

## EPISODE 25: DIABETIC NEUROPATHY

**Rita Kalyani, MD:** Welcome to *Diabetes Deconstructed*, a podcast for people interested in learning more about diabetes. I'm your host Dr. Rita Kalyani at Johns Hopkins. We developed this podcast as a companion to our Patient Guide to Diabetes website. If you want a trusted and easy-to-understand resource for diabetes, or to listen to previous podcasts, please visit [hopkinsdiabetesinfo.org](http://hopkinsdiabetesinfo.org). We are pleased today to welcome Dr. Limerick to our podcast. Dr. Limerick completed his MD and PhD in Cell and Developmental Biology at Rutgers University as well as a fellowship in pain medicine at Johns Hopkins. At Johns Hopkins, he has developed a clinic for the treatment of painful peripheral neuropathies with a specific emphasis on peripheral diabetic neuropathy. His practice involves a patient-centered multimodal approach, which includes oral therapies, specialized topical therapies and neuromodulation. Welcome, Dr. Limerick.

**Gerard Limerick, MD, PHD:** Hi, happy to be with you.

**RK:** We're happy to have you here. I was wondering if you could start off by telling us, what does peripheral neuropathy really mean?

**GL:** Yeah, that's a great question to get started with. Peripheral neuropathy just refers to any damage to the nerves predominantly in the limbs: the arms and the legs. When we talk about diabetic neuropathy in general, it's a result of metabolic micro-injuries to vessels from excess sugar in the bloodstream. Now, that's a lot more complicated than that, but that's a general description. Diabetic neuropathy can affect nerves anywhere in the body: the heart, the stomach, or some other common places. But when we talk specifically about diabetic peripheral neuropathy, we're typically talking about neuropathy that's occurring in the nerves of the limbs. There are a lot of different classifications for neuropathy. But when we talk about diabetic neuropathy, typically we describe it as a length-dependent neuropathy, which just basically means that the nerve endings of the longest nerves in the body are typically affected first. So a nice little bit of medical trivia: the longest nerve in the body is called the sciatic nerve. And I think many of you have probably heard of that. You've heard of people with "sciatica." What that means is that the nerve endings of the sciatic nerve are in the foot, and typically, since length-dependent neuropathy, that's where people tend to get symptoms first and also tend to experience the most severe pain from diabetic neuropathy. And then lastly, it is typically symmetric, which means that it's the same on both sides. And you can also have involvement of the motor nerves, but typically, the sensory nerves are affected first before the motor nerves.

**RK:** Just to clarify, when you say neuropathy, is that the same thing as nerve damage? Or are those two different things?

**GL:** Yes, those are essentially the same thing. Neuropathy is any sort of damage to the nerve that results and symptoms. These symptoms can be pain, when you're talking about sensory nerves. But if you're not talking about sensory nerves, they can manifest in different ways. If you have a diabetic related neuropathy of your stomach, for example, it can slow the rate at which food is digested and things like that. When we're talking about peripheral neuropathy, it is any sort of damage to the nerve that results in some sort of symptoms.

**RK:** You talked about how in diabetes, often it's more sensory neuropathy the sensation part not much the motor neuropathy moving your muscles. Why does neuropathy occur and people with diabetes to begin with?

**GL:** Having high blood sugar affects your nerves in a number of different ways. We really could spend probably a whole other podcast just talking about the different ways in which it affects your nerves. One of the things it does is it reduces the availability of molecules that help to fight free radicals. Some of you may have heard of free radicals if you've read about smoking and things like that. These are molecules that kind of run around and damage the bodies. It decreases the availability of molecules that fight free radicals but it can also directly cause production of free radicals. That's one way it does that. Another way is that it can actually reduce the blood supply to nerves by damaging the small vessels that carry blood to your nerves. Having high blood sugar can also cause swelling of the nerve itself, which can also cause pain. Additionally, sometimes the electrical stability of the nerve itself can be damaged. There are a lot of different ways that having high blood sugar can directly damage your nerves.

**RK:** It's true that blood glucose lowering is a central tenet for us in diabetes management and one of the complications we often talk about under the traditional microvascular complications are neuropathy- reducing blood glucose levels to prevent the onset of neuropathy. And it's interesting to hear about all the different ways that high blood sugar really can be detrimental to the nerves. Does neuropathy only occur in people who have difficult to manage blood sugars or can it occur in earlier stages of prediabetes and diabetes as well?

**GL:** There is some evidence that there may start to be changes in people who have prediabetes. In the field, it's commonly understood that you can have what's called silent neuropathy for some time before you start to develop symptomatic neuropathy. In the sciences, it's not

altogether clear yet, but it certainly is possible that people who are prediabetic can begin to have some changes in their nerves that predispose them to developing diabetic neuropathy later on down the road.

**RK:** In people who don't have symptoms, how do they know that they have nerve damage?

**GL:** It would be unusual to have some nerve damage without symptoms. Nerves are really, really sensitive. And again, the science, I think, is still developing around this. But if you don't have any symptoms, then for people like me, there's really not much to do, right? I'm here to help once symptoms kind of emerge. But again, for anyone with diabetes, the best thing you can do really the first line treatment for diabetic peripheral neuropathy is to just control your sugars- that's the best thing you can do. And it'll give you the best chances of avoiding diabetic neuropathy down the road.

**RK:** So prevention is clearly important, like you mentioned, in terms of keeping your blood sugars at target, whatever those individualized targets are that you discuss with your health care provider. But once the damage occurs, one of the things I often hear from patients is that when their blood sugars are high, they feel the neuropathy symptoms more. Is that something that you often see and why is that?

**GL:** That's certainly possible. As we mentioned, there are a number of different ways that having high blood sugar directly affects the nerves. One of the ways that I mentioned is that it can cause swelling in the nerve. There are some changes in fluid shifts that can happen if your blood sugars are really high. And one of those is you can have volume changes within the nerve itself. It makes perfect sense that if your sugar is really high, you feel your sugar go up, then it could be as a result of some of those fluid shifts. It is certainly possible that there are patients who are sure that their sugar was actually getting high just from the increase in pain. And of course, other ways that sugar affects pain in that if you're in taking a lot of sugar, it causes a pro-inflammatory state. And it's inflammation itself causes the release of a lot of other factors that can worsen pain. That's certainly something that can happen, and I'm sure there are many other reasons for that.

**RK:** I guess this all underscores the importance of keeping your blood sugars within the target range to really prevent the onset of nerve damage. And also, to prevent the symptoms if you have nerve damage already. Is it ever possible to have reversion of the neuropathy if someone has nerve damage for it to get better? Or once it occurs, is it kind of always there?

**GL:** Unfortunately, there's nothing that we can offer at this point that actually causes a reversion of the nerve damage. Once it's there, it's kind of there. The best thing that we can do is sort of offer different treatments and things to sort of help improve the symptoms. But certainly, again, prevention is really sort of the key here, right? Because very often, once those symptoms start to manifest, there's really no going back. Now there are some anecdotes out there of people who have had actual improvements, but there aren't any large studies of people really having significant reversal of the neuropathy.

**RK:** I fully agree with you. Prevention is so important, especially when you can't really reverse these complications once they have occurred. Prevention is critical to preventing them from happening in the first place. Now you mentioned how peripheral neuropathy is often length-dependent [and] that it affects the long nerves first. Really, we often see it in the toes, and we often ask about numbness and tingling in the toes, and maybe it'll go up to the ankles and knees, and then it takes a while before it could impact the hands. Is that right? Or when might you start seeing symptoms in the hands?

**GL:** That is correct, and that's a really good point. Typically, just as a rule of thumb, usually people don't start to get involvement in the hands until the neuropathy has reached the level of the knees or so. But if you're someone who comes in and says, "I have neuropathy in my hands and in my feet," but in your feet, it's really only up to maybe your ankles or maybe just your lower shin, then I have to think about whether or not this is actually diabetic peripheral neuropathy and whether there is some other neuropathy at play. And there are lots of other common neuropathies that can be screened for as needed. It's really too long to list the kind of detail here, but typically, you can get symptoms in your hands, but it's typically not until the neuropathy in your feet has usually reached the level of the knees or lower thighs.

**RK:** And, as we talked about, people with diabetes are at a higher risk of neuropathy that with optimal blood glucose control can prevent that from occurring. If neuropathy does occur, what does it feel like? What are the symptoms that people should be aware of?

**GL:** All sensory nerves are not equal. So there are some differences in sensory nerves. Typically, when we're talking about neuropathies, we make a distinction between symptoms that result from damage to large sensory nerves and symptoms that come from damage to smaller sensory nerves. So typically, in diabetic neuropathy, the larger nerves are affected first, although that's not always the case. There are exceptions to that; in about 25% of cases, you get small nerve damage and symptoms first. Typically, if you have large nerve damage,

those symptoms are a little different. Those are typically things like numbness in the feet or trouble with balance; some patients might describe some difficulty knowing where their feet are in space. And these large sensory nerve symptoms can cause falls, which can be a pretty significant source of morbidity and mortality. Those aren't typically the symptoms, though, that push people to come and see me. Typically, the symptoms that tend to be more bothersome or troublesome are the damage to the smaller sensory nerves. Patients describe that pain as burning, prickling, pins and needles, and sometimes shocking pain. And those are the symptoms that typically motivate people to seek further care. You can develop things like hyperalgesia. If I were to stick you with a small pin, it would hurt, but you wouldn't jump out of your chair per se. But for someone with diabetic neuropathy in their feet, if I stuck them with that small pin, they might try and kick me because there's an exaggerated pain response. So that's something we call hyperalgesia, that tends to take place as a result of that small sensory fiber damage. There's also allodynia. People with diabetic neuropathy can have problems with things such as just putting on socks or just lying comfortably in bed; sometimes just moving the sheets over their feet is enough to cause significant pain. When you have what we call a non-painful stimulus that's causing significant pain, that's what we refer to as allodynia. People with diabetic neuropathy can develop that as well. Those are some of the common signs and symptoms that we see in patients with diabetic peripheral neuropathy.

**RK:** Thanks for going through all those different symptoms. I've certainly heard those symptoms from my patients with neuropathy. One question that I had was, you described the symptoms of numbness and tingling, which were often the ones we asked about when we see our patients in clinic. But the pain symptoms, from what I've noticed, aren't in everyone with neuropathy. Is that just a smaller subset of people who have neuropathy? Or is that more later stage would you say of damage?

**GL:** Yeah, typically, in patients with diabetic neuropathy, most of them get large fiber symptoms first. Those would be the things that you described: the numbness; the trouble with balance; the stumbling. It's really only about 25% of patients who get those small fiber symptoms—sharp, burning pain—first. So it is entirely possible to have the large fiber symptoms—numbness and stuff—without having the small fiber symptoms. That is totally possible, and it's something that occurs fairly frequently.

**RK:** Now, we talked about blood glucose management being important. What about other factors such as blood pressure and cholesterol. Do those impacted development of neuropathy or not much?

**GL:** As far as we know, those probably have a much smaller role to play. I haven't seen much in the literature about that specifically. But as clinicians, there are inferences we can make. If you have high blood pressure that causes further injury to the vessels that are supplying blood, then it makes sense intuitively that if you damage your vessels further then it would have an adverse impact on the nerves. Although that might not be studied as much, it certainly makes sense that if you have high blood pressure or if you have elevated cholesterol by damaging your blood vessels, that you're certainly going to have some impact on your nerves over time.

**RK:** I guess one of the other questions that often comes up in clinics is: How would [you], from an examination, identify that someone has neuropathy? It seems like some of these symptoms, such as numbness, or sometimes you can stub your toe, and it might be numb, and sometimes it can be difficult to differentiate small trauma, for instance, from symptoms that might be worrisome for neuropathy. What might be the telltale signs that you see on exam that help you figure out if it's from diabetic peripheral neuropathy?

**GL:** Typically, there are a few different things that sort of help us shape the diagnosis of diabetic neuropathy—certainly a physical exam. We talked about some of the changes that take place. When I first sit down with a patient who I suspect has peripheral diabetic neuropathy, I'll ask them about the types of symptoms they get: "Are you feeling? Are you stumbling? Are you falling? Often? Is there any numbness in your feet?" And then I'll also ask about their pain: "Is it present all the time? Is it sort of spurred by doing things that shouldn't really cause pain?" Those are some of the things that I will ask for on history. On exam, when I'm actually looking at the feet, there are a couple of different things that we look at. I'm checking the pulses to make sure that you have good pulses. If the pulses are poor, then it's possible that you might have some ischemic pain that's kind of spurring the pain; checking sensation, which will give me a sense if you have large fiber involvement; checking proprioception, where your big toe is if I move it up or if I move it down; can you tell me the difference? That's something we'll look at; we can also use a hammer just to sort of check again whether or not you can sense changes in vibration. We'll also check temperature, if you can distinguish between hot and cold. And then also, if just lightly brushing my glove against your foot causes an increase in pain, then all these things together sort of help point us towards that diagnosis. So, of course, the exam is important.

Also looking at your hemoglobin A1C, if you're someone who's always had a well-managed hemoglobin A1C, it's less likely that this might be the primary cause, but it is still entirely possible. Although if you're someone who has always had an unmanaged hemoglobin A1C, it becomes a lot more likely to say, "Hey, this is probably from the diabetes." We don't really need imaging very often. Sometimes we'll do an EMG. If there are some confounding factors, say, for example, maybe you have pain in your back and in your leg, and we're trying to see, "Well, is this really your peripheral neuropathy? Or do you have a radiculopathy? Is the pain coming from a nerve being

squeezed in your back?” Sometimes, EMG can be helpful for that. And really, the only sort of invasive tests — I don’t really call invasive, but really the only tests that sometimes require any tissue, sometimes is skin biopsy. In cases where we’ve looked at the exam or looked at the history, we’ve looked at your hemoglobin A1C, and we’ve done EMG, but you still really just kind of want to nail the diagnosis. Really, the gold standard for looking for small fiber neuropathy is a skin biopsy. That’s something that we do sometimes as well.

**RK:** And I know in clinic, we often do the mono filament test, which probably in your neuropathy clinic, you do in much more detail. How helpful is that in detecting peripheral neuropathy?

**GL:** Yeah, it can be helpful, right? As you mentioned, those large-fiber symptoms typically develop before you start to get the real pain. Now, in my context, as a pain physician, I’m not racing too many patients who just have the large fiber symptoms. Typically, I’m getting people who have the pain itself. It’s already advanced to a point sufficient to really cause that pain. But certainly, yes, testing with a monofilament is an important part of a well-rounded physical exam, especially again if you’re not sure that the symptoms are being caused by diabetes. You know you really want to sort of be sure that you’re not missing something else, right? There are lots of other things: people who have had cancer, or sometimes chemotherapy causes symptoms, and HIV, Lyme disease, or syphilis. There are so many other causes of neuropathy. Again, it is important—really taking a look at the whole picture and making sure that all the pieces fit.

**RK:** And the monofilament task, could you just briefly explain what that is, and what it tests?

**GL:** Well, that’s a test for sensation. Typically, when I’m checking sensation in the feet, I typically will test by dermatomes. So usually three major dermatomes: L4, L5, and S1 on the feet, I’ll test along the inside of the ankle, I’ll test out to the great toe or your big toes, and I’ll also test along the heels. What’s important when you’re checking with a monofilament is not just to ask, “What do you feel?” But you’re also comparing side-to-side, right? Because, as I mentioned, typically in diabetic neuropathy, it’s symmetric. It’s not always the case; sometimes you can have a mono-neuropathy, which just means that one particular nerve is involved. It’s less common but certainly possible. But yes, typically with the monofilament test, we’re testing in a few different dermatomes just to ensure that it’s really sort of symmetric and kind of even, and not really limited to the distribution of one nerve. And then we’re comparing side-to-side, because the definition should be symmetric.

**RK:** And this is a filament that we apply to the foot at different pressures to see if the individual feels, as you mentioned, in different areas of the foot to see if it’s symmetric on both sides of the feet, but it also gives us a window into which nerve might be damaged. And I know for us in the diabetes clinics, it’s a very simple task that we can do just to get a first look into whether there might be this loss of protective sensation, which we know is important, particularly for the development of ulcers and that kind of thing to prevent. So it’s a task that I find very useful, and I appreciate you sharing how you’ve used it in your practice as well. Inspection of feet—that’s something that we often tell our patients with or without neuropathy to do routinely. Is that a simple thing that people can do to help, or do you think that... What’s the utility of inspecting the feet of people with diabetes?

**GL:** Yeah, that’s certainly an important part of, I think, good global diabetic care, right? Particularly if you are someone who has diabetic neuropathy, if there’s a small cut or anything that looks out of place, you definitely want to be able to catch it early before it develops into something more serious. And I have certainly seen lots of patients who, unfortunately, have had amputations just because there was something that they missed. They just didn’t feel it because of the neuropathy. And certainly, I’m not a podiatrist. But I certainly, whenever the patients come in, always have them take off their shoes and socks, even if I’ve examined their feet before, just to see if, between the last time I saw you and this time I saw you, anything looks concerning or out of place. Yes, certainly good foot care is a really important part of diabetes management.

**RK:** And moving on to treatment, which is the big question, we’ve talked about prevention with blood sugar management and diagnosis. But what treatments are available for people who have symptoms - really disabling symptoms of pain - for their neuropathy?

**GL:** Yes, the million-dollar question. Just sort of generally speaking, you can classify most of the treatments sort of into four, well, really kind of three major categories, but there’s a fourth that I’ll call a minor category. The major categories of treatment are oral medications, topical medications, and neuromodulation; the fourth, sort of minor category, is heat treatments. So we’ll touch on that just briefly. But really, oral treatments, topical treatments, just treatments that go into the skin, and then neuromodulation are kind of the three major classifications of treatments.

We can talk a little bit about oral medications first. There are three major categories of oral medications that we use for managing the pain associated with diabetic neuropathy. The first category is what we call anticonvulsants. These are medications that were traditionally used for helping to manage seizures, but we’ve done a lot of studies over the years that have shown that these medications can be helpful for

treating diabetic neuropathy. Really in that class of medications, the only FDA-approved anti-convulsant is pregabalin. That's usually one of the ones we reach for first. Sometimes gabapentin because some of the studies have shown that the efficacy of gabapentin is somewhat similar to the efficacy of Lyrica. It's often a lot more affordable for patients. Sometimes we reach for the gabapentin first, but typically gabapentin or Lyrica are the anti-convulsive medications that we use most frequently. There's also carbamazepine, which maybe is like a third-line option there, but typically, pregabalin or gabapentin are the two that we use most often. There are also anti-depressants; one of the medications that I've seen help quite a few patients with diabetic peripheral neuropathy is duloxetine. Duloxetine is FDA-approved as a first-line treatment for diabetic neuropathy. Typically, I'll start patients at a moderately low dose, usually about 30 milligrams. Let them kind of try it out for a week, and if that's fine, then usually we'll bump them up to 60. And usually anywhere between 60-120 milligrams is typically that sweet spot for helping to improve those symptoms. There are a few other antidepressants, such as nortriptyline, amitriptyline, and a couple others like venlafaxine. But I usually start with duloxetine first because, as I mentioned, that's the FDA-approved option within that group. And then really the last group of oral medications. It's the O word: opioids, right? And obviously, that's not something we start with, not only because of the well-known side effect profile but also because their efficacy compared to the efficacy of the anticonvulsants and antidepressants is less. For patients who have tried anticonvulsants, who have tried the antidepressants and who haven't really been able to move the needle on their pain much, then sometimes opioids can be considered. The only FDA-approved opioid for diabetic neuropathy is tapentadol. But that's something that we use sometimes for a number of reasons, many of which I'm sure are well-known to you. Typically, opioids are something that we tend to keep on the back burner as the last-line oral options. That's really kind of a quick summary of the oral medications that we use for diabetic neuropathy.

**RK:** That's interesting that there are many different options for medicines to use by mouth (oral medications) and great to know that they can all be helpful in different circumstances. You mentioned the topical medications, the ones that are applied to the skin as well. Could you tell us a little bit more about those?

**GL:** Sure, typically, one of the topical agents I'll recommend initially for patients to try is really topical lidocaine, which is available over the counter. But there are lots of good studies that show that topical lidocaine can be effective for helping to manage the symptoms. And in some cases, it might be comparable, you know, to the efficacy of some of the oral medications. It's a good option for people who, unfortunately, sometimes with the anticonvulsants people complain of things like sedation, fatigue, or they just don't feel like themselves. Sometimes it can sort of help those people who are struggling with those side effects to still kind of get some relief. So topical lidocaine is a great option; another great option is topical capsaicin. Capsaicin is the stuff that makes peppers spicy. Actually, a fun fact: the Nobel Prize in Medicine last year was awarded to the scientists who helped identify the ion channels that capsaicin binds. So we have a few different ways of applying it: There are over-the-counter capsaicin creams, maybe even 1% or 2%, that can be helpful; we're currently right now at Bayview getting ready to offer an 8% topical capsaicin patch, which studies have shown that with repeated treatments can actually really make a significant change in the amount of pain relief a patient gets. So that's a treatment that has to be done at the clinic in a monitored setting because 8% was pretty strong, and you don't want patients touching their eyes or other mucous membranes after you've touched it. It's something that we apply in the clinic. But it's another topical option that can be given and doesn't have systemic side effects that will make you sleepy or tired. But it can also really sort of help move the needle on pain relief.

**RK:** Well, that's interesting that they're topical options as well. And thanks for sharing the story about capsaicin. It's an interesting story and great to hear about its benefits for pain relief. Lastly, you mentioned neuromodulation. What is neuromodulation? And how does it help with diabetic pain?

**GL:** Yeah, neuromodulation is the thing that has everyone in the pain field excited. You'll notice many of us, if you ever sort of squeeze your finger like in a door per se, instinctively, we just sort of shake our hand without even really thinking about it. It's a reflex that's there from the time we're kids. I'm sure you've probably seen kids do it; you probably did it yourself as a kid. The reason we kind of do that intuitively is that when we shake our hand in that moment of pain, it sends another signal to the spinal cord. It's a kind of vibration, a kind of signal that's sent to the spinal cord. And essentially, what happens is—it's a little bit more complicated, but essentially, what happens is that when you send that signal to the spinal cord, it distracts the neurons from sending the pain signals to the brain. And really, it's a way of neuromodulation, which, from a bird's-eye view, is a way of kind of distracting the neurons from sending pain signals. And when neuromodulation was sort of first developed, most patients would feel sort of a buzzing sensation, kind of just in the background, but it would help filter out the pain signals. It's advanced a little bit over time now to where there are options where you don't feel that buzzing sensation at all, but you still get sort of that distraction of the neurons. It's something that is evolving; it's emerging. There are papers coming out about it all the time. But it is a great option for patients with diabetic neuropathy.

So the caveats are that it is invasive; the way we do this is that we make just kind of needle-sized holes just in the back, and we actually thread the electrodes up the epidural space just sort of inside the spine. We secure the leads to the outside, and then we send the patient home for a week. The patient goes home with the leads and a little, small remote with some different options on it. And they go home, play

around with the options a bit, and then come back to see us in a week's time. And either say, "Yes, this was the greatest thing for my pain. I walked five blocks and did all these other amazing things," or "No, this actually did nothing at all for my pain." Regardless of what they say, we pull the electrodes out. If it happens that they were really helpful, that it provided significant relief from the pain, then we bring them back in for a surgical implant of those electrodes to make it permanent. Of course, with diabetics, one of the big concerns is always wound healing and complications. So we certainly don't want to cause any damage there. We typically look for people who have well-controlled hemoglobin A1C. In the big study that was done, they used a hemoglobin A1C cutoff of 10. Typically, here we're a bit more conservative than that; we like to see it usually at like seven or less. But if you have a well-controlled A1C, then it can be a really effective option for treating patients who have painful neuropathy. So that's a little bit about neuromodulation.

**RK:** Well, Dr. Limerick, I'd like to thank you for sharing your expertise today. I know I've learned so much and I know that this information will be useful to our listeners. Thanks again.

**GL:** Absolutely. Glad I could join.

**RK:** I'm Dr. Rita Kalyani and you've been listening to *Diabetes Deconstructed*, a companion podcast to the Johns Hopkins Patient Guide to Diabetes website. For more information visit [hopkinsdiabetesinfo.org](http://hopkinsdiabetesinfo.org).

We love to hear from our listeners. The email address is [hopkinsdiabetesinfo@jhmi.edu](mailto:hopkinsdiabetesinfo@jhmi.edu).

Thanks for listening. Be well and see you next time.