from, from a mechanistic point of view, I think this is the new kid on the new kid on the block, right? Because, I mean, as you said, we during our conversations, but also during the more traditional approach to understanding the mechanisms behind anemia, chronic kidney disease, you know, the, what we discuss here, you know, iron, iron metabolism and erythropoietin production has been in the, you know, in the agenda in the research agenda for many years and legend discoveries that transformed the treatment. But really, the reduction in red blood loss cell span has not been that much investigated. I think just,

you know, hearing you say, you know, what is the impact of kidney disease on the, on the lifespan of a red blood cell. So, it really shows that this is significant, and probably clinically relevant. And so I do agree that this is a new area that has not been investigated enough, both from a mechanistic point of view but also in the perspective of becoming a potential therapeutic discovery. So I do believe that, first of all, that this is clinically irrelevant. And this might explain At least in part, why patients, a subgroup of patients, maybe about 10% of patients that we treat with anemia the way we treat today, even with all efforts, we cannot really achieve the targets, what we call erythropoietin agent, hyper responsive patients .And perhaps those patients, at least part of those patients might not achieve the targets, because for some reason, their red blood cell span is more severely reduced. Another challenge is how to monitor that. We don't monitor them on a regular basis. And that always causes a problem. It's very easy to monitor anemia, with hemoglobin levels, or even iron deficiency with the T seven ferritin levels. But there is no biomarker of red blood cells span. And that's when perhaps we will need to call people that my model physiology and clinical practice with mathematical models to help us to understand that. And I know that you have been collaborating with a group of mathematicians in this matter. And I think some of the information that came out of that really shows that from a modeling perspective, that seemed to be a relevant problem related to reduction in red blood cells span.

Peter Kotanko
And I agree, I mean, it would be terrific if you would have markers of red blood cell lifespan or red blood cell deaths, which is called erythro, eryptosis, if we could have easy markers to measure those. And this, this certainly could open in new field and even to think about how to treat patients with a red blood cell lifespan gets expanded. And as you said, the mathematical modeling plays a crucial role in elucidating this. Now, you are a very, very international clinician and researcher. And I'm wondering, in in low and low middle income countries, in your experience, from what you know, do they have access to drugs that they use to treat anemia? Or is there a real shortfall in those in those medications?

Roberto Pecoits-Filho
I think there's definitely a variation in access to care, in nephrology, in general for CKD patients, but in particular to anemia. I think the advent of developing biosimilar drugs, for erythropoietin for the synthetic Arab region was very helpful in increasing access. So if you go to Africa, or India, or South America, you would see a lot of those drugs at the much lower cost. And that I think that has had a significant impact in improving access to erythropoietin. Iron is another complicated issue because iron delivery to patients involves not only the availability of the drug itself, that supplement, but also the logistics around it. So particularly in patients that are not on dialysis. For those for instance, dialyze in your home, with peritoneal dialysis, or for those not yet on dialysis, the logistics around it also creates a difficulty. And I think it's possible to see the disparities in access to Iron treatment, particularly patients in that in that population that doesn't really go to the dialysis center to get this treatment. So I think the distribution of care, home or in center, and the availability of low cost therapies are really defining the disparities nowadays and you can really feel it. And then when you look at the results of this meaning the percentage of patients who live with a low hemoglobin, who live with anemia, with all the consequences in quality of life and long term, long term outcomes. I think we are really seeing

important disparities in relationship to the treatment and anemia and the achieved in targets in populations. I suspect that is this is actually a bigger problem in patients not on dialysis.

Peter Kotanko
So what about oral iron therapy, which is cheap, and then logistical may not be that challenging. You don't think that's an option because of the inflammation in those patients?

Roberto Pecoits-Filho
I mean, if we talk about the patients with more severe disease who are on dialysis, the degree of inflammation and demand of iron that these patients have probably will require in most patients, IV therapy and intravenous infusions. For the non-dialysis population and for patients on home dialysis, like peritoneal dialysis, I think there is a proportion of patients who could take oral iron. The problem is that the formulation, sometimes they are not very tolerated by patients. So compliance is another issue. And just in terms of perspective, Peter, the, you know, this is another potential advantage of the new therapies with the stabilizes of the XX that we discussed just a while ago, because different from ESA and iron, who really target a very specific part of the path, the pathophysiology of anemia in chronic kidney disease, the hip stabilizers, they actually do they interfere in both. So they first they generate this increase in endogenous erythropoietin up to something that is much more physiological than what we see in the exogenous administration that we use to treat patients for many years. But at the same time, the stabilization of XX leads to a better use of the iron stores. They're really blocking patients who are inflamed. And because of the actions of this new treatment target, let's say, a lot of this iron is more easily used. And this has been one of the characteristics of the findings in the trials that we've seen published already with this new agents that even patients with signs of inflammation and with lower iron stores, they seem to be responding very well with the stabilization of XX in increasing hemoglobin levels. So perhaps, you know, this new treatment paradigm might actually lead to something that deals better with the offer of iron XX

Peter Kotanko
Very interesting perspective. Roberto, we are coming to the end of our conversation, I've certainly learned a lot through this through talking with you, not only now, but over the many years, we're working together on a wide range of topics. For our audience, just to wrap this up, what are key messages you would like to, to convey to communicate to our audience before we close this.

Roberto Pecoits-Filho
First of all, Peter, likewise, you know, it's been a pleasure, you know, collaborating in this area and other areas with you and the Renal Research Institute. Group. And they have very happy to see, you know, that some of the things that we share with the audience today have been the consequence of this collaboration with many people involved both in the basic research area, like Andrea Moreno, and her group. But also, as we mentioned, you know, the group of mathematicians at Renal Research Institute. And I think that there really shows the value of collaboration in clinical science and science in general, when you bring together people from different backgrounds.

Roberto Pecoits-Filho
I think my final message is really a positive message that really supports the idea that the, you know, the best science perhaps is done when people with multiple backgrounds and different ways of thinking, join, open in, open discussions with a perspective that clearly has a an application at the end. And in this case, I think what we've done in the past, had always had a very strong motivation in improvement the life lives of patients with chronic kidney disease. And I would just like to, you know, leave it in this note that, you know, this is really what research is all about, right? You know, it's really trying to evolve in the field, with a focus on how this can potentially benefit our patients.

Peter Kotanko
I agree full heartedly, but you say, especially when it comes to collaboration of people with different backgrounds. I mean, this is really where new insights happen. Roberto, thank you so much for this for this really interesting conversation. And I'm looking forward to many more conversations to come. Be well.

Roberto Pecoits-Filho
Yeah, you too. Bye.

Peter Kotanko
That concludes this episode of frontiers in kidney medicine and biology. Thanks for listening. We hope you will subscribe and join us again for another episode.

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