

0:02

Good morning everyone.

0:04

Welcome to today's program entitled Demystifying Diabetic Peripheral Neuropathy with our guest speaker doctor Radhika ... from Michigan Medicine.

0:15

My name is Lindsey Kolbert, I'm the Executive Director of the Foundation for Peripheral Neuropathy.

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I want to thank you all for tuning in today and putting your faith in our organization to deliver top educational information about peripheral neuropathy and specifically today on diabetic neuropathy.

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Before we get started, just a few small housekeeping items to review.

0:38

First, we are recording this presentation.

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A link to the recording will be e-mailed to everyone joining us live in the next 24 hours.

0:46

The recording will also be permanently housed on our website for future viewing needs.

0:51

Second, we have carved out some time today at the end of the presentation for questions, for those that are joining today's session live, you can type in your questions in the questions box at any time during this webinar, and we will try our best to address them at the end.

1:07

Please try to keep your questions on topic and general in nature as we are not able to answer personalized medical questions. And instead, we encourage you to ask your primary care physician about those.

1:20

And lastly, if you're having trouble with the audio at any time, please dial in by phone.

1:26

Simply check your registration e-mail for those dial in instructions.

1:31

And now I am pleased to introduce you to our guest speaker today for the session on diabetic neuropathy, doctor over DECA ....

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She is a prominent diabetic diet ... at Michigan Medicine and a recognized leader in the field of diabetes and diabetes complications.

1:49

She's the Vice Chair for Clinical Research in the Department of Internal Medicine and the Associate Director of Clinical Research Mentoring and Developments of the Elizabeth Caswell Diabetes Institute at the University of Michigan.

2:02

She is the president-elect for Medicine and Scientist of the American Diabetes Association, And her research interests involve chronic complications of diabetes, particularly diabetic, peripheral, and cardiovascular autonomic neuropathy, as well as diabetic foot Complications, Diabetic kidney Disease, and cardiovascular disease, and the design and conduct of traditional and pragmatic clinical trials for patients with diabetes.

2:30

Doctor Pompa. So he has published more than 200 peer reviewed manuscripts, and book chapters, and received awards from the American Diabetes Association, and the University of Michigan.

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We are so very lucky to have doctor Pompa Tsui today to share her knowledge on this important topic that affects so many of the foundation's pop patients.

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We're Deka, thank you again, and at this time, I will happily turn the microphone over to you for your presentation.

2:58

My first of all, thank you so much, Lindsay, for these really very kind introduction, and also many thanks to the foundations of peripheral neuropathy for the invitation to share with all our audience, some information regarding these really, very challenging complications that people with diabetes are facing. And it is truly an honor to be here today, and share some of this knowledge and evidence that we have acquired today.

3:31

And with that introduction, I would just like to mention that during this 25, up to 30 minutes, I will very briefly revise some of the clinical forms of Diabetic neuropathy.

3:47

So, I will also give you some information, how frequent this complication is. I will review, which you, how it can be diagnosed in clinical care in clinical practice. Because it's so important that patients are aware of how these diagnostics that should be perform, and then discuss what is the most current evidence, and managing painful diabetic neuropathy.

4:17

And with that in mind, here, as this slide shows you that, in fact, Diabetic neuropathy have a very broad spectrum. And this is a summary that had been concluded based on evidence that the American Diabetes Association in its Statement and Diabetic neuropathy that I had the privilege to chair had published a couple of years ago.

4:41

By far however, the most prevalent people the most frequent forms is this this the symmetric polyneuropathy of peripheral diabetic neuropathy. And it does have several forms based on the damage of the nerve fibers, whether it's predominantly small fiber damage, large fiber damage, or mixed majority of form still are mixed. And then of course, we have a variety of mono neuropathy that are also part of the peripheral nervous system as well as autonomic neuropathy.

5:20

Having said that, why is it that peripheral neuropathy are so broad and so diverse? It's because for those of you that may not be aware, the peripheral nervous system has a complex meshwork and here are the net of fibers that are composing the system and we have ... fibers and and small ... and ... fibers. And these are in fact intertwine in this very complex network in the entire human body. Now, what is important to note is that diabetic peripheral neuropathy, it's truly very, very characteristic. And in general, to order all these nanofibers can be affected with the disease progression.

6:13

The smallest, ... fibers that have the least amount of protection against these toxic environment that is associated with diabetes are the ones that are affected first. Don't do eventually. All these forms of of, of fibers are being to be damage. But also what's very characteristic in diabetes that this is happening in the same symmetrical. In other words, both parts of the body and starting. but the very tip of the toes and and progressing towards more central part, the so-called stocking and the glove distribution if the symptoms and signs are not in this pattern and symmetric. Then the likelihood of having diabetic neuropathy, it's lower.

7:06

So how do we diagnose diabetic peripheral neuropathy?

7:10

Well, it is based on the fact that each of these Nanofibers carry very distinctive role and function in the human body with the smallest ..., and ...

7:24

fibers being responsible for pain, sensation, and temperature discrimination, In other words, discriminating between cold or hot temperature. And then, of course, later, protected sensation.

7:36

And by thought, the same time that dominates the small fiber damage is this pain. And I'm sure that many of you have experienced these pain as a burning electric shock are stabbing sensation, which in the more advanced forms, can be extremely difficult to tolerate. And people in my experience, pain, even if they catch objects that are not sharp or even just the clotting, like socks on the bed, clothing may produce pain. That's actually very correct. Any competition, your pain. And these ..., as I said, pain as in contact with, with non sharp object, are non painful stimulus. Is characteristic.

8:31

And in general, one, can evaluate small fibers by exactly evaluating pain sensation to a pinprick. Or how easy one can discriminate between hot or cold temperatures.

8:49

The largest fibers are mainly responsible for pressure and for balance.

8:55

People may experience numbness, tingling, and then the more advance, the damage to these nerve fibers. People may lose balance, they may fall and that's why neuropathy has so much implications on our daily life, and also respond fractures.

9:15

And one can evaluate these large fibers by testing for sensing vibration perception. And I will show you how that is done as well as reflexes starting with the anchors. And then this light touch sensation to let pentagram mono filament that many of you hopefully have been evaluated within clinic.

9:42

In fact, it's the very last one that disappears, and when that is lost, people may have quite severe neuropathy. That is why only having that evaluation may not be enough to really detect diabetic neuropathy.

10:01

And that is why, although for many years it had been considered that in order to diagnose diabetic peripheral neuropathy, people needs to be referred to. Neurology, needs to have these nerve conduction studies or other electro physiological evaluations. In reality, as we have highlighted from report this evidence in the American Diabetes Statement, none of these are really needed in clinical care to document the presence of diabetic peripheral neuropathy.

10:41

Because with this battery of simple instrument that include a tuning fork of pushpin, a reflex hammer, or a mono filament, one can, in fact, evaluate all these nanofibers or quickly in the office and not requiring

to schedule and long waiting time and cost for for electrophysiology. So, and as I said here, it's important to remember that diabetic better peripheral neuropathy always start at the tip of the toes So we start with Pushpin starting at the great toe and then moving.

11:27

A you know more approximately, the same, the vibration we started at great till. Similarly, the reflexes at the ankle is shown here, in this image. And then the ..., which I said, usually disappears quite late in the course of the disease and inch as as we have also documented and recommended combining at least two of these valuation ideally.

11:56

one measure of small fibers such as pinprick and one of large fibers such vibration, is recommended as well as actually documenting that these signs and symptoms are following the symmetric call stocking globe's distribution.

12:21

Because of this, symptom and signs are much easier to be done particularly standardized in an arch Patients which significantly lower cost of variety of screening instruments have been developed and validated over time, including the Michigan neuropathy screening instrument, Combination of symptoms, questionnaires, and couple of examination techniques, and the same the Toronto Clinical Property Screening Instrument and neuropathy disability score.

12:58

Now, of course, that in research, we do need to have additional measures and and the electrophysiology as well as the other forms including skin biopsies can be done in research to more of check dibley document changes, particularly when we passed a new medication for reversing neuropathy. But we are talking now about clinical care today.

13:30

Also very important for clinical care is the fact that many other forms of peripheral neuropathy could also happen in people with diabetes. And here are just such some of these examples.

13:47

Diabetes, of course, can be associated with typhoid problem, steroids, dysfunction as well as people with diabetes can develop more severe renal complications. So, we always have, to make sure, that we look, and document, that there is no additional, titled abnormalities or People Don't Have a Screener Disease. There is also this conditions called Chronic Inflammatory the Miley Meeting Poly Radical neuropathy, which can mimic diabetic neuropathy ensure that you probably have had webinar and these conditions. Usually the symptoms and signs have a very rapid onset and progression, which is different than diabetic neuropathy and then of course, that out a variety of drugs and other infectious or at a systemic diseases.

14:50

Among drugs and recreational substance use, I have to mention alcohol.

14:54

Because it is a big a risk for peripheral neuropathy is and some of the nutritional deficiency I'd like to highlight among those B 12 deficiency.

15:09

And the reason is that people with diabetes, particularly those with type two diabetes, are usually treated with metformin. Metformin it's a very good and safe medications.

15:22

But a small proportions of people who take metformin for a long term may develop a little bit of deficits in absorbing vitamin B 12, so they may develop B 12 deficiency, which is easily treatable and could help alleviate some of these symptoms and signs.

15:44

So what I'd like to highlight is that it is important for patients as well to share with their clinicians to make sure that other forms of peripheral neuropathy do not coexist with diabetic neuropathy just because these forms can be easily treatable by specific measures. So to highlight this part of the webinar, I would just like to say that there are situations in which, indeed, a referral to neurologist is needed Especially when the symptoms and signs are not symmetric.

16:23

So they are only on one side when there is a lot of weakness instead of pain and numbness, for instance.

16:31

And when these symptoms and signs very rapidly beginning and very rapidly progress progression, because in that case, a suspicion for a different cause of the symptoms, it's, it's quite high.

16:49

Um, I like to spend a couple of minutes on painfull Diabetic neuropathy because in fact, up to 30 to 40% of people with diabetic neuropathy will present with pain. And pain is extremely difficult to live with. It as I mentioned earlier, it is this burning pain that keeps you awake at night and will affect so many aspects. one person And we do have several, you know, instruments that have been developed to diagnose neuropathic pain, especially this dollar neuropathic for audience for instrument.

17:35

There are also other, more general pain related questionnaires that can be used.

17:44

Also, too, grade the severity of the pain.

17:49

And we also have several instrument that have been, finally, they did, that, have assessed the effect of diabetic neuropathy on a patient quality of life.

18:03

And I like to highlight that over the years, we, clinician and researchers, have understood the importance of really talking to patients, and making sure that we understand what patients feel, and what is important for patients. And so those questions are for pain, or quantity or plaques.

18:30

Basically based on what patients are reported and how patients are grading these various symptoms and signs, and it's actually a very important thing that we all know that.

18:48

unfortunately, because of this progressive loss of sensation, one of the most serious advanced peripheral neuropathy complication are this diabetic foot complication, particularly the diabetic foot ulcers. And 80% of all diabetic foot ulcers are in fact, due to diabetic neuropathy. And this is a problem, I mean, this is how they can look.

19:17

And it is a problem, because these shares in diabetes, unfortunately, may heal a very, very slowly, and sometimes people have quite huge problems in healing. They can get infected. And when they get infected. Unfortunately, that is the main cause of amputations for people with diabetes.

19:45

So, as an AWL viral, as you can see here in the slide, diabetic peripheral neuropathy has a meaning yet of effect in a patient.

19:57

The loss of sensation can, due to loss of balance, can then goes to force.

20:05

It can affect your daily capability in engaging in activities that are either needed for work or for recreation.

20:17

The pain that we have already addressed, and we will address later on can be extremely difficult to treat, unfortunately.

20:25

And when one develops this chronic pain, it does affect not only the sensation of pain, but it affects your sleep. Capability can induce insomnia.

20:38

It can affect your mood, it can induce anxiety, depression and then because it is so hard and difficult to treat, it could also induce polypharmacy and medication side effects. And then, of course, unfortunately,

because of these, put as, there's the risk of amputation, it's really very high in people with diabetic peripheral neuropathy.

21:00

And once a person has an amputation in fact, the mortality rate very, very high below and above the knee amputation have five year mortality rates as high as many cancers.

21:19

So how do we manage diabetic neuropathy? So, first of all, I like to say that, unfortunately, to date, we still do not have been able to find a medication that will reverse this. and that fiber damage and loss, we do not have, like we call it, a disease modifying therapy.

21:44

And that is why we have to concentrate in treating as well as possible.

21:54

The diabetes spot, the glucose, blood pressure lipids obesity because they all can lead to the development of diabetic neuropathy.

22:05

And we, of course, have the event upset by the twist to treat pain and the last part of this talk, I have concentrated on sharing with you what are our choices to treat, painful, diabetic neuropathy.

22:22

And we have several components.

22:26

A big part of treating pain for many, many years has been concentrated solely on ... logical agency, in other words, drugs.

22:37

But more recently, several tribes have in our Sudan on some of these new ..., and nutraceuticals means vitamins and other supplements, as well as non pharmacologic approaches. So let's let's talk a little bit about what type of medications do we have available to date to treat the pain in diabetic neuropathy.

23:02

So this is a summary of of all the evidence that we have also analyzed as part of the ADA statement in which we had the capability to assess clinical trials that have been than to test agents specifically for painful diabetic neuropathy. And we had the opportunity to evaluate data from both published and unpublished trials. For those of you who may be less aware of that, I'd just like to highlight that sometimes some trials when they are negative, at least in the past, were not necessarily published, and that is why the FDA, almost 10 years ago, mandated that in the future, and that's the case here. All trials, even if they are not published, have to put their data in publicly available datasets. So the effect of



specific agent can be much more. Much more accurately analyzed and we do have, to date, in the United States. Basically, couple of agents that are approved specifically for painful diabetic neuropathy.

24:17

From among those that are ordered, free gobbling, Abdul Oxetane are the two that carry FDA Approval. one eats an anti convulsants and the other one, it's an anti depressant.

24:31

But when we have analyzed the data regarding their true efficacy in reducing painful diabetic neuropathic pain, using this patient reported outcome, which was how patients perceive their reduction in pain from either 50% or 30% from baseline, As you can see here, although, only ... has been approved.

25:00

In reality, other agents that are generic and are not necessarily approved for painful VPN have very similar effect in the number needed to treat to reach these 30 or 50% improvement in pain. Of course, that, usually, to be effective, they require higher dosing. As you can see here up to 600 meter square per gobbling under 24 blocks setting and then up to 3 3600 for gabapentin or 100. For Ami Trickling in the higher the dose, the higher the risk of side effects.

25:40

Now, I just want to share with you a trial that has just been published basically yesterday in the handset, so this is just hot off the press.

25:48

Which demonstrates that with these agents, sometimes one may not be enough, but combinations of agents may also be associated with better pain reduction. And these trial actually randomized about 130 people, and they had a very interesting approach. The first six weeks, everybody was only taking one agent, either amitriptyline deluxe at in our pre gobbling That was tight rated, however, up to the maximum. And then, for those who did not have enough pain reduction using the six weeks than they have a combination. And as you can see, here, was a combination of all these three agents. In a given sequence, and as seen here, at the end of the day, all these three combination where pretty much similar.

26:42

Some people were able to remain on only one agent, but majority act require at least this combination to reach more active pain reduction, But I like to highlight that this, no medication approach has important limitations, And one of that is, first of all, in all these trials, even those that we have included in the ADA statement has been, in general short, 12 for maximum 16 weeks. Which is, of course, not enough information. When we know that, in many cases, people experienced the pain way beyond this timeline, many of this trial had very large dropout rates. In other, In other words, people didn't finish the trial when that heads. No question regarding how valid the data is, and then, of course, the higher the dose, as I said. And perhaps many of you have already experienced that the higher the dose that these active then people get.

27:44

However, we do have other options now. And one of such option it's a topical topical means that it's applied basically on your feet. And that is the capsaicin Patch capsaicin had been passed it in the past in lower concentration, but with these highly concentrated patch actually, the two people to try as. And one of the, it's shown in this slide, and as you can see, very quickly, that was a significant pain reduction with the capsaicin patch compared to the placebo patch.

28:22

In, in this trial, in, a, similar at a trial that lead to FDA approving the capsaicin 8% patch as specific agent to treat painful diabetic neuropathy. And that has the advantage, of course, that it does not have the side effects of oral agents. Although it has to be applied in a medical office, you cannot just take it at home and delete yourself, So that adds a little bit complexity, but that can be obviously a sorting out with your provider.

28:55

Very briefly, before I end, I'd like to provide you with some information on other options, Not just the cars are important because I know that in many instances, not just for peripheral diabetic neuropathy, people are tempted to, to take natural products, vitamins, or supplements.

29:16

And I have to say that they have been effective, quite extensively, used in clinical trials. This is just a summary that we have published recently looking at some of this most used supplement and vitamins specifically for neuropathic pain and gentlemen. Unfortunately, when one looks objective, Lena, in a randomized trial, none of this showed a clear effect, strictly for diabetic peripheral neuropathy. With one exception which was the ... acid, which, although, didn't show any effect on reversing, bam, each seems to be effective in some people to reduce these burning neuropathic pain. And this is actually a summary of the data of all ... trials.

30:11

And again, approximately, the dose needed to to reach this 50% reduction.

30:20

Would also like to highlight that in the last several years, there is a lack of evidence that has been gathered on other non pharmacological approaches. and I'd like to highlight two of those, those are exercise and dietary modifications.

30:39

And although for some of you, it may sound counter-intuitive, in fact, we have acquired more and more evidence that exercise, it's one of the most effective strategy to improve neuropathy. In fact, there are some evidence that our colleagues, doctor Gordon Smith, and Drop Singleton, and others around the country have acquired that exercise, may even reverse the fiber damage. But definitely seems to be quite effective for pain. And there is a large study in Europe that showed exactly the same thing. This

dietary modification weight, either reduced calorie diet, knowing that obesity it's such an important risk factors for neuropathy have also started to show some benefit.

31:29

And lastly, but not least, there is these newest strategy that has just been approved by the FDA, these high frequency spinal cord stimulation that has been now shown in a large long-term trial.

31:48

It went up to a year in fact to be effective for reducing painfull diabetic neuropathy.

31:57

So, to summarize, I'd just like to highlight this most recent algorithm that the American Diabetes Association had published taking into account UMD's most recent data. And all these new strategy Step: a county FDA approval, including those and the evidence for those who do not carry FDA approval. But have evidence for us. As you can see here, trading painful diabetic neuropathy.

32:25

It's more like putting together the pieces of it posited because one may require several of these intervention from taking 1 or 2 agents orally for a while, with a topical agent that can, in fact, help with reducing the dose of the oral medication or may be effective change. Just by itself. That's going with some exercise, healthy behavior. Combining some of the strategies, definitely using vitamins when some of the vitamins deficits have been identified, and then, of course, in these severe cases, the high frequency spinal cord stimulation, Which is how I lead a more invasive procedure. And with that, I'd just like to thank you for your attention. Disease.

33:14

You know, what I share with you is, in fact, the result of a lot of studies that we and others have done.

33:21

And I would only want to highlight, most importantly, all our research participants who have donated their time and work with us to high pass now acquired all this evidence that that can be applied to help all people with diabetic neuropathy when they are being seen by data providers. And, of course, I have to highlight all the funding that the National Institute of Health, the American Diabetes Association, JDRF, and actually, the Foundation for Peripheral neuropathy has been, you know, placing in these studies. Thank you so much.

34:00

Doctor Pompa Suey, thank you so very much.

34:04

We really enjoyed that presentation and before I open it up for questions, I wanted to share an interesting contest to everyone as well that's open until October first of this year.

34:17

It's called Speak for Your Feet, it's open to anyone who has Painfull diabetic peripheral neuropathy.

34:25

So read more on this slide.

34:26

If you're interested in submitting a mnemonic to win the contest, you can submit your entry at nerve pain and me dot com backslash contest, or you can scan the QR code that's displayed at the bottom right hand corner of this slide.

34:44

So thank you, again, and, again, just wanted to share this with some of our folks that might be online right now that would be interested in participating.

34:54

And now, let's get some of these questions answered in the remaining time that we have left here. I'm actually going to pop on screen as well, just so that everyone can see me. Doctor Pompa, Sue. If you'd like to join, as well, feel free.

35:09

We've had quite a few questions that have come in during your presentation. So let's start.

35:17

Let's start going through them The first is Could you explain what foot drop is exactly?

35:24

A little bit more Oh, Sure.

35:27

So, um, Foot drop, you know, can happen in in a variety of situations.

35:33

It may not necessarily be associated with diabetic neuropathy, but it's usually more like a manon neuropathy. and it is.

35:48

Again, there are several reasons that people can do that, and it could increase your risk of developing other foot complications, including this inequality in the pressure on your plan, that thought that could also lead to some of this foot asher's.

36:11

Sometimes more severe complications, but it's not necessarily only associated with diabetes diabetes.

36:20

OK, and you had mentioned Metaphor, man, which is obviously a drug that's used to treat diabetes. Do you know offhand of Metaphor, Man has the potential to cause neuropathy and some people because of the interference with B 12 metabolism?

36:39

Yeah, absolutely. And that is a very important question, and I, I tried to highlight it in, in the presentation. So, Metformin it. It's one of our longest use medication fluctuating type, two diabetes, and it has one of the safest court.

37:01

But in up to let's say, 10 to maybe 25% of people, we have learned that it can cause some problems in absorbing vitamin B 12, and then people may develop a B 12 deficiency. And as you may remember, during the presentations, if one dev and ops vitamin B, 12 deficiency, they may, in fact, develop peripheral neuropathy and some of the signs.

37:28

And symptoms are similar with diabetes, including this numbness, tingling, the alans issue that people may develop falls.

37:38

So, it is very important that, and we now, the American Diabetes Association, you know, those of you obviously have diabetes, the American Diabetes Association publishes every year. The standard of clinical care, and as part of that, for people who are on Metformin they are supposed to have the B 12 Levers capacity to once a year? Exactly. For that reason? But particularly, if you start having these symptoms?

38:09

Also, if you talk to your provider, that you have neuropathy, that you feel that your ... you know, the tingling and the provider says, You have neuropathy or may also want to bring up, Could I have maybe 12 best? It's just in case if you didn't have it.

38:25

Because as I mentioned earlier, if you do have B 12 deficiency, taking a B 12 supplement, a thousand micrograms a day, it's very, very active to replenish your stores. And most of the symptoms can completely disappear.

38:44

And I just kinda want to also highlight that getting tested for the deficiency is really important because in a supplement, actually isn't very helpful if you're not deficient.

38:54

So I think that's always important to highlight, that get your levels tested to see what you are deficient in so that you can accommodate what what you need to.

39:07

Absolutely. And that's very, very important. I mean, just taking B 12 without knowing you have a deficiency may not be a good idea either.

39:15

It has to be documented and then treat it, right. Could you talk about intermittent fasting as a part of a dietary treatment? What's your view on intermittent fasting? Is that something that you encourage for your patients, or not necessarily?

39:38

Well, I would like to say that, definitely obesity, it's an important risk factor for neuropathy.

39:47

In fact, you know, this, we call it diabetic peripheral neuropathy, but we know that people who have pre-diabetes can develop this form of neuropathy. And similarly, a lot of recent evidence that has been obtained here in US. And also in Europe and in other countries shows that obesity by itself, of course, obesity can be considered.

40:12

In many cases. A pre-diabetic stage has the same effect.

40:16

So, losing weight, or preventing to become obese, X, definitely important to prevent neuropathy to either occur or to progress.

40:31

But, as we know, very well, for obesity, and weight, loss trier's in Jana, over the years, multiple type of, let's say, diets have been pes starting weight, mediterraneans, starting, wages, low fat diet, more recently, this low carb diet, or keto diets, and all these other diets, including these intermittent fasting and wild.

41:02

Many of these have been shown to be effective in the short term to lose weight.

41:08

The sad reality is that for most of these diets, one cannot engage them indefinitely.

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And it's also there is no evidence whatsoever that if than indefinitely, they are safe.

41:21

Because most of these trials have been done maybe up to 12 months.

41:26

So I don't think that we do have this for these intermittent fasting for neuropathy.

41:34

We do not have any evidence that is better than others. Right.

41:40

So that that's my view.

41:43

Yeah. And I think on behalf of the foundation for peripheral neuropathy, we really try to encourage people to undertake a diet that is a sustainable life change that they can do for the foreseeable future. Because, to your point, if you can only do it for a few days and then you kind of fall off the wagon, lots of times you don't get the results the long lasting results that the patients are looking for.

42:08

And indeed, I mean eating less in general and moving more.

42:15

It's the most effective combination.

42:18

And we also have to remember that when we are sedentary, we need to eat much less, just like paying late.

42:27

If we continue to eat the same and we become sedentary, we are going to gain weight, so that's that's definitely not good.

42:34

So, a healthy lifestyle helps neuropathy: and, as I mentioned, during my lectures, we do now have quite nice trials that show that potential, as well.

42:46

And speaking of exercise, obviously, you and the Foundation, we've highlighted exercise as, you know, something that is encouraged in a healthy lifestyle, but how do you recommend a patient that might have some pain or balance issue, exercise? Do you have any thoughts, and what do you recommend for your patients that you see, that have those symptoms?

43:09

So, first of all, I think that, for someone who has not done any exercise up to, let's say, that moment, we always recommend to start slowly. So, we need to build our resistance. We need to build our fitness starting with smaller you, know, times walking. It's a one-way to delete and the pace and the distance.

And the duration can be also increase progressively, I know that some people say, well, I have pain and I am not going to walk.

43:44

But in reality, if we think that this neuropathic pain in diabetes, it's mainly present when people sit on at night lying in bed.

43:55

No moving, you will realize that we'll have pain. It's just a matter of, you know, mentally, also preparing ourselves, that that could be beneficial, and we need to try. And we need to do it of course, safely.

44:09

And we don't want to start running a monotone, but we want such slowly with with walking and more brisk walking and, for instance, in fact, as we know very well from the Diabetes Prevention Program, you know, high intensity walking, 30 minutes a day for up to five times. A week was very effective. Not only in preventing diabetes, but form for some of these complications as well. That's one way to do it. Now, of course, if people have more severe neuropathy and they have these larger fiber deficits, and they already have some balance, we need to be careful how we do the exercise.

44:52

Some of my patients found it quite easily when they have tried to man, and they put their hands on both the rails of the treadmill and they start with a very low pace and move on and pace and that that can be done safely.

45:10

Of course, there are walkers, if the balance issues, it's very, it's very severe, that other forms of exercise that can be consider not only iron or baking or resistance training, increasing muscle mass, It can be done seating, for instance, as well as swimming when someone has an opportunity. So there are lots of exercises. And, of course, talking to your providers talking with, you know, maybe engaging and ammunition physical therapy type of device will be helpful.

45:48

Know, and I think it's also very important to say that, you know, we never want anyone to undergo an exercise regimens without prior consent, but then, similarly, also, if it's causing pain. Or if you're extremely fatigued at the end of it, it's usually a sign that maybe you went a little bit too hard. Obviously, being tired and being wounded after exercises is normal, but we want to make sure that especially undergoing a new regiment, that you're doing it safely and appropriately so that you're not further damaging anything hurting yourself, injuring yourself or experiencing more symptoms than you normally would if you hadn't chosen that activity.

46:30

And, you know, along those lines, Lindsey, I still think it's, it's important that we would like to highlight, that you need to discuss with your providers, and the reason is that we need to remember the diabetes, it's in fact, a very complex disease, that people with diabetes who have neuropathy may not know, they



have other complications, and one of them is, for instance, a cardiovascular disease. And so you may feel shortness of breath, not necessarily because you are the condition on. this could be probably the cause, but you might have heart failure that you are not aware of, and that's important, because also, with the American Diabetes Association, we just published recently, a very large document. Don't the, demonstrating that people, many people with diabetes, don't know that they have heart failure, and that is a problem to that can give you shortness of breath and, and fatigue. So you need to make sure that you discuss with your provider, that you are well evaluated before starting an exercise program.

47:33

And, you know, I think you raise another kind of concern in that many of our patients don't know if they have what's termed mild or medium or severe neuropathy. So as a neurologist how do you?

47:49

How do you determine the severity of one's condition or the task that can be done, or how does a patient understand, really, whether they are on what side of the spectrum here?

48:03

While so first of all, of course, the more deficits in this, nanofibers, the more severe the disease, right?

48:10

So if one may have just pinprick sensation and pain, they may have, perhaps, an earlier form of neuropathy. Because we know that the smaller fibers and the one that I did first. So, I would say the more deficits, the more lack of sensations eyes, as you know, once you develop a diabetic foot ulcer. That's actually unless, you know, injure yourself and you've got infected because you didn't go to see your adapter for mild injury.

48:43

That's a form of more severe neuropathy, so that are the signs pain may or may not be necessarily a form of severe neuropathy, but nevertheless, it is very difficult to live with and needs to be treated, But that's that's how we do it. So we evaluate, I do evaluate my patients for our listeners fibers in the office, and I also ask about What do they feel?

49:13

And then that's how we evaluate, how, how severe it is, and Is there any genetic testing, does that ever play a role in either the diagnosis or the treatment following the diagnosis of neuropathy?

49:31

So I will start with the second part.

49:33

As I said, as I mentioned earlier, Although a lot of trials have been done, especially up until 2000.

49:43

None of those have been successful to reverse the nerve damage once it has been installed. There are some additional ongoing trials. We hope that we will be able to find something silly, so, to date, we do not have such a treat.

50:02

The genetic question, it's very interesting, and, in fact, as it is true for many other diseases and other complications, lots of these so-called genome wide association studies, looking at genes for neuropathy have also been tested.

50:20

And we couldn't really find something that would be specific for to tell us who may be more likely to develop peripheral neuropathy.

50:32

However, since we are talking about genes, ..., recently, we had the opportunity to come to do again, a pretty large genome wide association study. In a large cohort of people with type two diabetes that included almost 10000 people. This was called the aquatic try it. And in that situations, we found a gene that may be active. Now, as it is true for these big genetic studies, first of all, ones, you see a signal in a population. You need to validate it in a different population, and we were actually able to do that in another large cohort of people with Type two diabetes, also NIH funded, called Barry two D.

51:18

So, we did find that for people with type two diabetes, having a specific genotype on a gene related with sodium channels, which makes also a lot of sense for, for diabetics, peripheral neuropathy, has approximately 30% reduction in the risk of developing diabetic neuropathy. We tried to test that also in a large cohort of people with Type one diabetes. And these studies are ongoing to see whether that would apply for people with Type one diabetes, But this is ongoing as we speak.

51:58

And the last question that I wanted to raise is more just about current research or current studies that are out there for patients, either to learn more about some of the outcomes or new treatments that are out there, or, similarly, their ability to participate in some of these trials.

52:18

Do you have any resources or thoughts on what these patients can do too gain access, or be a part of the research? Absolutely. And, and perhaps here we can partner with the Foundation Lindsay. So, at Michigan, we are heavily involved in research, we have always been part of lots of this landmark diabetes trials that have changed.

52:43

In fact, how we deliver care for all people with diabetes, not just for peripheral neuropathy, but for everything for our complication, how we treat, how we develop these technologies are these new medications. So we do have, currently, couple of trials looking specifically at disease, modifying agents, they're still ongoing.

53:05

I know that there are several pain trials that are ongoing. And usually, if you are really interested to participate in research, one resource that it's freely available for everybody, it's clinical trials dot gov. And you can just search diabetic, peripheral neuropathy. What is open and where are these sites?

53:28

The data, as I said, several ongoing pharma trials that are looking at pain management, again, they are easily available on clinical trials dot gov of impact, every single trial, or whether it's NIH funded, Private foundation has to be registered and clinical trials dot gov before we start a trial.

53:51

And then, again, all the data has to be done, put that. And that's, again, for the same reason, as I had mentioned earlier, to avoid all these bias because prior in the nineties, most of the pharma trials that web not know, Paul's it the web not published. And then people I never knew whether something was negative. And that's something that we really cannot do moving forward in any type of research and science. But I seem to have the resources we do have in our webpage with Habitat Casual Diabetes Institute. We do have all the research and its ongoing. If you are close to Michigan. We always welcome any participants and as I said, we are so grateful for all our research partners from you, because without you and, you know, we can have ideas, but we need to have the opportunity to test them.

54:48

You know, and kind of further to your point or Diego, we have a page on our website as well for patients to find a clinical trial. We actually even filtered out some of those that are pertaining just broadly to peripheral neuropathy. So, for the diabetic patients, you just have to do a little bit more filtering within, but that can be found on our website at Foundation for P N dot org. Backslash find a clinical trial. But then further to your point, you know, we also partner with Michigan on one of our primary research programs, which is our peripheral neuropathy research registry. It's our biobank of human blood plasma and serum samples.

55:30

And patients that are around Michigan are welcome to enroll in this program.

55:36

It's an opportunity to participate in being a part of the research.

55:41

So, those are great opportunities that you mentioned, and, yeah, we're trying to facilitate as much as we can as well, for our patients, So, I'm happy to hear that we're not too far behind Michigan, and using you guys as a resource has been extremely helpful and beneficial to everybody.

55:59

So, thank you.

56:01

Oh, thank you so much, Lindsay. As I said, I mean, the foundation work, it's instrumental. And I think that that's that's the key for the future.

56:09

We all have to work as partners as team, and share every bit of, of, of evidence that we acquire, because that's how we have made progress of R&D. This is how we're going down.

56:22

Progressing, well, thank you again for your time today. For everyone that submitted questions that we weren't able to get to. We will try our best to answer those following the program. But, again, we thank everyone for joining. We're going to have this recorded, and up on our website shortly, so stay tuned for that. For those participants that are joining today, we're gonna have a survey that goes out at the end of our webinar. We always welcome feedback on how we can do better do things differently on different topics, and we hope that you will support us, financially, and you'll reach out to us if you have any other questions. And, lastly, we want to thank ... Pharma for sponsoring today's program. They were able to make this presentation possible. So, again, thank you to everyone who participated and joined in today's session, and we hope to see you again very soon. Thank you, again.

57:19

Aye.