

Management of Diabetic Peripheral Neuropathic Pain

a report by

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Diabetes remains the most common cause of neuropathy in the US, and neuropathy is the most common complication and greatest source of morbidity and mortality in diabetic patients. Additionally, emerging studies suggest that impaired glucose tolerance may lead to polyneuropathy, particularly painful small-fiber neuropathy. It is estimated from epidemiological studies that the prevalence of neuropathy in diabetic patients is approximately 30% in hospitalized patients and 20% in community-dwelling diabetic patients.

However, the epidemiology of the diabetic neuropathies has been difficult to establish with precision because the criteria for diagnosis vary, epidemiologic studies are limited to patients receiving medical care, and diabetes remains undiagnosed in a large population of subjects. Therefore, diabetic neuropathy may be implicated in 50% to 75% of non-traumatic amputations of lower limbs.

Neuropathic pain is defined by the International Association for the Study of Pain as “pain initiated or caused by a primary lesion or dysfunction of the nervous system”.¹ Neuropathic pain can be thought of as pain that arises from abnormal nervous system physiology, with diverse clinical manifestations and can affect virtually every tissue of the body. Members of an International Consensus agreed on a simple definition of diabetic neuropathy as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes.

Approximately 10% of peripheral neuropathy in diabetes appears to be of non-diabetic etiology. For this reason, it is very important to conduct a careful clinical examination and always consider that absence of symptoms must never be equated with absence of neuropathy.

Several randomized controlled clinical trials completed over recent years have demonstrated the effect of improved glycemic control on microvascular and

neurological complications of diabetes among the most representative in type 1 diabetes is the Diabetes Control and Complications Trial (DCCT) trial and in type 2 diabetes the UK Prospective Diabetes Study (UKPDS). The DCCT shows us that the intensive treatment group achieved a median glycosylated hemoglobin (HbA_{1c}) of 7.2% during a mean follow-up of 6.5 years and a dramatic 64% reduction for confirmed clinical neuropathy. The UKPDS failed to support a similar correlation between incidence of neuropathy and glycemic control in type 2 diabetes patients, but the progression of diabetic neuropathy is dependent on glycemic control.

In one of the largest trials to date, the Rochester Diabetic Neuropathy Cohort, two-thirds of patients had type 1 diabetes and one-third type 2 diabetes. Peripheral neuropathy of some type was found by objective testing in 66% of patients with type 2 diabetes, though only 15% had symptoms at the moment of clinical assessment. The diabetic neuropathies comprise several different clinical syndromes, which may occur in isolation or in varying combinations. In this study, distal symmetric polyneuropathy was the most common neuropathy in type 2 diabetes, affecting 54% of patients, and only 13% were symptomatic. Median mononeuropathy at the wrist, carpal tunnel syndrome, was second, affecting 33%.

Current understanding of the pathophysiology is complicated and incomplete, but recently numerous competing and/or pathological pathways have begun to intersect and complement each other opening the future development of new potential therapeutic targets (see *Figure 1*). The biochemical alterations more studied are the formation of advanced glycation end products, oxidant stress, the polyol pathway, and protein kinase C (PKC).

Recently, endothelial function has gained increasing attention in understanding vascular health and disease. The endothelium plays a vital role in vascular homeostasis, regulating vascular tone, vascular smooth muscle cell proliferation, transendothelial leukocyte migration, and thrombolysis. Endothelial dysfunction



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Table 1: Classification of Diabetic Neuropathies

Main Groups	Subtypes
Generalized neuropathy	<ul style="list-style-type: none"> Hyperglycemic neuropathy Symmetric distal polyneuropathy with/without autonomic neuropathies Acute painful sensory neuropathy variants
Focal and multifocal neuropathy	<ul style="list-style-type: none"> Cranial neuropathies Focal limb neuropathies Thoracolumbar radiculoneuropathy Lumbosacral radiculoplexus neuropathy (Bruns-Garland syndrome)

Table 2: Blood Biochemical Tests in a Patient with Diabetic Neuropathy

B12 and folate values	Glucose
Serum protein electrophoresis	HbA _{1c}
ANA/ENA/rheumatoid factor	HDL-cholesterol
Thyroid function	LDL-cholesterol
FBC/ESR, U&Es and LFTs	Tryglycerides

ANA = antinuclear antibody; ENA = extractable nuclear antigen; HDL = high-density lipoprotein; LDL = low-density lipoprotein; FBC = full blood count; ESR = erythrocyte sedimentation rate; LFT = liver function test; U&E = urea and electrolytes.

Table 3: Painful and Non-painful Symptoms in Diabetic Neuropathy

Non-painful	Painful
Asleep	Prickling
Thick	Tingling
Stiff	Knife-like
Prickling	Electric sensations
Tingling	Squeezing
Numbness	Constricting
	Hurting
	Burning
	Freezing
	Throbbing
	Allodynia*
	Hyperalgesia

*Allodynia: the perception of pain from a non-noxious stimulus.

Table 4: Chronic and Acute Neuropathies

	Chronic Sensorimotor	Acute Sensory
Mode of onset	Gradual, insidious	Relatively rapid
Symptoms	Burning pain, paresthesiae, numbness; weight loss unusual	Severe burning pain, aching; weight loss usual
Symptom severity	0 to ++	+++
Signs	Stocking and glove sensory loss; absent ankle reflexes	Mild sensory in some; motor unusual
Other diabetic complications	Increased prevalence	Unusual
Electrophysiological studies	Abnormalities unusual in motor and sensory nerves	May be normal or minor abnormalities
Natural history	Symptoms may persist intermittently for years; at risk of foot ulceration	Complete recovery within 12 months

has also been considered an important event in the development of diabetic neuropathy.

Diagnosis

No single test can demonstrate that the primary cause of nerve injury is diabetes. Consequently, diabetic neuropathy is both a clinical diagnosis and a diagnosis of exclusion. A careful history and physical examination are critical and often reveal patterns conforming to a single known diabetic syndrome or some combination of the known syndromes (see *Table 1*).

The possibility that the diabetic patient may also develop a neuropathy from a cause other than diabetes is always present. On the other hand, in patients with neuropathy but no previous diagnosis of diabetes, a glucose tolerance test may be useful to exclude diabetes (see *Table 2*).

The diagnosis of the various forms of neuropathy requires awareness of the differing manifestations of these abnormalities, with sensory neuropathy causing numbness as a late manifestation and excessive function with prickling, stabbing, or burning symptoms characteristically seen earlier. Motor neuropathy leads to wasting and weakness, typically found late in the clinical course and usually less severe as clinical manifestations than the sensory abnormalities (see *Table 3*).

Chronic Sensorimotor Neuropathy

Chronic sensorimotor neuropathy is the most common presentation of neuropathy in diabetes; up to 50% of patients may experience symptoms, most frequently burning pain, electrical or stabbing sensations, paresthesia, hyperesthesia, and deep aching pain (see *Table 4*). Many patients are asymptomatic, and a neurological deficit may be discovered during a routine neurological clinical exam.

Acute Sensory Neuropathy

Acute sensory neuropathy is rare, tends to follow periods of poor metabolic control or sudden changes, and is characterized by the acute onset of severe sensory symptoms (see *Table 4*).

Insulin Neuritis

The term insulin neuritis describes the condition of neuropathic symptoms developing soon after institution of insulin therapy. Patients develop distal sensory symptoms, mainly in the lower limbs, on commencing insulin for the first time. A few

abnormalities are found upon neurologic examination or electrophysiological study, but the cause is not known.

Pharmacological Management

Metabolic Control

Data from a number of observational studies suggest that stable glycemic control is of the greatest importance. A recent study using continuous glucose monitoring confirmed that painful symptoms were associated with erratic blood glucose control. A large number of therapeutic agents have been proposed for the management of painful symptoms – only those that have demonstrated efficacy in randomized, controlled studies are discussed (see Table 5).

Tricyclic Agents

The use of tricyclic drugs in the management of neuropathic pain is supported by several randomized, controlled studies. However, their use is restricted because of the frequency and severity of side effects. Tricyclic antidepressants have an analgesic action that is demonstrated to be independent of their antidepressant effect. The analgesic response is thought to occur at lower doses than the antidepressant effect, although there is no systematic evidence of this.

The mechanism of action of the tricyclic agents is not clear but may occur through inhibition of reuptake of norepinephrine and serotonin, but also through effects on sodium channels and the NMDA receptors. Although these agents are most useful in the management of neuropathic pain, it is, once again, their side effect profile that limits their use. Side effects, which are typically predictable and related to atropine-like actions, include dry mouth, blurred vision, cardiac arrhythmias, sedation, urinary retention, constipation, and postural hypotension. Although nocturnal administration helps reduce the sedative side effects, up to about one-third of all patients cannot tolerate these agents. Amitriptyline and imipramine are the most commonly used, although desipramine has fewer anticholinergic side effects and is less sedative.

Selective Serotonin Reuptake Inhibitors

Trials of selective serotonin reuptake inhibitors (SSRIs) as treatment for diabetic neuropathy have been generally disappointing. Such agents work by the inhibition of pre-synaptic reuptake of serotonin but not norepinephrine. There is some evidence to support the use of paroxetine and citalopram in dosages of up to 40mg/day from small controlled studies.

Table 5: Drugs used in Painful Neuropathy Management

Drug Class	Drug	Daily Dose (mg)	Side Effects
Tricyclics	Amitriptyline	25–150	++++
	Imipramine	25–150	++++
Selective serotonin reuptake inhibitors	Paroxetine	40	+++
	Citalopram	40	+++
Anticonvulsants	Gabapentin	900–1,800	++
	Pregabalin	160–600	++
	Lamotrigine	200–400	++
	Carbamazepine	up to 800	+++
Antiarrhythmics*	Mexiletine	up to 450	+++
Opioids	Tramadol	50–400	+++
	Oxycodone CR**	10–60	++++

All medications in this table have demonstrated efficacy in randomised controlled studies. *Mexiletine should be used with caution and with regular electrocardiogram monitoring; **Oxycodone controlled release (CR) may be useful as an add-on therapy in severe symptomatic neuropathy.

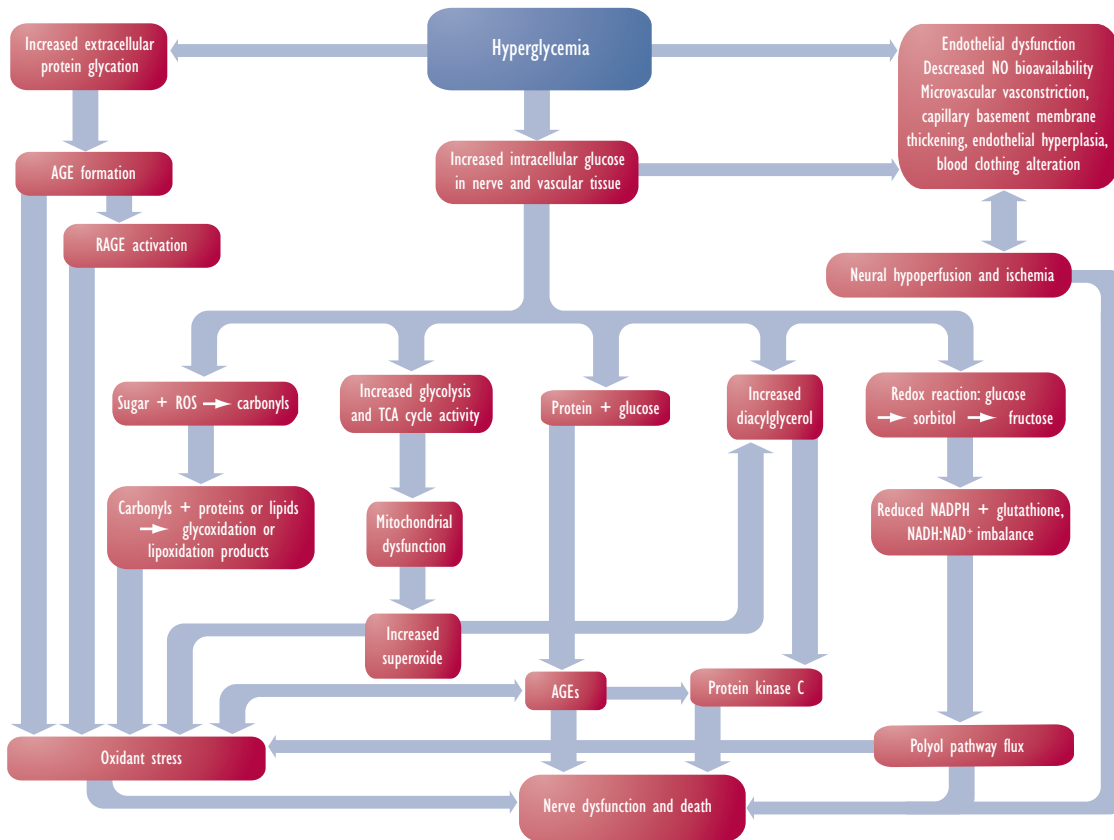
Anticonvulsants

Anticonvulsant drugs act by a variety of different mechanisms, including effects on sodium or calcium conductance, increases in gamma-aminobutyric acid (GABA) levels, decreases in glutamate levels, and other unknown mechanisms. These agents have been used in the management of neuropathic pain for many years, but only limited evidence exists for the efficacy of phenytoin and carbamazepine.

Gabapentin is now widely used for neuropathic symptoms. This agent is structurally similar to the neurotransmitter GABA and was introduced some years ago as an anticonvulsant for complex partial seizures. The efficacy of gabapentin has been confirmed in two placebo-controlled clinical trials. The side effect profile appears to be less than that of the tricyclics. The precise mechanism of action of gabapentin for pain relief is unknown; however, a specific calcium channel binding site has been identified, and regulation of calcium may play a role. Reported effects include sedation, dizziness, headache, pedal edema, and weight gain. It should be noted that the average dose required for pain relief in clinical trials was about 1.8g/day. Slow dose titration may reduce the incidence of side effects, but it has been suggested that many patients are not being treated with a sufficiently high dosage. Recently, the National Polytechnic Institute, Mexico, described the existence of a synergism between gabapentin with thiamine and hydroxycobalamin in diabetics that may reduce the gabapentin dose with the consequent decrease in side effects.

A newer drug, pregabalin, which is a central nervous system active compound and an analog of GABA, has recently been introduced. Pregabalin shares gabapentin's binding site on a subunit of voltage-dependent calcium channels. Preliminary evidence suggests that this agent may be a useful addition to the anticonvulsants that are

Figure 1: Pathophysiology of Diabetic Neuropathy



helpful in the management of neuropathic pain. A number of other anticonvulsant agents have confirmed efficacy in randomized, controlled trials. These include lamotrigine and sodium valproate. Thus, some of the newer anticonvulsants are increasingly being used due to their superior side effect profile and novel mechanism of action.

**Local Anesthetic
Antiarrhythmic Agents**

Lidocaine results in sodium channel blockage, dampening both peripheral nociceptor sensitization and ultimately central nervous system hyperexcitability. Although early studies suggested that intravenous lidocaine administration might be beneficial in relieving neuropathic pain, the potential side effects and the need for intravenous administration was problematic. The oral analog of lidocaine, mexiletine, has been reported to be of benefit in some studies, but it is not widely used because of side effects and the need for regular electrocardiogram monitoring with its use. There are now preliminary data to suggest efficacy from the use of a 5% lidocaine patch in diabetic polyneuropathy. In an open-label study, the use of a maximum of four patches of 5% lidocaine per day was

associated with relief of neuropathic symptoms without serious adverse effects.

Opioid Analgesics

Opioids have not traditionally been used in the management of diabetic neuropathic pain, but recent trials of two agents do suggest efficacy. First, tramadol, which is an opioid-like, centrally acting synthetic narcotic analgesic, that has low affinity for the μ -opioid receptors (approximately one-tenth the strength of codeine), and weak inhibition of norepinephrine and serotonin reuptake. It has been confirmed to be efficacious in a randomized, controlled trial, and a follow-up study suggests that it can be used safely for up to six months of sustained pain relief.

More recently, two studies have confirmed the efficacy of controlled-release oxycodone. The side effects of both drugs are predictable and include somnolence, nausea, and constipation; addiction is also problematic. It may be that opioids such as tramadol and oxycodone may be considered as add-on therapies for patients failing to respond to non-opioid medications in the first instance. ■

Further Reading

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