Diabetic Neuropathy: New ADA Position Statement for Primary Care

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Diabetic neuropathies are the most prevalent chronic complications of diabetes—and they are often devastating for the patient. Estimates of the incidence and prevalence of diabetic neuropathies vary greatly, but several large observational cohorts and other studies suggest that they occur in at least 20% of people with type 1 diabetes after 20 years of disease. Distal symmetrical polyneuropathy (DSPN) may affect at least 10%-15% of patients with newly diagnosed type 2 diabetes, with rates increasing to 50% after 10 years of disease.1-4

The American Diabetes Association recently released a new position statement on diabetic neuropathy. Medscape spoke with the lead author, Rodica Pop-Busui, MD, PhD, about how these recommendations can assist primary care providers (PCPs) in the prevention, early recognition, and appropriate management of neuropathies in patients with diabetes.

Medscape: What types of diabetic neuropathy should PCPs be aware of, and how common are they?

Dr Pop-Busui: DSPN is the most prevalent form, and the best studied. DSPN is associated with several known severe complications, such as ulcers and infections, which can lead to lower-limb amputations. But even before that, the progressive damage of the various populations of nerve fibers may cause pain and/or lead to progressive loss of sensation, which decreases sense of balance and thermal discrimination; these factors increase the risk for falls or burns and affect patients’ daily function.

In addition to DSPN, the autonomic neuropathies, such as cardiovascular autonomic neuropathy, are relevant to clinical practice. More evidence has been unveiled in the past decade to further underline the seriousness of the consequences of diabetic neuropathies.

Medscape: The position statement emphasizes that the key to treatment of diabetic neuropathy is to prevent it in the first place. Are there any new strategies—beyond the recognized importance of adequate glucose control—that PCPs should be instituting in patients with diabetes or prediabetes?

Dr Busui: Evidence is emerging about the role of lifestyle interventions in the prevention of DSPN, which is quite exciting. A couple of studies show that, especially for patients with prediabetes and neuropathy, exercise and some types of diets seem to have a beneficial effect in prevention and possibly even reversal.5-7 However, we don’t have the same strength of evidence that we have for the benefit of glucose control in type 1 diabetes. These data have to be confirmed, but lifestyle interventions are cited in the statement as promising therapeutic options.

Medscape: What type of exercise? How much exercise is required?

Dr Busui: We cited studies that tested the types of exercise used in the Diabetes Prevention Program: typically 30 minutes daily of moderate to intense exercise.6,7 Other studies have looked at more intense exercise, but most studied the level of exercise used in the Diabetes Prevention Program.

Is Prevention Possible?

Medscape: According to the statement, enhanced glucose control is very effective in preventing diabetic peripheral neuropathy in patients with type 1 diabetes, but is less successful in those with type 2. Why is that?

Dr Busui: Patients with type 2 diabetes are typically very different from patients with type 1 diabetes. They also have other risk factors. Most are overweight or obese. Many have hypertension, metabolic syndrome, and the dyslipidemia associated with metabolic syndrome. All of these factors have been shown to be important in inducing nerve fiber damage, and may explain in part why glucose control alone has not been as effective in preventing diabetic neuropathy in patients with type 2 diabetes.
Patients with type 2 diabetes may also live with the disease for years without it being clearly diagnosed. It is thus likely that most of the patients included in interventional studies that looked specifically at glucose control, and captured some measures of neuropathy, may have been already in a more advanced stage of the disease.

In contrast, the Diabetes Control and Complications Trial (DCCT)\(^1\,^4\) included patients with type 1 diabetes early in their course of disease, with no neuropathy at baseline, hypertension, or other complications, except very minimal retinopathy in a subgroup by study design. In addition, a most comprehensive assessment of neuropathy was conducted in the DCCT cohort at baseline and over time in a standardized fashion. Other trials that included patients with type 2 diabetes, such as ACCORD,\(^8\) UK Prospective Diabetes Study (UKPDS),\(^9\) the Veterans Affairs Diabetes Trial (VADT),\(^10\) or BARI 2D,\(^11\) involved patients with more advanced disease.

Another possibility is that neuropathy has been defined differently in many of these trials, or some very insensitive measures were used. For instance, in the VADT, neuropathy was defined only on the basis of patient-reported symptoms, which have a high degree of subjectivity.

DSPN in patients with type 2 diabetes typically presents at a more advanced stage because these patients have a constellation of risk factors that can induce nerve damage.

Medscape: So, is it correct that the factors that make prevention less successful in patients with type 2 diabetes are essentially the same factors that lead to a larger proportion of these patients progressing to DSPN?

Dr Busui: Yes. And, as I noted, it's also possible that the true duration of disease in those patients may be much longer than years since diagnosis.

Symptomatic and Asymptomatic Neuropathy

Medscape: The statement also notes that up to one half of cases of DSPN may be asymptomatic. Why is that important?

Dr Busui: Some patients may experience pain, and some may experience numbness, although many have neither. DSPN is associated with a progressive lack of sensation, which is a risk factor for foot injuries or burns. It may result in patients using inappropriate footwear that can predispose them to more severe complications. In addition, a progressive loss of sensation may cause impaired balance, and may prevent patients from doing even usual activities that are important in their daily function.

Understanding the degree of dysfunction is important, because then the physician can advise the patient specifically about the type of activities that they may want to pay particular attention to, or the things that they need to avoid to prevent these complications. The position statement analyzed the evidence about the key parts of the examination that are easily done in the office, and the degree of deficits that are easy to identify. This will help providers avoid spending an enormous amount of time examining these patients or ordering unnecessary and expensive evaluations (such as nerve conduction studies) when the findings of the clinical examination, with or without symptoms, are very typical.

Medscape: The high proportion of asymptomatic patients points to the importance of screening. What are best practices for screening for DSPN? Should patients with prediabetes, or those who have other components of the metabolic syndrome, be screened?

Dr Busui: We emphasized in the statement the features that have been found to be consistent with a diagnosis of neuropathy. They can be assessed with simple instruments that can be carried in the coat pocket, such as a tuning fork, a monofilament, reflex hammer, or pushpins for a pinprick sensation test. We grade the evidence for these screening tests. Combining two of these evaluations increases the sensitivity and specificity of uncovering deficits.
Image from Science Source

associated with neuropathy, especially if some symptoms are present and the findings are symmetrical.

Sometimes just asking a patient, 'Do your feet feel numb?' is enough to make them aware that they have that sensation. Sometimes just asking a patient, "Do your feet feel numb?" is enough to make them aware that they have that sensation. "Do you have some numbness in your hands when you wake up in the morning?" screens for another type of symptom.

We said that physicians should consider screening patients with metabolic syndrome or prediabetes, especially if they have some symptoms. A large body of evidence now demonstrates that when all three factors associated with metabolic syndrome are present, the likelihood of neuropathy is much higher. The fact that peripheral neuropathy can be present in patients with metabolic syndrome has been reported by several groups of independent investigators.[12]

Pharmacotherapy of Diabetic Neuropathy

Medscape: Let's turn our attention to treatment. The statement notes that glycemic control is not effective in management of pain. There are three US Food and Drug Administration (FDA)-approved therapies to treat the pain that is so common with DSPN: pregabalin, duloxetine, and tapentadol. However, the evidence for opioid therapy is weak, which leaves clinicians with pregabalin and duloxetine. What do you recommend in terms of pharmacotherapy? Is either agent preferred for a specific population?

Dr Busui: The position statement offers a much more comprehensive approach. We do indeed note which agents are FDA-approved, but after saying that, we provide the evidence for all therapies supported by available randomized clinical trials, published and unpublished. That's how we came up with Table 4 in the statement, in which we critically considered dose titration, adverse effects, and number needed to treat from randomized clinical trials, and graded the level of evidence.

As our main outcome measure in judging the efficacy of pain reduction, we used either a 50% reduction in pain from baseline, or a 30% improvement in pain, which was shown in a very large study to be what is meaningful for the patient. The position statement also is trying to be patient-centered. Most patients feel that if they can reach that 50% reduction in pain, that's great, and 30% is acceptable.

The table also lists, besides the FDA-approved drugs duloxetine and pregabalin, other drugs (such as gabapentin) that may not have the FDA stamp of approval but are at least as effective as those that do, and may offer the advantage of a substantial cost difference.

In addition, we provide an algorithm for how to combine two or even three agents at lower doses, to help clinicians have a more flexible approach and mitigate the side effects that are associated with the highest dose of each agent alone. That is also different from what was included in the previous position statement.

We make a strong case against prescribing narcotics for treating the pain associated with diabetic neuropathy, given the large spectrum of serious side effects and addiction risks compared with their effectiveness in this case.

Autonomic Neuropathies

Medscape: Cardiovascular autonomic neuropathies are quite common in patients with longer-duration type 2 diabetes. In your experience, are most clinicians aware of the incidence of these types of neuropathies?

Dr Busui: The level of awareness seems to be increasing. A lot of the literature now confirms that cardiovascular autonomic neuropathy in particular clearly increases the risk for both major cardiovascular events and cardiovascular death.[13] That has been now confirmed, both in type 1 and type 2 diabetes, in large cohorts, where investigators adjusted for multiple cardiovascular risk factors. Physicians are becoming aware that having cardiovascular autonomic neuropathy places an additional risk on these patients.

Unfortunately, until the very late stages, this complication may be completely asymptomatic. Thus, a certain level of suspicion has to exist. Cardiovascular autonomic neuropathy may affect those with longer duration of disease or poor glucose control, but also young women, or patients with, impaired glucose tolerance or metabolic syndrome.
The presence of cardiovascular autonomic neuropathy can be also used as a tool to guide a patient's adherence to certain therapeutic strategies, and to increase the awareness of physicians about how to titrate some of the medications that are used to treat hyperglycemia, especially in patients with type 2 diabetes, and to avoid hypoglycemia in patients who take insulin, whether they are type 1 or type 2. Rapid changes in blood glucose levels may trigger important arrhythmic events.

**Medscape: Are the strategies recommended for prevention of DSPN the same strategies that may be effective in preventing autonomic neuropathy?**

**Dr Busui:** In type 1 diabetes, glucose control instituted as early as possible is very effective in preventing cardiovascular autonomic neuropathy as demonstrated by the DCCT/Epidemiology of Diabetes Interventions and Complications study. In type 2 diabetes, we have somewhat stronger evidence that a multifactorial intervention addressing several risk factors (blood glucose, blood pressure, lipids, lifestyle) does seem to prevent progression of cardiovascular autonomic neuropathy, as shown by the Steno-2 trial, a randomized trial conducted by the Steno Diabetes Center in Copenhagen that compared conventional vs intensive therapy.

**Medscape: Can you tell us about heart rate variability in these patients—is that a screening mechanism appropriate for primary care? Or should that be left to the cardiologist and the diabetologist?**

**Dr Busui:** We have not recommended that all patients with diabetes should be screened for heart rate variability at this stage. It may not be necessary in all patients. But screening is recommended in patients who have a more complicated course; when we contemplate a certain medication change in patients who are already at high risk for hypoglycemia; or in those undergoing surgery, because that is a very high-risk state.

**Medscape: For the PCP, the most critical thing is to be aware of these autonomic neuropathies, and to expect them in patients who exhibit cardiovascular symptoms or symptoms indicative of gastroparesis, such as early satiety, nausea, and bloating. Is that the main message—that clinicians should be aware of these complications and avoid indiscriminate testing to search for other pathologies?**

**Dr Busui:** As far as gastroparesis is concerned, we do want clinicians to be aware that several classes of medications used to treat diabetes, including glucagon-like peptide-1 receptor agonists or pramlintide, can delay gastric emptying as one of their mechanisms of action. If a patient treated with one of these agents is experiencing nausea and vomiting, you may want to advise the patient to reduce portion sizes and slowly titrate the medication—because that would effectively mitigate the symptoms without the need to perform gastric emptying studies and/or prescribe prokinetic agents, which will defeat the purpose of the antidiabetic agents.

And, of course, this same effect—delayed gastric emptying—occurs in patients who are taking opioids, which are unfortunately prescribed too easily for treating pain in general or pain associated with neuropathy.

Obviously, gastric emptying studies are completely unnecessary in these patients. In some cases, delayed gastric emptying has serious consequences that can affect the patient's glucose control. Patients on insulin may experience early hypoglycemic events if, as a result of delayed gastric emptying, their food is not absorbed, and then they can have late hyperglycemia. They can develop a vicious cycle between hypoglycemia and hyperglycemia. The physician should consider changing the pain medication regimen in this case, and use an algorithm that would be effective for the pain, but without such an adverse effect.

**Medscape: Do you have any final words for our readers?**

**Dr Busui:** I would like to stress that this document was the result of a very productive collaboration between endocrinologists and neurologists with known expertise in diabetic neuropathy and thus represents current consensus from both perspectives. Although the statement presents the currently available evidence for diabetic neuropathy, we have also included a section that summarizes still-unmet needs, especially with respect to early diagnosis and reversal of disease, that we hope will guide future research in a more unified fashion.

**References**


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