ABSTRACT

Diabetic peripheral neuropathy (DPN) affects approximately 50% of patients with diabetes and is a pivotal early step in the development of lower-limb diabetic complications. Metabolic pathways that contribute to oxidative stress (especially the polyol pathway) are thought to be of central importance in the pathogenesis of DPN. Although tight glucose control can significantly reduce the incidence and the progression of neuropathy, the control of macrovascular factors such as blood pressure is also important. In most cases, neuropathy can be detected quickly and easily by the application of a pinprick, tuning fork, or monofilament to the dorsum of the great toe. A number of new agents for the prevention and/or treatment of DPN are currently being evaluated in controlled clinical trials, and initial clinical results suggest that inhibiting oxidative stress or increasing blood flow improves nerve function in patients with diabetes. Other approaches, such as the use of growth factors to promote angiogenesis or nerve regeneration, may also improve nerve function but have not yet been extensively characterized in controlled clinical trials.

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producing DPN. The importance of the polyol pathway in the development of DPN is further illustrated by recent genetic studies that have demonstrated that patients with polymorphisms in genes that code for the enzyme aldose reductase confer an increased risk of developing more severe neuropathy.5,6

**FACTORS THAT INFLUENCE DPN PROGRESSION**

Tight glycemic control reduces the incidence of microvascular complications among patients with diabetes. For example, in the United Kingdom Prospective Diabetes Study (UKPDS), the incidence of any microvascular endpoint (retinopathy requiring photocoagulation, vitreous hemorrhage, fatal or nonfatal renal failure) in patients with diabetes was strongly associated with glycosylated hemoglobin A1c (HbA1c) concentration: the incidence increased from fewer than 10 microvascular endpoint events per 1000 person-years at HbA1c values of 5.5% to 6.5%, to nearly 60 events per 1000 patient-years at HbA1c values of greater than 10%.7 Similarly, clinical studies have found that the incidence of DPN is closely related to the duration and severity of hyperglycemia.

One recent study examined the importance of several risk factors for the development of DPN in patients with type 1 and type 2 diabetes with DPN.8 In patients with HbA1c values of 9% or lower, the nerves conducted signals between 1.8 m/s and 3.6 m/s faster compared with patients with HbA1c values 9% or greater. Peripheral nerve amplitude was also lower in patients with poor glycemic control. The duration of diabetes was also a significant independent predictor of the severity of neuropathy for both nerve conduction velocity and amplitude measures. However, even patients with prediabetic impaired glucose tolerance are at increased risk of microvascular complications. In a study of patients with painful idiopathic neuropathy but without diabetes, 35% had impaired glucose tolerance (serum glucose values of 140-200 mg/dL 2 hours after a 75-g glucose load), a percentage much higher than would be expected by chance in a random population sample.9

In addition to hyperglycemia, systemic vascular factors also significantly influence the incidence of microvascular complications of diabetes. For example, data from the UKPDS have shown that mean systolic blood pressure is strongly associated with the development of microvascular diabetes complications. Patients with mean systolic blood pressure values 160 mm Hg or greater developed microvascular complications at a rate of approximately 45 events per 1000 patient-years, whereas patients with systolic blood pressure values of less than 130 mm Hg developed complications at a rate of approximately 15 events per 1000 patient-years.10,11

**THE PROGRESSION OF DPN**

Epidemiologic studies have suggested that DPN is very common. Dyck and colleagues, in a community-wide cross-sectional study in Rochester, Minnesota, found that 66% of patients with type 1 diabetes had some form of neuropathy, and that 55% had DPN. In patients with types 2 diabetes, 59% had some form of neuropathy, and 45% had DPN.12 It should also be noted that the reported prevalence of DPN will depend to some extent on how the neuropathy is defined: studies in which detailed electrophysiological tests are performed may report higher prevalence rates than studies that report only symptomatic neuropathy.

DPN ultimately results in the loss of both large- and small-diameter fibers, usually beginning with the smaller fibers. Vascular changes, such as occluded vessels, shunting, and dilated capillaries, accompany the progressive loss of nerve fibers. As DPN advances, the axons atrophy and are lost, and the nerve is depopulated. This loss of nerve fibers is responsible for the manifestations of DPN, including ataxia, erectile dysfunction, abnormal position sense, and abnormal deep tendon reflexes, as well as other microvascular compli-

**Table. Sural Nerve Fiber Density and Clinical Variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>FD if Present</th>
<th>FD if Absent</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy</td>
<td>2102</td>
<td>3353</td>
<td>.0063</td>
</tr>
<tr>
<td>Ataxia</td>
<td>1754</td>
<td>3153</td>
<td>.0480</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>2401</td>
<td>4290</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Abnormal position sense</td>
<td>1549</td>
<td>3153</td>
<td>.0303</td>
</tr>
<tr>
<td>Abnormal deep tendon reflex</td>
<td>2827</td>
<td>4172</td>
<td>.0192</td>
</tr>
</tbody>
</table>

FD = fiber density.
cations, such as retinopathy (Table).13 Neuropathy is the
most important step in a series of events that culminates
in lower-extremity complications of foot ulceration and
amputation. In patients with neuropathy, even minor
trauma may produce skin ulceration, poor healing, and
eventually gangrene. Even in the absence of lower-
extremity complications, neuropathy can cause signifi-
cant functional impairment, including painful
paresthesia, sensory ataxia, and Charcot arthropathy.

**Assessing DPN**

The development of the signs and symptoms of DPN
is a long, insidious process. Early phases include general-
ized asymptomatic dysfunction of peripheral nerve fibers
that is detectable by nerve conduction studies; lack of
heart rate variability during deep breathing; and an
abnormal Valsalva. The progression of neuropathy con-
tinues with a decrease or loss of vibratory sensation of the
great toes, followed by panmodal sensory loss involving
the toes, feet, and distal legs; abnormal deep tendon
reflexes; autonomic abnormalities; eventual weakness of
the small foot muscles; and ankle dorsiflexion.

Neuropathy screening can be performed
using several simple tests, including the monofil-
ament, vibration, or pinprick. The monofilament
is very popular because it is also used to evaluate
patients for insensate feet, who are at high risk for
foot ulceration and amputation. Pinprick testing
is conducted using a disposable pin that is
applied to the dorsum of the great toe. Similarly,
the Semmes-Weinstein 5.07 (10-g) monofila-
ment or the 128-Hz tuning fork may also be
applied to the dorsum of the great toe. Some
clinicians recommend that the reflexes be tested
routinely, although the findings are often vari-
able, and may be affected by patient age and
relaxation. Sensory testing is sufficient to identi-
fy neuropathy in most cases. Neuropathy is
proven by finding more than 4 incorrect respons-
es out of 8 tests using pinprick, monofilament, or
tuning fork examination.14 This evaluation is eas-
ily performed in a minute or less.

Other diagnostic tests are also available for
special situations. Nerve conduction studies pro-
vide objective, reproducible, and reliable findings
that directly measure the function of the large
fibers of the peripheral nerves. These studies are
reserved for patients who are atypical, have asym-
metrical neuropathy, or are suspected to have neuropa-
thy from nondiabetic causes. Vibration perception
thresholds, which are psychophysical measures of
peripheral and central nerve dysfunction, provide a
quantitative evaluation similar to nerve conduction stud-
ies, but lack their specificity and reliability. Vibration
perception threshold testing is not routinely recom-
manded but can be used in research trials and as a con-
firmatory evaluation.

**Prevention and Treatment of DPN**

Control of blood glucose significantly reduces the
risk of DPN. In the Diabetes Control and
Complications Trial (DCCT), the investigators com-
pared the incidence of neuropathy between patients
who were randomized to tight glucose control or to
conventional treatment.15 The intensive treatment regi-
men was associated with approximately a 60% reduc-
tion in the incidence of neuropathy over 5 years of
treatment. Whether measured by clinical examination,
autonomic nerve study, or nerve conduction study, tight

![Figure 1. Effect of Diabetes Management on Development of Diabetic Peripheral Neuropathy](image)

Whether evaluated by neurological examination, autonomic nerve study, or nerve conduc-
tion study, conventional diabetes management was associated with a higher rate of diabetic
neuropathy than more intensive treatment.

Reprinted with permission from the Diabetes Control and Complications Trial Research
Group. The effect of intensive treatment of diabetes on the development and progression
glucose control substantially reduced the risk of neuropathy (Figure 1). These results, and similar findings from other studies, have provided the rationale for the current recommendations that HbA1c values should be reduced to less than 6% whenever possible.16

Although this study and others have clearly demonstrated the benefits of lowering HbA1c to below 6%, most patients find this goal difficult to reach. The participants in the DCCT were young, highly motivated patients with type 1 diabetes, yet only about 15% were able to attain HbA1c values below 6%. Therefore, other approaches to interrupt the pathophysiological cascade that leads to DPN are needed to improve outcomes for the large number of patients who cannot attain good glycemic control with the currently available therapies. Preventing the progression of neuropathy is especially important because, once established, the neuropathy may be irreversible. Although peripheral nerves do possess the capacity to regenerate, these regenerative mechanisms are often significantly impaired in patients with diabetes. At present, it is not clear whether DPN is permanent or can be reversed by pharmacological or other treatments.

Several new therapeutic approaches are currently being evaluated for the prevention or treatment of DPN. As described previously, aldose reductase is an important regulatory enzyme in the polyol metabolic pathway. Aldose reductase inhibitors have long been considered a potential therapeutic strategy to prevent the microvascular complications of diabetes. These agents are intended to block the polyol pathway and reduce the accumulation of sorbitol in nerves. Although some early studies reported promising findings with these agents, most of those older aldose reductase inhibitors were associated with unacceptable toxicity. A number of newer aldose reductase inhibitors have recently been developed, and the clinical evidence to date suggests that these agents possess fewer problems with safety and tolerability. Some of the recently developed aldose reductase inhibitors include fidarestat, which has recently been evaluated in phase 2 clinical trials; ranirestat, which has just begun a phase 3 clinical trial;17,18 and epalrestat, which is currently available in Japan.

The metabolic and clinical effects of the aldose reductase inhibitor ranirestat on DPN were recently examined in a randomized, double-blind clinical trial of patients with mild to moderate DPN as documented by nerve conduction studies and vibration perception thresholds.19 Patients were randomized to treatment with either placebo or one of 2 doses of ranirestat (5 or 20 mg per day) for 12 weeks. Treatment with ranirestat inhibited nerve sorbitol concentration by 65% and 84% at the 5-mg and 20-mg dose, respectively (P <.0001). Nerve fructose, another product of the polyol pathway, was also reduced to a similar extent (Figures 2A and 2B). After 12 weeks of therapy, the 20-mg dose was associated with significant improvement in nerve conduction velocity in the left and right sural nerves (P <.05) and in the proximal median sensory nerve, with increases from baseline of at
least 1 m/s (P < .01). This result is clinically meaningful as shown by the relative large change in nerve function in small numbers of patients treated for a short interval, and because this improvement in nerve function was associated with improved clinical scores based on the sensory examination. Antioxidants (eg, alpha-lipoic acid), a second class of agents currently in clinical development, are also intended to reduce oxidative stress by preventing the generation of oxygen free radicals. Alpha-lipoic acid is currently being evaluated in a long-term phase 3 trial in North America.20

Nerve hypoxia may also be important in the development of DPN. Hypoxia may be reduced by agents that improve nerve blood flow or that stimulate angiogenesis. Gene transfer with vascular endothelial growth factor (VEGF), an endogenous stimulator of angiogenesis, is currently being evaluated as a potential treatment for DPN.20 However, it is possible that VEGF may worsen retinopathy. Inhibitors of PKC-β may also improve nerve blood flow, and this strategy is being evaluated in a phase 3 trial. PKC inhibition with ruboxistaurin has been shown to produce clinically significant improvement in a phase 2 clinical trial of sensory nerve function.21 A total of 205 patients with type 1 or type 2 diabetes were randomized to treatment with placebo or one of 2 ruboxistaurin doses (32 or 64 mg). On the Neuropathy Total Symptom Score-6 rating scale of DPN, both ruboxistaurin doses produced greater improvement from baseline than placebo after 12 months of treatment, although the difference was only statistically significant with the higher dose (P = .014). In a subgroup analysis of patients who developed early, symptomatic peripheral neuropathy, both doses produced significant improvement from baseline in vibratory sensation, compared with placebo (P = .006 for low-dose ruboxistaurin, P = .028 for high-dose ruboxistaurin). Finally, C-peptide deficiency may be very important in patients with type 1 diabetes. C-peptide replacement, which may improve nerve blood flow, is being evaluated in phase 2 clinical trials.20

**TREATMENT OF PAINFUL DPN**

One of the most troubling symptoms for many patients with DPN is pain. Several interventions provide effective pain relief for pain associated with DPN. Tricyclic antidepressants such as amitriptyline are widely used for the treatment of neuropathic pain. Clinical trials that have examined the selective serotonin reuptake inhibitors (SSRIs) for painful DPN have produced conflicting results. Many clinicians believe that these agents are useful for painful DPN, although others are not convinced by the currently available data. A novel dual-action antidepressant, duloxetine, has been approved recently by the US Food and Drug Administration (FDA) for the treatment of painful neuropathy. This agent is a combination SSRI and inhibitor of norepinephrine reuptake. Antiepileptic drugs, such as gabapentin, carbamazepine, and topiramate, are effective in controlling painful symptoms of DPN,22-26 as are the opioids tramadol and oxycodone.27-28 Treatment of painful DPN should begin with a low medication dose, which is titrated upward until the appearance of analgesia or unacceptable side effects. Treatment usually produces an improvement in pain, although complete pain relief is rare.

Other therapies have been proposed for DPN but have not been extensively studied in controlled clinical trials. It has been suggested that magnet therapy may improve painful neuropathy, and one randomized, placebo-controlled study appeared to demonstrate some beneficial effects of application of magnets to the soles of the feet.29 Topical capsaicin and local anesthetic creams may be beneficial. Low-intensity laser therapy, or infrared therapy, did not produce significantly greater improvement than treatment with a sham laser in a blinded clinical trial.30 Near-infrared energy laser therapy has been approved by the FDA for the treatment of pain.31

The ideal therapy for DPN would promote nerve regeneration and relieve the symptoms of neuropathy. Several pharmacological agents that may lead to neuronal regeneration are being evaluated currently, and the results should be available within the next 1 to 2 years. At present, the only treatment known to prevent degeneration and the progression of DPN is optimal glycemic control and the control of modifiable risk factors, such as hypertension.

**SUMMARY AND CONCLUSIONS**

The progression of DPN is strongly related to blood glucose levels, and also to macrovascular factors such as elevated blood pressure. Neuropathy may be assessed by simple, rapid clinical measurements such as the application of a pinprick, tuning fork, or monofilament to the dorsum of the great toe. Although tight glycemic control has been shown to significantly reduce the risk of DPN, it is difficult for many patients to achieve the currently recommended target HbA1c value of less than 6%. New
strategies for the prevention or treatment of DPN are currently being evaluated in clinical trials. Initial clinical reports suggest that agents that inhibit the polyol metabolic pathway (eg, aldose reductase inhibitors) or improve blood flow (eg, PKC inhibitors) significantly reduce the progression of DPN. Treatments that promote angiogenesis or the regrowth of peripheral nerve fibers may also be beneficial in patients with DPN but are in earlier stages of clinical evaluation.

**REFERENCES**