

**FLORIDA DEPARTMENT OF HEALTH  
DIABETES PREVENTION & CONTROL PROGRAM  
DIABETIC NEUROPATHY**

**Moderator: (M) Bowers  
June 22, 2005  
11:00 am CT**

Operator: Good afternoon. My name is Lindsey and I will be your conference facilitator today. At this time I would like to welcome everyone to the Diabetic Neuropathy conference call.

All lines have been placed on mute to prevent any background noise. After the speaker's remarks there will be a question and answer period. If you would like to ask a question during this time, simply press star then the number 1 on your telephone keypad. If you would like to withdraw your question, please press the pound key.

Thank you.

Miss Bowers you may begin your conference.

(M) Bowers: Good afternoon everyone. Continuing with our series of audio teleconferences, the Florida Department of Health Bureau of Chronic Disease Prevention and Health Promotion and the Diabetes Prevention and Control

Program welcome Dr. Rodica Pop-Busui, who will discuss the topic of diabetic neuropathy with us today.

Dr. Pop-Busui is currently an Assistant Professor of Medicine and Physiology Division of Endocrinology and Metabolism, and Attending Physician in the Department of Medicine and a faculty member of the graduate school of the Medical College of Toledo in Ohio.

She is a member and co-chair of the 2005 peer review committees of the American Heart Association, a member of the Council for Clinical Research of the American Association of Clinical Endocrinologists, and a member of the research advisory committee for the Office of Interuniversity Research Collaboration of Ohio.

And what I just discovered from her is that she's going to be moving over to Michigan and working over there come July. Is that right, Dr. Pop-Busui?

Dr. Rodica Pop-Busui: That is correct.

(M) Bowers: Dr. Pop-Busui earned her medical college medical degree and her PhD in molecular biology from the University of Timinsora School of Medicine in Romania. She completed a residency in family medicine and a residency in internal medicine at University Hospital in Romania where she was also an attending physician.

She is board certified in both general medicine and internal medicine in Romania. Following her residency, she served as a visiting physician in training at the Royal Hallamshire Hospital in Sheffield, U.K. And is a research fellow and later a clinical fellow and fellow physician at the Department of Internal Medicine Division of Endocrinology and Metabolism

at the University of Michigan Medical Center in Ann Arbor, which is where she's going to be moving to in July.

She is currently board certified as a medical doctor in both Michigan and Ohio. She has been the principal investigator or co-investigator for numerous NIH and other major grants and is widely published in peer reviewed journals and books. She has also received many honors and awards including the American Diabetes Association Endocrinology Fellow of Excellence award in 2001.

We are honored and delighted to have Dr. Pop-Busui with us today.

Now just a couple comments about the CEU that we are offering today. As a reminder, all participants listening in should already have completed a pretest. In addition, each participant needs to sign in on the participant attendance sheet, complete the post-test impact survey and pertinent CEU paperwork. You may refer to the syllabus or the continuing education instruction sheet for submission details.

I'm now going to give you some important CEU information related to today's call. I ask that everyone please refer to the continuing education credit instruction sheet.

Continuing education credits have been approved for the following healthcare professionals: nurses and dieticians. The Big Bend Area Health Education Center has approved this program for 1.5 contact hours. Nurse provider number SBN2654. This is not a national provider.

Nurses and health educators in other states, states other than Florida, must request approval from the professional board in their state. All CE credits will

be reported to Florida's CE broker monitoring system. Nurses who want to receive CE credits must complete the appropriate CEU paperwork and register with the correct license number.

The Commission on Dietetic Registration has approved this program for a nationwide dietetic continuing education credit. CPEU level three 2.0 major session topic code CL0312. Dietitians who want CE credit must complete the appropriate CEU paperwork and register with the correct license number.

Individuals interested in receiving CEU credits must submit the pretest, fax in the sign in sheet, the posttest, the post survey, and register for CE credit via our website. Email confirmations have been sent out to everyone who completed the pretest online prior to 11:15 this morning.

Dietetic practitioners are now under the new professional development portfolio process. Although the commission on dietetic registration no longer requires that the Department of Health submit sign in sheets or roster, we still require that all participants sign in and fax or mail the sign in sheet to us.

All activities on step four must relate to a learning need from your step three learning plan. You are responsible for choosing your own learning needs and updating your learning plan as necessary. Please remember that you have 120 days to update your learning plan if you attend an activity that is not relevant to your current learning plan.

Credits will not be issued to participants who have not signed in, completed the required forms, and registered for CEU credit. All paperwork must be in our office by 5:00 pm Eastern time by next Friday – or next Wednesday June 29. Paperwork will not be accepted after that date.

All right. I think now we're ready to turn the program over to Dr. Pop-Busui.

Dr. Rodica Pop-Busui: Good afternoon. It is a pleasure to be here today. And we will discuss some of the most important topics related to diabetic neuropathy.

As you can see in your handout, looking at the slide number 2, before entering the diabetic neuropathy topic itself, I would like to briefly to review the overwhelming importance of diabetes in today's health management. As you can see the actual prevalence of diabetes, of 130 million is expected to be increased at 300 million by 2025 as data from the World Health Organization has reported.

And moving to slide number 3, you can see that this increased prevalence, which can be name that has reached epidemic proportions, is practically quite high in the United States. In this slide here you have practically six states the prevalence of obesity in the upper panel and diabetes in the lower panel by state as a comparison of the end of 1991 shown here in the very left part of the graph. And which the end of 2001, which is shown on the right.

These maps are speaking for themselves. As you can see both the prevalence of obesity has increased to an average of approximately 21% of all American adults. And as a parenthesis, obesity has been defined as a body mass index, whose definition you have in your handout, of 30 and higher. The same is true for diabetes shown here in the lower maps whose prevalence has increased from 4.9 at the end of 1991 to approximately 8% in the end of 2001. So this is quite suggestive and significant.

The diabetes impact on overall health is further illustrated in the slide number 4.

As you can see here, diabetes is practically the leading cause of renal failure in U.S. and throughout Western world. It's also the leading cause of blindness. And the presence of neuropathy which is induced by diabetes has been shown to be up to 70% of all patients.

In addition, as many of you might be already aware, diabetes increases dramatically the prevalence of arteriosclerosis as well as the date of onset. Increasing therefore the cardiovascular risk up to four fold and reducing the life expectancy with about 13 years as most recent data has reported.

With this in mind, let's start discussing our major topic, which is reviewing the presence of diabetic neuropathy. Diabetic neuropathies are one of the most common complications of diabetes and it's probably the most – less understood complications. As you can see in slide number 6, there is quite broad difference in the definitions of diabetic neuropathy and therefore that also has a consequence on the overall prevalence.

But anyway, in the literature there are – the prevalence of neuropathy varies from 10% within one year of the diagnosis of diabetes up to 80% in patients who have diabetes for more than 25 years duration. And one of the quite important epidemiological studies that has looked specifically at the presence of neuropathy is described in slide number 6. That study has been practically published by Pirart in 1977 and showed that diabetic neuropathy was present in 50% in patients with type two diabetes, which had a long diabetes duration.

Another important thing to remember is that most recent evidence has demonstrated that there is no difference in the prevalence of diabetic neuropathy between patients with type one and type two diabetes.

Let's move now to slide number 7 – actually number 8, which has listed the most important diabetic neuropathy syndromes. And these are discussed in distal symmetric sensorimotor polyneuropathy, autonomic neuropathy, and focal neuropathy. We're going to review together today the most important physiopathological, morphopathological, and clinical features of these syndromes.

As you see in slide number 9, it is important that we understand what is the structure of the peripheral nerve in order to understand the clinical manifestation of this syndrome. And you can see that in this slide you have a section of pathological section of peripheral nerve, which are composed of flat myelinated fibers, which are shown with the arrow, myelinated fibers and unmyelinated fibers.

It is also important to remember that in diabetes, the smallest nerve fibers are the first to become damaged.

The next slide, slide number 10, I think is also quite informative describing in even more detail the structure of a normal nerve axon in which you can see the presence of myelinated axon and unmyelinated axon. And schematically that transmission of the matter of attention, which is important in release of the different neurotransmitters. And the same, practically the same, information is shown in slide number 11.

Let's move now to slide number 12 because here quite interestingly is the progressive loss of these fibers. In the upper left panel, which shows you a micrograph of pseudo nerve biopsies, you can see quite normal nerve density and distribution of various types of fibers that we have discussed. So that has a biopsy obtained from a not normal subject.

You can see moving toward the right, a mild large – actually towards the small unmyelinated fibers. More progressive defect is being shown in the lower left panel. And, of course, quite severe fiber loss shown in the lower right panel that is a micrograph, which was obtained from a patient with long standing diabetes for more than 30 years. Quite important nerve deficit and trophic ulcers.

Slide number 13 is a cartoon, which practically depicts a simplified review of the various nerve fiber with the functions that they are practically responsible. So we have shown that we have large myelinated fibers, which have mainly normal and those large fiber or A-alpha and A-alpha-theta are responsible mainly of muscle control, the motor component, and the control of touch, vibration, and position perception.

The sensory, a thinly myelinated or A-delta fibers are mainly responsible for the cold perception and some of the pain perception. Whereas the unmyelinated or C fibers, small unmyelinated as you have seen back in a previous slide are responsible for warm perception, pain, as well as of the autonomic control of heart rate, blood pressure, and other autonomic functions.

With this in mind, let's move now to slide number 15. We should skip number 14 because it's pretty much a repetition of the above one. And this slide is important because it does show a quite broad spectrum of clinical presentation, which are present in various diabetic peripheral neuropathy. As you can see here, we have quite a broad spectrum structure with femoral neuropathy shown here in the middle panel. Mononeuropathies involving mainly brachial or cranial nerve and we'll briefly review each of these types of peripheral neuropathy.

Some of the pressure palsies but concentrating at the very last panel, by far the most frequent clinical presentation is associated with the symmetrical diffuse sensorimotor neuropathy in which the sensory loss is distal involving the peripheral nerve in that so called stocking and glove resolution. That's by far the most frequent one.

Let's move now to slide number 16, I think. Yes. And review briefly what has the most important clinical features of these symptoms. So in this slide you have pictures of a patient that has just presented with proximal motor neuropathy. And most importantly from clinical standpoint these people present with proximal muscle weakness.

And severe muscles wasting as you can see. One of the most important clinical features is also very severe pain, which is usually located in the lateral aspect of the thighs. And that pain together with the proximal muscle weakness makes this quite – makes for them quite difficult to raise out of a chair, to climb stairs. They are also quite depressed and the pain has an impact on the overall food intake. And that is why, in the past, was called diabetic ataxia.

Slide number – let's move and skip slide number 17, which is a repetition of this syndromes and move to slide number 18, which shows some of the clinical features of the different focal neuropathies, specifically here there is a patient who presents with mononeuropathy and cranial nerve three, which is one of the most common involved. In general, the mononeuropathies, as you can see in the last panel are due to vasculitis and subsequent ischemia or infarction on different nerves as you can see here in panel A.

What is important is that in general they heal spontaneously and that a normal clinical course results in about 6 to 8 weeks. And as I mentioned, the cranial

nerve are most frequently involved, however, we can see also the involvement of thoracic nerve and lateral peroneal nerve.

Let's move now to the next slide. Give me just a second. In that I have technical difficulties with my computer.

And we should review together in slide number 19 about the most important clinical features between mononeuritis versus entrapment. This is important because patients with diabetes quite often present symptoms of single nerve involvement, mainly on the median or ulnar or peroneal, the most common carpal syndrome, carpal tunnel syndrome. And as you can see, whereas the mononeuritis have a quite sudden onset, usually involving single nerve and we have already mentioned what are the most common nerves involved. It's not progressive and resolves spontaneously usually with a symptomatic sickness whereas the entrapment syndrome has quite gradual onset. They are progressive and they will require eventually more significant treatment some of them even a surgical devisement.

In slide number 22, if we move there, we can review together what are the most important clinical features of the distal symmetrical sensorimotor neuropathy. These we have established that this is the most common form of diabetic neuropathy. And it also sometimes caused the C type neuropathy because these people experience quite frequent symptoms due to the involvement of the C small unmyelinated fiber.

These symptoms are pain, which is experienced as burning, shooting or stabbing pain. Sometimes it might be exacerbated by various activity but typically is quite bad at night. Sometimes these people experience, so called pins and needles, parastesis, and they also have quite increased sensitivity to touch, so called allodynia or hyperalgesia. They also experience numbness

and these symptoms altogether can have a significant impact on their balance due to the loss in proprioception.

As you can see in slide number 23, there is also description of the most important sensory loss associated with small fiber neuropathy incurred especially incurred warm and cold sensations. The hypoesthesia that we have discussed and also due to the involvement of the autonomic fibers, which are also C type of fibers we see expressed and a decreased sweating, which will eventually lead to changes in the skin, cracking, very dry skin. And of course, due to the change in the foot architecture, which it says here in the right panel with changes in the joint architecture area of high pressure are being formed in these people and that those studies for formation of ulcers.

Slide number 24 shows some of the most commonly found features of the large fiber neuropathy. One of the hallmark clinical findings is impaired vibration perception. That can be easily tested in clinic as we will see in few minutes by measuring the vibration using a tuning fork. But as you can see probably as you probably have seen already, most of the clinically available methods of testing are testing the large fibers and usually to test the small fiber that are the first ones to be involved is a little bit more complex.

Looking at slide number 25, you see patient, which has severe marked wasting. Remember that the large myelinated A-alpha fibers are also motor fibers that are involved in the muscle control. You see here a severe wasting of the lower limbs. And also there is change in the tendon of Achilles structure, which is associated with change in the angle of the foot, which is higher than 90 degrees. This is a goniometer that sometimes can be available in our clinic for exam.

Moving at slide number 26, there is another picture of another patient, which has large fiber neuropathy involving this time the small muscle of the hand. You can see here in the left panel that there is significant wasting of the small muscle showing a diamond shape, open faced, and that also extend to the right wrist. See this patient is unable to extend his hand beyond 90 degrees. Again, that has been documented using the same gonial meter.

Let's move to slide number 27, which shows a patient, which has charcot neuroarthropathy. Some of you are probably quite familiar. This is a quite severe complication. I would say end stage part of large fiber neuropathy. In the left panel you have a picture of this is called hot foot since it is quite warm and when we see patients at the onset of charcot neuroarthropathy they present features of acute inflammation. That is why it's quite easy, if we are not aware, to mistaken that for infection. It's not an infection. It's, as I said, an end result of the large fiber neuropathy.

In the right panel, you have the picture of a radiography, which has been taken of this patient. You should note the rarefaction and osteopenia, which is present mainly in the calcaneus area and there is this color of the mid foot, which a lot of doctors put architecture, which also predisposes further to other information.

Let's review now some of the unfortunate consequences of neuropathy, which are separated now in slide number 28. And you have here a variety of real patients, unfortunately starting with quite early tissue damage shown in panel number one. Moving with changing in the toes architecture or clawing toes, callus formation, and the superficial ulcerations on the right – and actually on the right again are pictures of charcot neuroarthropathy.

In panel number three there is a typical neuropathic plantar ulcer, which is significant callus formation also on both feet. And here another patient here in panel number four, which has bilateral plantar ulcers, which after being – after the removal of the callus, the ulcer becomes more prominent.

Again in slide number 29, more evidence of the lesions of the feet as plantar ulcers, which are easily complicated by infection as shown here in panel C. And considering that the vast literature in the periphery always affected in diabetes and knowing that diabetic neuropathy is also a microvascular complication, it's not surprising that so many of these people unfortunately end up with different degrees of amputation.

Again, in slide number 30 more dramatic clinical cases starting with plantar ulcers to infection as well as shown here in panel number three quite extensive infection, and gangrene in slide number four. Unfortunately, these patients, as you have seen already, due to the very dramatic loss of sensation in some of them not knowing the proper measures to be taking as far as foot care, they end up sadly advanced stages of ulceration and infection.

Let's review now some of the most important diagnostic tests available for us in office for, you know, diagnosing the presence of peripheral neuropathy. And so some of these are depicted in slide number 31. In general, every patient with diabetes should have the feet examined every three months at the time of office visit, which should involve a routine foot exam, the measurement of vibration, which is actually shown here in the upper part of the slide using a regular tuning fork, which is quite useful tool for screening.

But I would like to remind you that vibration sensation is a measure of large fiber and sometimes patient might have normal vibration sensation but with

already involved myelinated small fibers. In general we should measure the second that the patient feels the vibration, which is quite easy to be done.

More complex testing, which can practically assess different type of fibers are the electric physiology and quantitative sensory testing. This is probably the most sensitive one as it has the possibility of testing both large and small myelinated fibers as well as C fibers.

In addition, we can perform light conduction studies, which are relatively easy to perform, however, again, their limitation is that they mainly assess the large fast conducting fibers. More recently, of course, the most specific test would be the morphological assessment by performing sural nerve biopsy. However, we cannot perform sural nerve biopsy as a routine method. It's an invasive method and therefore, usually it is used only in clinical research.

However, recently there is a quite evolving body of evidence that has demonstrated that by performing skin biopsies of the calf, we can quite accurately assess the number of fibers that are penetrating that epidermal facing membrane and that has been shown to correlate significantly with sural nerve biopsies.

As you can see in slide number 33, actually 34, there is a cartoon, which depicts different type of fibers starting with panel A with the normal density of epidermal nerve fibers and ending with panel C, which you can see there is a complete absence of nerve fibers in the pipe. The advantage of skin biopsies is that they don't require at all large amounts of tissue. Sometimes it could be punch biopsies and can be performed at different level starting with a very distal site and progressing proximally. Since we know that the peripheral diabetic neuropathy has quite a progressing pattern starting with the tip of the toes and progressing proximally.

So far we have reviewed some of the most important clinical features of the peripheral diabetic neuropathies as well as some of the clinical testing available to document the presence of peripheral diabetic neuropathy. However, as we have mentioned initially, diabetic neuropathy does not comprise only peripheral nerve and I think that it is quite important to mention as least briefly the involvement of the autonomic neuropathy. Since we know very well that cardiovascular disease and cardiovascular death is extremely prevalent in people with diabetes and we also have data that especially in the autonomic neuropathy of the cardiovascular system plays an important role.

In slide number 35, I have practically summarized all the organs that are regulated by the autonomic nervous system. And as you can see, they are quite numerous starting with the eyes, lungs, liver, pancreas, bowel, kidney, bladder, and heart and vessels.

In slide number 36 – actually 36, there are some of the effects of neuropathy on mortality rate. But before describing this slide I would like to mention that due to the limitation in time, we will not be able to review all the autonomic neuropathy features. And I have chosen to concentrate on the cardiovascular autonomic neuropathy due to the involvement in the overall cardiovascular risk.

And as you can see in slide number 36, which practically summarizes the results of nine different studies that have specifically looked at the active heart rate by ability or normal heart rate by the ability and total impact on mortality rate. As you can see in the lower part of this slide, as higher abnormal heart rate variability, which is shown here as HRC, the highest mortality rate in all these studies. So certainly autonomic neuropathy has a role.

And that has been also demonstrated in many other studies. I will cite here probably one of the first studies that has been published by Ewing in 1980. And that is shown here in slide number 37. And in this slide the five-year survival curve for general population or control shown here with blue has been compared with diabetic subjects with either normal autonomic function tests, and these are in purple. Diabetics which had no symptoms and completely normal cardiovascular reflex testing, which are a measure of diagnose the presence of autonomic cardiovascular neuropathy.

And as you can see here in this slide, in patients with diabetes and autonomic neuropathy manifested both as symptoms and cardiovascular reflex testing shown here in green, the five-year mortality rate was extremely high. Was 50% higher as compared with non-diabetic or diabetic without autonomic neuropathy.

And the same findings have been reported in other studies published ten years later, which is depicted in slide number 38. This study looked specifically at the patients with types of diabetes and again, as you can see, group number four, which has advanced abnormal cardiovascular testing have a progressive increase in the mortality rate over an eight years period as compared with patients with no autonomic neuropathy.

So with this in mind, let's see what are our available tools to manage this important complication. And in slide number 39, you see that we certainly have to work hard in eliminating all risk factors and contribute to the onset and progression of neuropathy. We should certainly try to develop therapeutic strategies based on the mechanism of this complication and unfortunately a symptomatic is necessary to see probably the only one available so far.

There are multiple risk factors that can and have been shown to contribute to the progression of neuropathy and these are shown in slide number 40.

Certainly the poor glucose control is by far the most important, however, we have to keep in mind that the presence of hypertension, hyperlipidemia, the presence of smoking as heavy alcohol use also has an important role.

I have mentioned that hyperglycemia is certainly extremely important and that has been demonstrated in multiple clinical studies. I will refer to the first clinical effective study shown here in number 40 – the slide number 41, the DCCT diabetes control and complication trial. Everybody is aware of the importance of this study.

And basically what you see in this slide is that an aggressive therapy against hyperglycemia aiming at HbA<sub>1c</sub> of 7 in the extensively treated group as compared with an A<sub>1C</sub> of 9 in the conventionally treated group has dramatically decreased the onset and progression of all microvascular complications. Retinopathy shown in red and nephropathy in yellow. Or retinopathy shown in blue, nephropathy in yellow and neuropathy in red and the prevalence of neuropathy has been decreased by 16%.

And to complete this slide, recently the edict study has shown that even at the end of the study after the A<sub>1C</sub>, hemoglobin A<sub>1C</sub> has been practically equalized between the groups the effect of an intensive control early – in early stages of the disease has maintained beneficial inference on the rate of progression of these complications even 11 years after the study has been practically stopped.

Let's move now at slide number – we will skip the next slide due to time.

There is also – it shows that hyperglycemia certainly has an important role on overall risk of amputation and foot ulcers. EURODIAB study shown here in

slide number 43 has aimed to look at the effect of multiple risk factors in addition to hyperglycemia and the progression of neuropathy.

And after adjusting for diabetes duration and hemoglobin A<sub>1C</sub>, as you can see in the next slide, slide number 44, the investigators concluded that an association existed between the odd ratio for the development of neuropathy for every quintile change in the glycosylated in hemoglobin.

Another study, which also looked at multi-factorial intervention mainly on cardiovascular disease, which was the main aim of the study was set up to study. And in this study, patients with type two diabetes were followed for a median of 7.0 years. In addition to an intense assessment of glycemia on aggressive treatment of hyperlipidemia, hypertension, smoking has been achieved.

But what is quite interesting for our presentation is depicted in the lower part of the graph showing that an intensive multi-factorial intervention has significantly decreased the risk of autonomic neuropathy as well.

As well as now practical tools in managing some of the consequences of neuropathy certainly the presence of foot ulcers is a significant issue since diabetic neuropathy is by far the leading cause of non-traumatic amputation. Recently it has been reported that more than 85,000 amputations are due to diabetic neuropathy in U.S. only per year.

So this – the slide number 47 shows a paradigm of approaching patients with ulcer, whether they do or do not have the presence of infection and what are the measures to be taken.

Slide number 48 reviews also the target that we can manipulate to control pain. These we have already discussed and we have also shown that pain is probably one of the most common extremely bothersome symptoms of which diabetic neuropathy. Of course controlling pain is a symptomatic treatment and as I mentioned, it's probably one of the treatments that are broadly available.

This slide shows different targets, different neurotransmitters, which are involved with different type of fibers and what are the agents that have been tried so far starting with SSRIs, anti-depressives, carbamazepine and other anti-epileptic drugs, local agents such as capsaicin and more recently Gabapentin, and the newly approved agent, which is Lyrica.

Unfortunately, most of these patients due to severe pain and sometimes ease of prescription of narcotics are becoming narcotic dependent and that is certainly not desirable.

In slide number 49, you have a graph and a cartoon showing what is the mechanism of these SSRIs in modulating the diabetic pain knowing that serotonin and norepinephrine are neurotransmitters that are – hello?

Hello? Hello?

(M) Bowers: We're still here.

Dr. Rodica Pop-Busui: Oh, okay. I heard a beep so I wasn't sure.

(M) Bowers: Oh no. We're still here.

Dr. Rodica Pop-Busui: Okay.

Serotonin and norepinephrine are moderators neurotransmitters of the pain.

Let's move to slide number 59, which practically shows how most of the data with the newly approved SSRI cymbalta, which appears to have rapid effects in diabetic peripheral neuropathy controlling both depression, which is associated with the pain and pain itself.

I hear a constant beep. Is there a problem?

Hello?

(M) Bowers: No. We're not getting it here on my end. Is anyone else experiencing that?

Dr. Rodica Pop-Busui: Hello?

(M) Bowers: I think we're doing okay here.

Dr. Rodica Pop-Busui: Okay.

(M) Bowers: All right.

Dr. Rodica Pop-Busui: All right.

So before ending, if we look at the slide – the next slide, which is a cartoon of some of the mechanisms that are involved in the peripheral nerve dysfunction and I don't want to go over all these details regarding the aldose reductase pathway, which certainly plays a role. I have also shown some of the data, which have been published by the use of aldose reductase inhibitors. Early

trials have been quite disappointing due to either inability of penetrating the nerve or the unacceptable side effects.

However, fidarestat, as you can see in slide number 54 is quite promising and it seems to have a beneficial effect in both controlling the subjective nerve symptoms and improving some of the clinical features.

Of course that's the mechanism of peripheral neuropathy is quite complex that is shown in some cartoons present in the next two slides. And I think that the future is to really understand all the mechanisms starting with increased oxidated stress, aldose reductase, pathway involvement, protein kinase C involvement, abnormal endoneurium flow, sympathetic neuropathy, apoptosis, and the developing agents that specifically address the defects involved in peripheral nerve dysfunction.

I think that I will stop here. I would like to mention in the end that we can certainly review much more about diabetic neuropathy as you can see due to the involvement of both peripheral and autonomic nervous systems, this is a quite serious consequence and that has interest and summary of the clinical features and some of the diagnostic tools available as well as of the overall involvement of these complications as far as the broad spectrum of diabetic complications.

Thank you very much for your attention.

(M) Bowers: Thank you very much Dr. Pop-Busui.

At this point we can conduct the question and answer session. Lindsey I have about one o'clock and Dr. Pop-Busui is available until about 1:05, 1:10 at the very latest. So please keep that in mind all right?

Operator: Okay.

(M) Bowers: You can proceed now if you would like, Lindsey.

Operator: Okay. Thank you ma'am.

As a reminder, the question and answer session will be conducted electronically. If you would like to ask a question, please indicate so by pressing star followed by the digit 1 on your touchtone phone. If you're using your speakerphone, please make sure your mute function is turned off to allow your signals to reach our equipment.

We'll proceed in the order you signal us. And we'll take as many questions as time permits.

Once again, please press star 1 on your touch telephone to ask a question. If your question has been answered, you can remove yourself by pressing the pound key.

We'll pause for just one moment to assemble the roster.

Again, to ask a question, it's star 1.

There are no questions from the phone lines.

(M) Bowers: Well, I guess that's going to conclude most of our session today. I guess I'd like to thank everyone for participating. And Dr. Pop-Busui we appreciate you giving us your time and expertise. These insights will really be useful for improving diabetes care nationwide.

Just another couple comments for those on the phone. Participants who have attended our past programs may have noticed some changes in our educational audio teleconference series registration and evaluation process. We hope that you find the new process reduces the amount of paperwork and streamlines the registration process as we're trying to figure out how to best serve you.

As a reminder, nurses and dieticians who would like CEU credits for this program need to have completed forms and registration in our office no later than Wednesday June 29 of next week. The link for our CEU registration form is listed online for the continuing education credits. This information is also listed in your syllabus and the continuing education instruction sheet.

If you have any questions, please feel free to contact our diabetes office. Our website is – or our email address is [diabetes@doh.state.florida.us](mailto:diabetes@doh.state.florida.us). Or use this phone number, which is 850-245-4330. We would appreciate any comments you have regarding the quality, registration process or suggestions for our teleconference series. Please include remarks on the post impact survey form.

So thank you again. I'd like to also thank everyone for participating on today's call. We really hope you have a wonderful day.

I will now turn the call over to the operator for call completion.

Lindsey.

Operator: And that concludes today's Florida Diabetes Prevention and Control program conference call. We thank you. We thank everyone for your participation. You may now disconnect at this time.

(M) Bowers: Thank you everyone. Goodbye.

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