Optimizing Kidney Health With a Low-Acid Diet: A Special Interview With Dr. Lynda Frassetto

By Dr. Joseph Mercola

JM: Dr. Joseph Mercola
LF: Dr. Lynda Frassetto

JM: Welcome, everyone. This is Dr. Mercola, helping you take control of your health. Today, we are joined by Dr. Lynda Frassetto, who is a nephrologist over at the University of California San Francisco (UCSF), where she's professor emeritus in the department of medicine. She is going to share with us some really exciting information about acid in your diet and how it affects your longevity in kidney health, which is a real significant issue because lots of people as they age have problems with their kidneys. Welcome and thank you for joining us today.

LF: Thank you for asking me. I appreciate it.

JM: Yeah. I saw your presentation at, I think, Ancestral Health Symposium. It's definitely one of the, probably the best one I saw there this year, aside from Chris Knobbe, who was really one of my favorites. I don't know if you had the opportunity to see him there, but man, he's just – I'm interviewing him in a few more weeks about his concept. He's like the Weston Price of the 21st Century. He's an amazing guy. So you are a nephrologist. Can you tell us a little bit about your background and where you're working at? I think UCSF is where Dr. Robert Lustig works out of too.

LF: Yeah. Bob is at UC. Exactly.

JM: Yeah, yeah. Another great guy. Alright. Let us hear a little bit about your journey into where you got now, how you started nephrology and what brought you to this understanding of the integration with the diet, the evolution and its impact on health.

LF: Right. You know, kidney medicine is something that even though I'm an internist – A lot of internal medicine doctors, for them, the kidney is kind of a black box. If there's some problem, it's like, "Oops. Off to the kidney doctors." When I was in internal medicine training, I happened to have a really super mentor, a guy named Dr. Eli Friedman at the State University of New York (SUNY) in Brooklyn, who is just this incredible, enthusiastic guy. He made nephrology sound really interesting.

And so after I've been in – after I finished my residency and I was an internist, actually a hospitalist for a couple of years, I decided to go back and do nephrology, because people who did nephrology just had this better understanding of physiology than most internists do. I thought that would help make me a better doctor.

After I finished my residency, excuse me, my fellowship, I started working with a guy named Anthony Sebastian here at UCSF. He was interested in diet acid load in people who were relatively healthy. The kidneys do a lot of things. One of the things they do is they get rid of acid. We know

that as kidney failure progresses, you have trouble getting rid of the acid, and it accumulates in your system, and it has a lot of bad side effects. We also know, as you said, as you get older, your kidneys tend not to work as well. And so what Tony was looking at was, "How about in otherwise healthy, older people, whose kidneys just aren't working as well as they did, let's say, 40 or 50 years earlier? Did eating a high-acid diet, did that have any potential side effects?"

Really, it was working with Tony that we really started working on either neutralizing the acid in the diet with bicarbonate or maybe about 10 or 15 years ago, we started looking at low-acid diets. If you look at that, if you say, "Where are the acids coming from in foods?" Well, all foods contain precursors that are metabolizable to acids. But fruits and vegetables contain a lot of alkali precursors that are metabolizable to bicarbonate, like citrate or malate.

So then we started looking at "The Paleo Diet" from Dr. Loren Cordain, because Cordain had been looking at this for many years. What he was saying was that there are a lot of things in our diet that weren't available to our human ancestors, like dairy products after infancy or processed grains or processed sugars. And that we would be healthier if we ate a diet more like the one our human ancestors ate, which is essentially, you throw out all the processed foods and you get rid of dairy for everybody, except infants. That and any diet with a lot of fruits and vegetables in it will be a relatively lower acid diet. That was really how I got interested.

JM: Yeah. And it's interesting that's a similar approach that Dr. Chris Knobbe evolved to from a different perspective as an ophthalmologist. It's essentially the elimination of all these processed foods. It appears to be the genesis of almost every chronic degenerative disease, you know, cancer and heart disease. In Chris' case, age-related macular degeneration. It seems to be the critical variable. Prior to the introduction of these foods, we didn't have these problems. They were rare events. Now, it's the leading cause of death.

I have a foundational question for you to set the perspective. Because there are essentially two populations. There's this population that you referred to or implied that was eating an ancestral-type diet, no processed foods, essentially optimal and healthy. And they will progress to a certain level of kidney dysfunction as they age. And then there's almost everyone else who's eating processed foods and processed oils and sugars, and they're going to accelerate much more rapidly. I'm wondering if you looked at those populations separately and have a comment on the incidence of the progression of kidney disease in those populations.

LF: Yeah. If you look at any large population and you just look at the average kidney function over time, on average, everybody's kidney function declines. But if you look at specific individuals, kidney function either declines much more slowly or may even level out. The question is, "How related is that to eating a low-acid diet or doing things that wouldn't bother your kidneys?" This has actually been looked up by a guy named Dr. Donald Wesson, who's a nephrologist at University of Texas (UT) Southwestern. He's looked at both alkalized supplements and fruits and vegetable diets in people with what's called Stage 2 kidney disease, which is estimated GFR between 60 and 90, and Stage 3 chronic kidney disease (CKD), which is estimated GFR from 30 to 60.

JM: For those of us who aren't nephrologists, GFR is glomerular filtration rate.

LF: Glomerular filtration rate. That's an estimate of kidney function. And so if you're – I'm just going to use averages now. If you're 50 years old, your GFR is about 90. If you're 80 years old, your GFR is about 60. On average, people who are older are going to have what we would call in a kidney failure patient, Stage 2 or Stage 3 CKD. Donald Wesson showed in these people that if you either gave them alkalized supplements, like baking soda, or you put them on a fruits and vegetable diet, or a diet with more fruits and vegetables, that you could slow the rate of decline with kidney disease. And so if you extrapolate that from people with kidney failure to just older people, the idea would be that maybe you can slow the rate of decline of your kidney function, even if you're otherwise healthy and just getting older. That's the idea.

JM: Okay.

LF: Everything that you do, everything, is related to kidney function in some degree. Because the kidneys get rid of a lot of things. The worse the kidneys work, the worse everything works. Because the kidneys have such an important role in the whole body's physiology, my idea, which is not really incredible, is that you would be better off if your kidneys are functioning better. And that if you can – if eating lots of fruits and vegetables is going to help slow the damage to your kidneys and otherwise keep you more healthy in an overall sense, then it would make sense to try to do things that would slow damage to the kidneys.

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JM: Okay. There appears to be different rates of progression in these populations. I've interviewed another nephrologist who you might be familiar with, Dr. Jason Fung, who's up in Toronto. He's most well-known for espousing fasting for treating kidney problems. He practices in Canada, so it's socialistic medicine. He doesn't have a lot of time or resources to help his patients. He became quickly frustrated with his inability to make an impact on what he perceived the progression of this disease, which seemed to be mostly related to diabetes or problems with insulin resistance, which should also resolve in hypertension and heart disease.

I'm wondering if it's, in your experience, more than just the high or low-acid high-acid buffering diet with plants and vegetables, but also integrating periods of not eating to obtain metabolic flexibility that might ultimately be a final resolution.

LF: So a little bit of background. Most kidney disease in western countries is especially more advanced kidney disease. It's due to high blood pressure and diabetes, and 3 out of every 4 patients on dialysis are on dialysis because of high blood pressure and diabetes. You could see why diabetes is a really big deal. I think in terms of diabetes control, I think anything that improves diabetes control will ultimately help improve kidney health.

There are many ways to do that. Intermittent fasting is one. Exercise is another one. Watching your weight is another one. The combination of all of these may be really good. Taking your medications. I work with a diabetologist. One of the most frustrating things for doctors who take care of people with CKD is that we can tell you what to do, but you have to do it. If you don't do

it, then it's not going to help. I mean I've been a doctor for over 30 years. I tell people you should eat right and exercise.

JM: Yeah. And to actually handhold them through their process requires enormous time and investment and really a team, a specialized team to do that, which is why Jason came to that conclusion, because he didn't have to do that. He just said, "Don't eat." That's simple. It doesn't take a lot of handholding. Just don't eat. He gave them some little guidelines, but it was simple, which is why he really embraced that process.

LF: I'm going to say if you can get your patients not to eat, great. I'm going to say that I have enough trouble trying to get my patients to do one-tenth of what I ask. So I've kind of gone to the "Anything you can do that would help is good."

JM: Which makes your recommendation of low-acid and then acid buffering strategies make more sense in that context. Let's step back another point because I am curious as to your perspective on the contribution of the acid damage versus the protein damage. Because it's at least conventionally thought, and it may not be true, that high-protein diets, because of the ammonia that's generated in the necessity of that being filtered through the kidney, could cause kidney damage. Do you think it's more of a protein issue, or is it the acid or both?

LF: So proteins are – All proteins contain acid precursors. If you're eating a high protein load and you don't have enough alkali to help the kidneys either to help the body buffer this or to help the kidneys get rid of the acid, then we do actually believe that that's ultimately bad for your kidneys. But you do need to eat – You have to eat a certain amount of protein.

JM: Enough protein. Yes, absolutely.

LF: Or you're going to have problems building things too. This is really a balance question. It's not that protein is bad. It's that I think that if you're eating a lot of protein, you should also be eating a lot of alkali. That will help you not use the body systems in order to be able to neutralize or buffer the acid in your system. The whole idea is that you want to maintain your blood pH within the range that is considered to be normal.

To do that, you either move the acid inside the cells, you break down the muscles to supply glutamine, ultimately to the kidneys, to excrete the acid as ammonium. You break down your bone, which is calcium hydroxyapatite, which is the alkali. Or you have to decrease the amount of endogenous acids that you produce in order to be able to maintain your blood pH.

Your body has a lot of ways of dealing with the acids that the kidney has to get rid of. And so if you're giving the body exogenous alkali, meaning you either take bicarbonate or you eat a lot of fruits and vegetables, you don't need to break down your bones and muscles in order to be able to neutralize the acid in your system, which your body really cares about. Hydrogen ions are balanced at the level of 10^{-9}, which is a super, super low level of free hydrogen ions in the body. And the changes that you can make to that without going outside the range of normal and becoming ill is not very big. There are only a couple of things you can do here. Either you're going to break down your body systems or you give your body exogenous alkali.

JM: Okay. Well, thanks. Because I think I was confused on this too. Just to give you a little personal history, my kidneys were challenged because of an acute mercury insult from having my mercury amalgam fillings removed in the '90s by a non-biological dentist. I just had a massive mercury exposure, which damaged the kidneys.

As a result, I've been sensitive to high proteins. I noticed that when I go on a low-protein diet – I mean it's definitely sub-therapeutic. I was, for a time there, very fearful of mammalian target of rapamycin (mTOR) activation and all of its consequences, not understanding the importance of cyclically activating it. I would go like 60 to 70 grams of protein for a long time. I noticed my kidney function would improve. I didn't realize it was largely related to the low-acid load. I thought it was just the metabolism of the protein. It appears not to be.

But when I increase that – We'll definitely get into the alkali because that's really the meat of your work. Because I do a lot of alkali, I didn't notice the buffering. I still noticed that as I increased the protein intake to like double, like 120 or 150 grams, that my kidney function started to decline, even though I was taking the acid or the alkaline buffering. But maybe I guess it sounds like the acid contribution for the increased protein exceeded the buffering capacity of the supplements.

LF: The answer to that one is maybe yes, maybe no. In advanced kidney disease, we do actually give alkali, because it's been shown to slow how quickly we have to put people on dialysis. When you say, "How do we improve kidney function?" We keep the blood pressure under control. We keep the diabetes under control. We control the proteinuria, which is damage to the glomerular barrier, and we use medications to do that.

And then we give alkali. How much alkali to give? If you read nephrology textbooks, they'll say that bicarbonate distributes in the total body water, which is if you're 70 kilograms, is about 40 liters. And that in order to raise the bicarbonate levels, you'd actually need to give a lot of bicarb. But in practice, it turns out that we don't have to give that much bicarb in order to be able to raise the bicarbonate levels into the normal range.

So these days, for example, if your bicarb is 20 and you want to make it 24, which is in the normal range, and you weigh 70 kilograms, we would give you 20 millimoles, milliequivalents of bicarbonate in order to try to raise the bicarb levels up. Not as much as you would definitely think.

JM: Yeah. Let's translate that for the lay audience. First of all, to get those measurements, is that only possible through an arterial blood gas (ABG) test?

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LF: No. Typically, that's done off of venous blood, which is the type that you routinely get when you have blood drawn from a vein. And then this is one of the normal measures if people get what's called an electrolyte or a renal panel. It'll have this serum bicarbonate in it. The normal range is 23 to 27 or 28, something like that. But if your GFR isn't that good, it might be 18, 20 or 21. So then we want to move it up into the normal range. And so it's a little – I could go into how

to do this. But I don't really think people should be doing this unless they have a doctor looking over their shoulder to make sure it's a good idea.

JM: Yeah. We can give a caution to only do this with professional guidance and consultation.

LF: Yeah.

JM: Because it could be dangerous.

LF: Yeah. I find that I get notes from people who have done these things. I'm like, "Why are you doing that?" I prefer not to give actual medical advice.

JM: Okay. Alright. But how do you translate the millimole recommendation you gave earlier to an actual quantity?

LF: Yeah. It depends on how you take it. Millimoles are the molecular weight of something. You need to be able to figure out what the molecular weight is. And then you would turn that into milligrams. So for example, sodium bicarbonate has a molecular weight of 100. If you want to give five millimoles of bicarbonate, that would be 500 milligrams of bicarbonate.

JM: Okay. Alright. That's pretty straightforward. Millimoles is the more scientific term to use because it does factor in the molecular weight.

LF: Right. And when you talk about acids, we actually turn them into milliequivalents, because we're really concerned about neutralizing the charge. And different things have different amount of charge on them.

JM: Okay. While we're on the bicarb, I think I just have a few questions on this, because obviously there are two – well, there are a number of ways, but there are two primary ways that you can give bicarb. One is the sodium. The other is potassium. It would seem that it would be better to use potassium bicarb because most people are deficient in that, at least according to the recommended dietary allowance (RDA), which is questionable because they just change the standards again. Do you have any strong opinions on that one or the other?

LF: Yeah. You know, you can only sell over-the-counter bicarbonate, which is 5 millimoles of potassium bicarb. You know, the reason for that is that if you have kidney failure, potassium accumulates and it can kill you. We don't want people taking potassium bicarbonate if you have a kidney problem. Whereas sodium bicarbonate is baking soda and it's sold over-the-counter in large quantities. It's a lot easier to get sodium bicarbonate. And with advanced kidney failure, that's what we use. Sodium bicarbonate, sodium citrate, a combination.

JM: And how effective are the citrates, like potassium?

LF: Well, some people actually prefer citrate because citrate is also excreted by the urine. For example, it helps keep the urine not very acidic. Some people are prone to kidney stones. If you eat a typical Western diet, so a typical high-acid diet, the urine pH is very low. That predisposes

you to calcium oxalate and uric acid stones. If you have a lot of citrate in your urine, it's one of the things that helps prevents stones. A lot of people use citrate rather than bicarbonate.

JM: Okay. Is it a pretty much milligram per milligram equivalent for the bicarb?

LF: No. Because citrate has a different molecular weight.

JM: Okay. It would be more or less?

LF: More. Citrate has a higher molecular weight.

JM: Okay. So you need more citrates. And still, I would imagine along the same lines, you would be adverse to recommending potassium citrate because of the potential for accumulating –

LF: It's not the citrate that's the problem. It's the potassium that's the problem.

JM: Right. That's good to know because that's not why they know. There is a woman named Sally Norton who's really become appreciated as one of the leading experts in oxalates. She's a nutritionist, a registered dietitian (R.D.), and really talks a lot about this. Citrates are one of the strategies she uses to remove the oxalate load from the body. Certainly it increases the solubility of the urine, but it also helps remove it from the tissues, because you can build up quite a high body burdens from these oxalates. And even if it doesn't cause kidney stones, there are a lot of interesting, compelling clinical data suggesting there are other toxicities aside from renal.

Let's go into some of the other mechanisms which are interesting, because there's this anti-aging protein called klotho. It's related to this whole discussion. I'm wondering if you could review the klotho and describe what it is.

LF: Yeah. This is one of these emerging ideas that I think is really fascinating. So klotho, from a kidney point of view, is used to help get rid of phosphate. Phosphate is another one of those acids that has to be excreted by the kidneys. But in small animals, if you overexpress the klotho gene, those animals live 10% to 40% longer. There's something –

JM: Is this a genetic variant or is this an animal that has been genetically edited?

LF: That's right. They put more klotho genes into these animals. These are transduced animals.

JM: Okay.

LF: And they do this and they overexpress the klotho genes and those animals live longer. But what klotho does in the body is it's a membrane transporter and it's a soluble protein. When you eat a high-phosphate diet, one of the things that happens is you release something called fibroblast growth factor 23 (FGF23), which then goes to the kidneys. It attaches to klotho as a cofactor. Part of the klotho breaks off and it goes to the proximal tubule and the kidneys. It removes the transporters that allow the kidneys to reabsorb phosphate.

The kidneys filter the blood and then the filtrate goes through the kidney tubules. And because the transporters aren't there, then you just pee out the extra phosphate. This helps get your phosphate balance back into normal. As you keep eating a high-phosphate diet – And phosphate is in everything, so it's hard not to eat a high-phosphate diet – So as we keep eating a high-phosphate diet. As you get older, you have to use more and more and more FGF23 in order to be able to get rid of the phosphate.

And FGF23 does a couple of interesting things. One of the things it does is it prevents the function of an enzyme called 1-alpha hydroxylase. That's necessary to make active 1,25 vitamin D. 125 vitamin D is necessary for the production of klotho. So as you get older, as you keep eating high-phosphate diets and as your FGF23 goes up and up, your vitamin D levels go down and down. And your klotho levels go down and down. That's bad for you, because now the kidneys are reabsorbing more phosphate. And that's actually damaging to the kidneys.

In small animals where you can do things, like you can knock out the klotho gene and you can knock out the phosphate transporters, you can do tests to show that the animals' kidneys do much poorer if you knock out either of those.

JM: That's interesting. It's not commonly appreciated, I think, that high-phosphate diets are impairing the body or kidney's ability to make that final conversion and the second hydroxylation for the vitamin D precursor.

LF: This is all relatively new, actually. I mean this has really been, in the last decade –

JM: Yeah. Just let me finish my question. Because the question is, "Is it just the 1,25 – Does the high phosphate inhibit that second hydroxylation or is that the first?" It's an important distinction because if it inhibits just the second, then the typical vitamin D assay that's done is 25-hydroxyvitamin D, not the 125, so you have to do the complete panel to see that phosphate was impairing that.

LF: You're right. Sooner or later, we're going to be able to actually clinically use FGF23. Right now it's a research assay. But as soon as it becomes clinically available, it's something that we're going to be watching. Because presumably, as that goes up and up and the change from 25 to 125 vitamin D is going to go down and down, it's a way for us to actually follow what's going on better than we can now.

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JM: Alright. You've given us two clues to help improve our kidney health, and secondarily, our general health. One is a low acid diet, which is an optimal-protein diet. But additionally, a relatively moderate-phosphorus diet, so avoid high-phosphorus, which is more accurate.

LF: What is a high-phosphate diet? We have this discussion routinely with our patients.

JM: The reason I'm asking you is because we can take nutrient trackers, like Cronometer, and you could pretty much to a milligram figure out how to calculate how much phosphorus you're eating.

LF: First off, dairy products. All dairy products contain essentially four things: calcium, phosphorus, protein and fat. Because they're designed to build bones and muscles. And so for kidney failure patients, we pretty much eliminate dairy products. And then colas. They add phosphatidic acid to a lot of things, including colas. We try to get people not to drink stuff that has phosphatidic acid in it. And then there are some other specific foods, like chocolate and nuts that we tell people with advanced kidney failure to avoid.

JM: Those are some of them. There are others. But what is the threshold? How many milligrams are you trying to get them below per day in an advanced case? And what would you think, secondarily, what you'd recommend for a healthy person to keep their kidneys in health.

LF: Nobody knows the answer to how much to limit phosphate intake in a normal, healthy person. Because we don't look at that. It's only this whole thing with the FGF23, the vitamin D and the Klotho over the last decade that the people have started to say, "Maybe we should be limiting phosphate intake not just when the blood phosphate levels are high, but maybe before that." This is theoretical so nobody knows the answer to that one.

JM: Do you have any intuitive feelings because I suspect you're looking at this and you could measure that, or at least you could analytically figure it out? So I would think like under a gram a day, 1,000 milligrams, might be a wise target.

LF: Nobody knows the answer to this one. I mean I'm being very specific about this because in the nephrology literature, there is this question that has come up. We don't know how much to limit it to.

JM: Darn. Gosh. We've got to slap some of those nephrologists around. They need to do their homework, because that's a basic question. It's so fundamental to the kidney health. You would think they would have done the studies to figure this out.

LF: You know, really, I'm very serious about the fact that our ability to understand this better is not old. It's really only been in the last few years.

JM: Okay. So the research has been done.

LF: Now we understand better what to do. But no, it wasn't done before. But I don't really mean to put in a plug here, but that's actually one of the reasons why I like Cordain's "The Paleo Diet," because he does actually specifically say adults shouldn't be eating dairy products. You know, it's one of those things that –

JM: And there are other foods too. He avoids, I believe, legumes, which are another source of phosphate, if I'm not mistaken.

LF: Yeah. Beans are another high source of phosphate.

JM: Yeah. I think there's probably some value in it. I'm actually going to do a little homework on this because it seems to make a lot of sense. I really wasn't aware of this association prior to me hearing your presentation.

LF: Right.

JM: And it makes a lot of sense.

LF: I mean this is really chemistry. All these things are acids.

JM: Yeah, yeah. Basic stuff. Maybe you can touch a little bit more on klotho. Because for those of us who study anti-aging, it does come up quite a bit. You talked about its role in the phosphate, but talk about its role in anti-aging and telomeres.

LF: That's a really good question. I'm going to say that there are a lot of similarities between things that happen in aging and things that happen as kidney failure progresses. That's actually how I got interested in this. Because some of the biochemical things are, you have increases in transforming growth factor beta (TGF- β), which causes scarring. You have increased cell death and apoptosis, which occur both with kidney failure and aging. You have shortening of the telomeres. We know that increased telomere length and increased telomerase activity keep you alive longer too, at least worms. And you have increases in advanced glycation end products in both uremia and aging.

I actually think that maybe some of the things that are occurring as we're getting older are occurring because our kidneys are getting worse as we're getting older. And so if what's happening to the kidneys as the kidneys fail, if we can slow progression of kidney damage, potentially we could slow some of the aging progression, some of the breakdowns that occur as we get older too. Because they may be related. And that's actually something that we're trying to look at more, one of the research projects that I'm working on.

JM: Yeah. Is there anything more to klotho than just the association with telomere length? Or do you think it's a correlation and not a causal issue?

LF: I think that they are two different factors that are associated with aging. And I think that because klotho levels go down and telomeres get shorter in kidney failure, independent of how old you are, and telomere length goes down, and klotho declines with aging, and kidney function declines with aging, I'm questioning what the relationship is and whether or not some of that is actually the same problem.

JM: Yeah. And just to repeat for those who might be interested in this, unless you have a research lab, you're not going to be measuring your klotho levels. It's not a commercially available assay. But this FGF23 –

LF: FGF23 is also not commercially available.

JM: Yet. But soon to be by your –

LF: I anticipate that this is something that people are really going to want to look at, especially kidney doctors. I mean this is something that we would really like to know what's going on. We can't look at serum phosphorus levels because that doesn't tell us the overall status. It's kind of like, "What's your blood sugar?" and "What's your hemoglobin A1c?" Blood phosphate levels tell us what your blood phosphate level is now. But what we would like to know is, "What's the overall status?" And that's what FGF23 would do.

JM: So I'm wondering maybe we should have had this discussion at the beginning. But as a nephrologist, if you could give your recommendations for how someone might monitor their own kidney function at a base level and work your way. So obviously you've got your creatinine and blood urea nitrogen (BUN). If you could give your recommendations then when they exceed certain levels. Obviously you need professional guidance to do this, but just to help people understand what the process is and what the next step is and when will you do a GFR test and are there other assays, like cystatin C, which you'd recommend? I would be curious – Your explanation to patients who are beginning the journey to kidney failure.

LF: Okay. Everybody's doctor routinely checks a renal panel. That will give you the blood urea nitrogen level. It'll give you the serum creatinine. We calculate GFR based on your gender and your age and your serum creatinine. There's a factor for race too. And so that will give you this number that –

JM: That's calculated. It's not measured.

LF: It's calculated. Right. Exactly. But we measure the creatinine. And so which kidney test to do depends on a couple of different factors, which mainly have to do with whether or not you think the number might be wrong. There are some people where we don't know how much muscle mass they really have. And so creatinine is a measure of muscle mass. A creatinine measure might be wrong there. Cystatin C, which is another protein that is filtered through the kidney, is affected by inflammation. If you have a bad infection or you have some sort of acute inflammatory process, then cystatin C will be high because of that and not related to the kidney function.

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So you choose the kidney test that you want to do based on whether or not you think that there's something interfering with that test. In terms of just looking at kidney health, there are two things that we look at. One is, "What is that eGFR number?" Two is, "Do you have any protein in the urine?" Those can be two separate problems. Protein in the urine, in and of itself, is bad for kidney function we think. This was discovered many years ago by a guy named Dr. Barry Brenner, where he did five or six nephrectomies in rats and showed that the remaining kidney, the so-called nephron remnant, had to hyperfilter in order to be able to clear all the blood. That hyperfiltration through the glomerular membrane was bad for the membrane, so the membrane started to leak protein.

And so we now know that there are a number of kidney problems where the membrane is leaking protein. That causes the kidney to be more damaged. If you had to do just two things just to see

how healthy you are, the first would be to get a blood test to see where your kidney function is. The second is to get a urinalysis. Pretty much anytime you go in for a primary care visit, those are the two tests that they usually do.

JM: Yeah. And actually, you could to the urinalysis yourself. I mean you could easily, on Amazon, pick up these urine dip sticks that can tell you if you have protein. That's what they test in the commercial labs anyway. They use dip sticks. I don't think they measure it precisely, unless you're doing a specific quantified urine test.

LF: Some labs do and some labs don't. Some labs can give you a quantitative guess, like 30 milligrams per deciliter or 100 milligrams per deciliter, greater than 300 milligrams per deciliter.

JM: I'm curious as to where your threshold would be of concern for serum creatinine, or you just go by the estimated GFR. When the estimated GFR hits one level or the serum creatinine hits another level, do you go for measured GFR?

LF: Yeah. These days we routinely get both of them reported at the same time. So what a normal creatinine is would depend on what your muscle mass is. If you are a little tiny, little old lady with not very much muscle mass, your creatinine –

JM: With massive sarcopenia.

LF: No. Just little old ladies. I mean you have small Asian women who are 30 years old, for example. They don't have enough muscle mass. Normal creatinine level for them might be 0.7, okay? And if you have a 6-and-a-half-foot-tall football player, a normal creatinine for him might be 1.6 or 1.8.

JM: Really?

LF: For the small Asian woman, 1.8 is super high, okay? I wouldn't expect anybody who has a lot of muscle mass to have a creatinine of 0.7 no matter what. I might expect there is a problem with the measurement.

JM: Yeah. That's a good point.

LF: So the number is not like, "Oh my God, it's this," okay?

But we use that number to do a calculation that takes into whether you're male or female and how old you are and whether or not you're African American or not?

JM: I'm curious, what is the issue of being an African American?

LF: Yeah. I'm going to say that this was an empirically derived equation. So the guys who came up with these various equations, looked at a massive amount of data, like actual data, and then fit the equation to the data and came up with this equation and said, "Which factors are important?" So this is an empirically derived number.

JM: Okay? All right. So it's not really clear why that's –

LF: No, no. This is just to make the numbers come out right.

JM: Okay. Alright. But there's still, at some point, even if that point means that you're confused because you can't really determine the person's precise muscle mass. When does it make sense to get the measured one? Which involves, as I understand, a collection for 24 hours of the urine and then sending it to the lab to actually measure it.

LF: So that's a creatinine clearance that you're talking about.

JM: Can't you derive –

LF: Why don't I do that?

JM: Can you derive from there?

LF: I don't routinely do 24-hour urines for creatinine clearance unless I'm doing a research study. Or in very, very advanced kidney disease, we do 24-hour urine collections for urea and creatinine. And then we average the two to try to guess what the GFR is.

JM: Okay.

LF: But normally I don't do that.

JM: Well, how do you measure – I mean as opposed to estimate, how do you measure GFR?

LF: Well, we don't normally measure GFR.

JM: There's the confusion. That's why I'm confused.

LF: We only estimate GFR.

JM: I thought there was a laboratory test that you could measure it. How foolish of me.

LF: Not the way it's normally reported, no.

JM: Okay.

LF: Not without doing special tests. I mean, if you really want to measure – This is a little bit in the weeds for those nerds out there. But what you really want to do is find a compound that after it's filtered isn't reabsorbed by the kidney tubules and isn't secreted by the kidney tubules. So if we really want to measure GFR, we give something that is only filtered, like iohexol, for example, or inulin, was the old way we used to do this. So it is possible to actually get a true GFR measurement, but we don't routinely do that.

JM: I'm curious. I'm wondering why not? Was it a bit – I mean, it was a commercially available lab test. It was just abandoned because they didn't find utility in it?

LF: If you're talking about the 24-hour urine, the reason, one is you have to get people to do it, number one. Two, they have to do it correctly or it doesn't help you. In my experience because I do these for research purposes, even after having people watch a video, tell the nurse what to do, give them written instructions on what to do, about 10% get it wrong. So, you know, it's not just, "Oh, just do it," okay? You've got to work at it a little bit.

JM: Yeah. Complexities. But it's still commercially available.

LF: It still is. Yes, of course. And we do use it, but not just as the routine, you know, primary care, "Let's just check your health" visit.

JM: Yeah. Because of the practical challenges of implementation and compliance. Okay. Well, that makes sense. I think many people will find that discussion useful. Thank you for sharing that perspective. Are there any other insights from your decades of research in this area that you'd like to share?

LF: You know, most of what we've done is look at acidotic stress, okay? But what most people are familiar with is oxidative stress, which is where the oxygen molecules have too many electrons. So oxidative stress is one kind of stress, and acidotic stress is another kind of stress. My belief is that they're actually both important, okay? It's not just one or the other. It's really both. And so that's – I believe that that's important towards progressive kidney disease. It's been shown to be important in aging too.

A friend of mine named Dr. Elissa Epel has looked at the relationship between telomere length, telomerase activity and oxidative stress. [She] has shown, for example, in people who are under a lot of stress to have shorter telomeres and abnormal telomerase function, that they have higher levels of oxidative stress. I think they're both important. It's not – I happen to have done more research on the one thing, but really, I think it's a combination of both.

JM: Yeah. I read her book. She co-wrote it with Elizabeth Blackburn, who won the Nobel Prize.

LF: Right.

JM: "The Telomere Effect" is the name of the book.

LF: Yeah.

JM: So I'm curious if you have insight as to how the successive oxidative stress causes the damage. Is it biologically? Is it in the mitochondria? Or is it actually in the renal tubules or both?

[-----50:00-----]

LF: My guess is it's both. I think that because the body really doesn't like to have free protons and free electrons floating around, because they attach themselves to different molecules and damage the molecules. My belief is that this really works at a fundamental chemical level and not just on one thing but on lots of different parts of the body. And so the whole idea would be to lower the amount of oxidative stress and lower the amount of acidotic stress, and therefore limit the damage to the body.

JM: Yeah. It's probably target-specific too. Because excessive or extra protons can actually be beneficial if they're in the mitochondria and you're pumping them through Complex V, adenosine triphosphate (ATP) synthase, to generate ATP. But with the excessive protons you're referring to, I would have assumed they're interstitial.

LF: Well, I think that they're intracellular. They're interstitial. You know, pH, what pH really is is a measure of the free protons in the body. Because this is anti-logarithmic, so the higher the pH, the lower the actual number of hydrogen or hydrogen protons floating around. So for example, normally if you have advanced kidney function and your blood pH is let's say 7.30 or 7.35, you have a lot more free hydrogen protons floating around in your bloodstream than you would if you have 20-year-old kidneys and your blood pH is 7.45. So it's out there. We're actually talking about measures of, you know, like these free protons floating around damaging things.

JM: Yeah, absolutely. So do you have any good resources you advise people if they're interested in following a low-acid diet and how to implement that?

LF: Yeah, eat more fruits and vegetables. This is a balanced thing, okay? It's not so much that you're not supposed to eat protein. It's that if you're eating a lot of protein, you should be eating a lot of fruits and vegetables. And my personal belief is you should probably limit the amount of dairy products that adults eat.

JM: Yeah, there's been a lot of arguments against dairy products. But from my perspective, this is probably one of the most compelling that I've ever heard. It's that the high phosphate levels that contribute to premature kidney aging and general cellular aging. So that's a pretty strong argument.

LF: It's an argument. Yeah.

JM: Yeah, yeah. It makes some sense. I mean, there's certainly value for milk but, you know, people ascribe, "This is only for babies," and maybe that's right. I mean, it certainly, biologically, that's what appears to be the case. I mean, it can be used therapeutically, but you've got to be careful with that phosphate. So well, any other comments or recommendations you'd like to provide us with?

LF: Probably the one thing that I would say to a general audience is when kidney doctors think about, you know, kidney problems, by the time people are sent to us, typically they've lost about three-quarters of their kidney function. And if you really want to make a difference, this is really, you really have to catch it much earlier. And so it's really super important that people, you know, go and get regular checkups so that if they're starting to develop a problem, we can find out about it early, when there's still something that we can do. As opposed to, you know, when your GFR is

like 25 and we're working with the last couple of thousand nephrons, when really our ability to you know, really slow things down is just much, much more limited.

JM: Yeah. That kind of reminded me of another question to ask. Before I went to med school, I actually was coordinator of the kidney transplant team for the University of Illinois and was responsible for harvesting the kidneys for transplant. I'm wondering – But that was many years ago. That was in the 70s. So I'm wondering what your experience now is with transplants because obviously, once you reach end-stage renal failure, you're dead unless you're on dialysis or some form, either peritoneal or hemo, or you're getting a transplant. So has the transplant process improved nowadays?

LF: Yeah. That's a really great question. And so the main problem with kidney transplant is the limitation on the number of organs that are being harvested and transplanted. And the fact that the number of living donors has not increased dramatically over the last two decades. So the number of people on dialysis awaiting transplantation goes up and up. And the number of kidneys available really has not gone up very much at all. And so the gap is widening more and more. And it's clear that after about the first year, not only are kidney transplant patients healthier, but it's more cost-effective to, you know, keep them healthy. Dialysis is both extremely expensive and just barely keeps you alive. So, you know, transplant would definitely be better.

But, for example, that's what promoting this whole new government kidney initiative, which came out about six months ago. One of the things that I'm working with here at UCSF is the artificial kidney guides run by Dr. Shuvo Roy and Dr. William Fissell at Vanderbilt University. What they're trying to do, as our other groups, is trying to come up with a filtration system, as well as a kidney tubular system, so that instead of doing the kind of dialysis that we do now, which is just the filtration part, we have the kidney tubules in there. The kidney tubules can do a lot of things that we can't do. It can respond to signals from the body so that we get a much better control of how much you reabsorb and how much you're getting rid of. So, you know, it's in the future. And this is like, at least a decade away.

We'll be able to actually transplant artificial kidneys, which are, you know, partially mechanical filtration and partly biologic. And then the ultimate Holy Grail is we would actually be able to grow kidneys, like real kidneys, and then we'd be able to use your cells to grow a kidney that looks just like your kidneys, so that we would just be able to put it into you and we wouldn't need to worry about rejection of the transplanted organs.

JM: Even worse, taking the anti-rejection drugs. But I personally think that the cloning kidney is going to happen before the artificial one, because they're making some exponential progress on it. Every year it gets better and better. But there's a point too that – I'd just like to include that most people aren't aware – certainly you are – that once you hit end-stage renal failure. It's a very costly procedure or process, as you alluded to. But you don't have to worry about it because once you're there, you're in Medicare. Even if you're 10 years old, you're covered. So pretty much the –

LF: All end-stage renal disease is covered by Medicare in the United States. The problem, of course, is that Medicare only really covers the cost of the dialysis and there are a lot of things that

are not covered very well by Medicare, including medications, for example. There's a lot of extra expense that comes with end-stage renal disease that's not necessarily covered by your insurance.

JM: But without the Medicare, they couldn't afford it. Most people couldn't.

LF: Without Medicare, nobody can afford it. Yeah. That's right.

JM: Well, not nobody, but very few people, that's for sure. And most of these people would be dead in a few weeks, for sure.

LF: You know, right now it costs about $90,000 a year and the cost is going up about 1,000 to 2,000 dollars a year. That's not including surgical procedures or medications or anything. So yeah, I mean, some people could afford it, but not very many.

JM: Yes. That's right. When they do dialysis is most of it peritoneal now?

LF: No. In the United States, most of it is hemodialysis that's done in special dialysis centers. If you go to Canada, actually, the majority is peritoneal dialysis, but not in the U.S.

JM: Okay. All right. Well, thank you for answering that.

LF: These are questions that we get asked a lot and the whole kidney initiative. One of them is to be able to do, for example, more dialysis at home. Because then you could maybe do dialysis more often and we know that that's better for you.

JM: Yeah. It's a complex problem.

LF: Complex problem.

JM: So like almost any disease that we have, the answer is not the sophisticated end-stage techniques and therapies. It is prevention. And that's why I was so intrigued with your presentation and wanted to have you on. Because you're really providing us with some strategies that prevent end-stage renal diseases if you catch it early enough. So the things we know of clearly, but also this new twist, which is not really widely known. People knew about the low acid, but didn't appreciate that this phosphate, even that the kidney specialist didn't appreciate until a few years ago. And the researchers have even done it with the levels are now. But lowering your phosphate levels to as low as you can reasonably do, and avoiding the high-phosphate foods could be a tremendous benefit to improving your kidney function and maintaining your kidney function.

LF: Yeah. Especially if you're older and your kidneys aren't working as well. I mean, I would particularly say that those are the people that I would particularly want to like to have – Like if I had to choose, say, I think you should focus on this.

JM: Yeah. Well, I greatly and deeply appreciate your contribution. It's a really an important message. And it's so simple. If you think about it. It's not that hard to go online and find low-phosphate foods or go to Cronometer and actually measure it yourself.

LF: Yeah. The National Kidney Foundation actually has a whole website dedicated to diet in renal disease, so you can get like every food known to mankind on this list. So yeah, absolutely. It's available.

JM: Yeah. And that's good. But you know, if you really want to be precise, I would put a plugin for Cronometer.com, C-R-O-N-O-M-E-T-E-R. It's free. You could just put – It takes a little effort to input your foods, but you can measure your food directly. You don't have to go and look it up on the list. It'll calculate everything for you. You don't have to add all the foods up a day. It's just, boom, one number. There you have it.

LF: Okay.

JM: It couldn't be easier. Thank God for technology. I mean, the 21st century offers some major amazing benefits we didn't have back then.

LF: Yeah. I agree to that.

JM: Yeah. It was just crazy back then. So anyway, again, I want to thank you for your contribution and for helping us understand I think this really important part of kidney and total health.

LF: Well, I appreciate your asking. Thank you so much.

JM: All right.

LF: Okay, great. Bye.

JM: Bye.

[END]