

Dr. Farhad Emadi Neurologist

DIABETIC NEUROPATHIES



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@Dremadi



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Diabetic neuropathy is a generic term defined as the presence of symptoms and signs of peripheral nerve dysfunction in individuals with diabetes after the **exclusion** of other causes.

The mere association of neuropathic symptoms with diabetes mellitus is **insufficient** for the diagnosis of diabetic neuropathy

diabetic neuropathies, being common disorders, may coincide with **other** conditions that cause similar manifestations including **CIDP**, **vitamin B12** deficiency, **alcoholic** neuropathy, and **endocrine** neuropathies.

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In general, the diagnosis of a definite diabetic neuropathy should be based on **clinical symptoms**, objective neurological **signs**, and **EDX** confirmation.

The risk of developing symptomatic neuropathy in patients without neuropathic symptoms or signs at the time of initial diagnosis of diabetes is estimated to be **4% to 10% by 5 years and up to 50% by 25 years.**

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patients presenting with a chronic “idiopathic” axonal polyneuropathy have nearly a **twofold** higher frequency of undiagnosed diabetes mellitus and impaired fasting blood glucose than age-matched controls.

an **axonal neuropathy** may be **the presenting** or the earliest manifestation in diabetes.

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BOX 107.14 Classification of Diabetic Neuropathies

GENERALIZED SYMMETRICAL POLYNEUROPATHIES

Distal sensory or sensorimotor polyneuropathy
Small-fiber neuropathy
Autonomic neuropathy
Large-fiber sensory neuropathy

FOCAL AND ASYMMETRICAL NEUROPATHIES

Cranial neuropathy (single or multiple)
Truncal neuropathy (thoracic radiculopathy)
Limb mononeuropathy (single or multiple)
Lumbosacral radiculoplexopathy (amyotrophy, proximal neuropathy)

COMBINATIONS

Polyradiculoneuropathy
Diabetic neuropathic cachexia



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Clinical Features

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Distal Symmetrical Polyneuropathy (DSP).

DSP is the **most common** form of diabetic neuropathies.

DSP :
large-fiber and small-fiber variants.

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Small Fiber

sensory deficits predominate

autonomic symptoms usually correlate with the severity of the neuropathy.

There is only a **minor motor** involvement affecting the distal muscles of the lower limbs.

Sensory disturbances have a **stocking-glove** distribution.

Early sensory manifestations begin in the **toes**, gradually spreading proximally; when these reach above knee level, the fingers and hands become affected.

In more advanced cases, sensation becomes impaired over the **anterior chest and abdomen**, producing a truncal wedge-shaped area of sensory loss.

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The **small-fiber** neuropathy frequently presents with **pain** of a **deep, burning,** stinging, aching character, often associated with **spontaneous shooting pains** and **allodynia** to light touch.

Pain and temperature modalities are impaired, with relative preservation of vibration and joint position sensation and muscle stretch reflexes. The small-fiber variant is often accompanied by autonomic neuropathy.

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An acute **painful neuropathy** may be precipitated following **initiation of treatment** of a diabetic patient **with insulin** (treatment-induced neuropathy). **Burning pain and paresthesias** develop in the distal lower extremities shortly after the establishment of glucose control.

Pain persists for **weeks** or up to several **months**, with spontaneous resolution to follow. Pathological studies demonstrate **active axonal regeneration**, which may act as generators of spontaneous nerve impulses.



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large-fiber

The neuropathy variant presents with **painless paresthesias** beginning at the toes and feet, impairment of **vibration** and **joint position** sense, and diminished muscle stretch **reflexes**.

In advanced cases, significant **ataxia** may develop secondary to sensory deafferentation. Large-fiber involvement is often **asymptomatic**

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hyperglycemic neuropathy

Patients with newly diagnosed diabetes may experience transient pain and paresthesias in the **distal lower extremities**. The symptoms will usually resolve when the hyperglycemia is brought under control.

Diabetic neuropathic cachexia

refers to an acute and severe painful diabetic neuropathy associated with precipitous severe **weight loss**, **depression**, **insomnia**, and **impotence** in men.

Although it is rare, it imparts major challenges in diagnosis and treatment. The syndrome is more common in men with poor glucose control. abnormalities



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Acrodystrophic Neuropathy

Sensory loss makes patients with diabetes susceptible to repetitive, often unnoticed injuries that set the stage for foot ulcers and distal joint destruction. Chronic foot ulceration is one of the more severe complications of diabetes mellitus, occurring in **4% to 10%** of patients, and is due to a combination of unnoticed traumatic tissue damage, vascular insufficiency, and secondary infection



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Neuropathic arthropathy

or a **Charcot joint formation**, is a complication seen in patients with diabetes who often have foot ulcers and autonomic impairment.

Unlike the Charcot joint seen in syphilis, diabetic arthropathy tends to involve the small joints in the feet.

The term **diabetic pseudotabes** is applied to patients having severe lancinating pains, loss of joint sensation, and diabetic pupillary abnormalities (pseudo-Argyll Robertson pupils).



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Autonomic Neuropathy



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Autonomic neuropathy **usually correlates** with the severity of somatic neuropathy.

The spectrum of autonomic involvement ranges from **subclinical** functional impairment of cardiovascular reflexes and sudomotor function to **severe** cardiovascular, gastrointestinal, or genitourinary autonomic dysfunction

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Orthostatic hypotension, resting tachycardia, or diminished heart-rate response to respiration are the hallmarks of diabetic cardiac autonomic neuropathy.

Orthostatic hypotension occurs mainly because of failure of the sympathetic nervous system to increase systemic vascular resistance in the erect posture and impairment of compensatory cardiac acceleration.

It is crucial to exclude confounding effects of medications or coexisting hypovolemia when diagnosing neurogenic postural hypotension.



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Vagal denervation of the heart results in a **high resting** pulse rate and **loss of sinus arrhythmia**.

An increased incidence of **painless or silent myocardial infarction** is reported in diabetic patients with autonomic neuropathy. It is important to investigate the cardiac autonomic neuropathy of diabetes by appropriate noninvasive autonomic function tests, because the presence of such autonomic dysfunction predicts cardiovascular morbidity and mortality



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Gastrointestinal motility abnormalities involving the esophagus, stomach, gallbladder, and bowel, as well as fecal incontinence may occur. Delayed gastric emptying, usually of solids, leads to **nausea**, **early satiety**, and **postprandial bloating**.

Diabetic diarrhea due to small-intestinal involvement typically occurs at night and is explosive and paroxysmal.

Constipation due to colonic hypomotility is more common than diarrhea. is rare. Bacterial overgrowth may occur and can often be successfully treated with small doses of **tetracycline** (250–500 mg/day in a single dose given at the onset of a diarrheal attack) in adult patients.

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Impaired bladder sensation is usually the first symptom of urinary autonomic dysfunction. **Bladder atony** leads to prolonged intervals between voiding, gradually increasing urinary retention, and finally overflow incontinence. The symptoms of urinary autonomic dysfunction develop insidiously and progress slowly. Patients with diabetes who have neurogenic bladder should be encouraged to void routinely every few hours to prevent urinary retention.



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Impotence is often the **first manifestation** of autonomic neuropathy in men with DM occurring in more than **60%** and causing serious emotional distress.

Autonomic dysfunction involves both **erectile failure** and **retrograde ejaculation**.

The majority of diabetic men with impotence have some evidence of associated **DSP**

Autonomic neuropathy is not the only cause of impotence in diabetic males, and other factors such as **vasculopathies**, **hormonal** alterations, and **psychological** issues are equally important.

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Sudomotor abnormalities result in distal anhidrosis, compensatory facial and truncal sweating, and heat intolerance.

A peculiar hyperhidrosis called *gustatory sweating* is characterized by profuse sweating in the face and forehead immediately following food intake.

This often becomes difficult to treat and socially embarrassing. Oral or topical *glycopyrrolate* may prove partially effective in some patients.

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Pupillary abnormalities

include **constricted pupils** with **sluggish light reaction**, which occurs in 20% of unselected diabetic patients. This results from early involvement of **sympathetic nerves** that dilate the iris and an imbalance between parasympathetic and sympathetic function.

A **blunted autonomic response to hypoglycemia** produces an inadequate sympathetic and adrenal response and hence an unawareness of hypoglycemia that may seriously complicate intensive insulin treatment

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Lumbosacral Radiculoplexopathy (Amyotrophy, Proximal Neuropathy).



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Diabetic amyotrophy, thoracolumbar radiculopathy, and proximal or diffuse lower extremity weakness should probably be grouped under the single term, diabetic **lumbosacral radiculoplexopathy**, since these disorders seem to be different presentations of the same basic involvement of multiple nerve roots or proximal nerve segments.

The onset is **unrelated to the duration of diabetes**, and the condition may develop in patients with longstanding NIDDM during periods of poor metabolic control and weight loss, but it can also occur in mild and wellcontrolled diabetics or be the presenting feature of diabetes.



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Typically, **unilateral severe pain** in the lower back, hip, and anterior thigh heralds the onset of neuropathy.

Within days to weeks **weakness** ensues, affecting **proximal** and, to a lesser extent, distal lower-extremity muscles (iliopsoas, gluteus, thigh adductor, quadriceps, hamstring, and anterior tibialis).

In some cases, the opposite leg becomes affected after a latency of days to months.

Reduction or absence of knee and ankle jerks is the rule. Numbness or paresthesias are minor complaints.

Weight loss occurs in more than half of patients

The progression may be steady or stepwise and may continue for many months.



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Often beginning as a **DSP**, this disorder comes to involve **proximal** segments of the PNS including multiple lumbosacral roots, thoracic posterior primary rami, and (less commonly) cervical myotomes.

The **trigeminal blink reflex** is often spared in advanced diabetic neuropathy and polyradiculoneuropathy, providing an important method to distinguish between this and immune-related polyradiculoneuropathies

Much less commonly encountered is diabetic **polyradiculopathy**, in which peripheral sensory nerve conduction studies are normal.

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The result is often a **debilitating, painful asymmetrical motor neuropathy with profound atrophy of proximal leg muscles.**

Pain usually recedes spontaneously long before motor strength begins to improve.

Recovery takes up to **24 months** because of the slow rate of axonal regeneration. In many cases, mild to moderate weakness persists indefinitely.

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Truncal Neuropathy

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Diabetic truncal neuropathy or thoracic radiculopathy involving the T4 through T12 spinal nerve roots causes pain or dysesthesias in areas of the chest or abdomen, thereby producing diagnostic confusion.

Bulging of the abdominal wall as a result of weakness of abdominal muscles may also occur

Patients describe burning, stabbing, boring, beltlike pain.

Contact with clothing can be very unpleasant.

The onset may be either abrupt or gradual and in some patients preceded or accompanied by a profound weight loss.

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The clinical picture can mimic **intra-abdominal**, **intrathoracic**, or **intraspinal** disease, or even **herpes zoster**, requiring careful differential diagnostic consideration.

Neurological findings are limited to hypoesthesia or hyperpathia over the thorax or abdomen.

The symptoms may persist for several months before gradual and spontaneous resolution within **4 to 6 months**.

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Limb Mononeuropathy

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two basic mechanisms:

nerve infarction or **entrapment**.

Mononeuropathy secondary to nerve **infarction** has a stereotyped presentation, with abrupt onset of pain followed by variable weakness and atrophy. recovery tends to be slow.

The **median, ulnar, and fibular** nerves are most commonly affected.

Mononeuropathies due to nerve entrapment are more common than nerve infarctions. These two conditions can usually be distinguished by clinical and electrophysiological features.

EDX studies demonstrate axonal loss in nerve infarction in contrast to focal conduction block or focal slowing often mixed with axonal loss in entrapment.



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Diabetes is found in 8% to 12% of patients presenting with CTS.

Electrophysiological abnormalities consistent with CTS without symptoms are found in one fourth of diabetic patients, whereas population-based studies have shown symptomatic CTS in 8% of diabetics.

The risk for CTS is more than twofold for patients with diabetes

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Multiple Mononeuropathies.

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As in mononeuropathy, the **onset is abrupt** in one nerve, and then other nerves are involved sequentially at irregular intervals.

Multiple mononeuropathies involving the **proximal** nerves are considered the cause of diabetic **amyotrophy**.

Because multiple mononeuropathies occur most frequently in **systemic vasculitis**, this possibility should always be considered in the differential diagnosis of diabetic multiple mononeuropathies.

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Cranial Mononeuropathies

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A **third nerve** palsy is the most commonly encountered diabetic cranial mononeuropathy.

Pupillary sparing, the hallmark of diabetic third-nerve palsy, results from ischemic infarction of the centrifascicular oculomotor axons due to diabetic vasculopathy of the vasa nervorum.

With decreasing frequency, **the fourth**, **sixth**, and **seventh** nerves are also affected. Patients with **Bell palsy** have a significantly higher frequency of diabetes than an age-matched population. Most make a full recovery in 3 to 5 months.

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Two serious infectious syndromes occur occasionally in patients with diabetes mellitus and characteristically affect one or more cranial nerves by local inflammation. **Rhinocerebral mucormycosis** and “**malignant**” **external otitis** were often fatal before the advent of early diagnosis and effective treatment strategies



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Treatment



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The cornerstone in the treatment of diabetes and its complications remains **optimal glucose control**.

Symptomatic treatment for pain, autonomic manifestations, and the complications of sensory loss can be offered to mitigate the impact of neuropathic symptoms.

It should be remembered that about **20%** of patients with chronic painful diabetic neuropathy of over 6 months' duration demonstrate a complete remission of symptoms over time

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Patients with symptomatic orthostatic hypotension are advised to sleep with the head of the bed **elevated 6 to 10 inches**.

Practical suggestions include drinking **two cups of strong coffee or tea with meals**, eating **more frequent small meals** rather than a few large ones, and increasing the daily **fluid** intake (>20 oz/day) and **salt ingestion** (10–20 g/day).

Elastic body stockings may be beneficial by reducing the venous capacitance in bed but are poorly tolerated by many patients.

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Plasma volume expansion can be achieved by **fludrocortisone (0.1–0.6 mg/day)**. **NSAIDs**, which inhibit prostaglandin synthesis, represent the next class of drugs to be considered; ibuprofen, 400 mg 4 times a day, is better tolerated than indomethacin.

Phenylpropanolamine (25–50 mg 3 times a day), a direct-acting α -agonist, was once used to manage orthostatic hypotension.

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Midodrine, an α 1-adrenergic agonist that causes vasoconstriction, is also effective.

Similarly, subcutaneous recombinant human **erythropoietin** has proved effective in some patients with orthostatic hypotension and anemia.

Octreotide may improve orthostatic blood pressure by inducing splanchnic vasoconstriction.

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Delayed gastric emptying is often relieved with **metoclopramide**; therefore, as it is a dopamine antagonist, extrapyramidal symptoms may occur at higher doses.

Diabetic diarrhea may be treated with short courses of **tetracycline** or **erythromycin** if appropriate. In some cases, **clonidine** has been reported to reduce the troublesome diarrhea.



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Genitourinary complications of diabetic autonomic neuropathy require close collaboration with a urologist. Patients with a neurogenic bladder should be encouraged to adhere to a **frequent voiding** schedule during the day, which helps diminish the amount of residual urine. For more severe involvement, **manual abdominal compression** or **intermittent self-catheterization** may be needed.

Treatment of erectile impotence should be directed by a urologist, who can counsel the patient regarding the options of either oral treatment with **sildenafil** or similar drugs, direct **injections into the corpora cavernosa**, or penile **implants**.

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Proper skin care in diabetics with cutaneous sensory loss, impaired sweating, and vascular disease is extremely important to prevent foot ulcers.



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PAIN CONTROL

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Antidepressants

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Tricyclic drugs

In a placebo-controlled, double-blind, randomized cross-over trial, [amitriptyline](#) and [desipramine](#) were equally effective and superior to [fluoxetine](#) or placebo.

The benefit of the tricyclic drugs was noted **within two weeks** and continued to increase at **six weeks**.

[Amitriptyline](#) and [nortriptyline](#) are both **contraindicated in patients with cardiac disease**. In these patients, we consult with the patient's cardiologist and give either [doxepin](#), the least cardiotoxic tricyclic antidepressant, or antidepressant drugs unrelated to the tricyclic family such [duloxetine](#) or [venlafaxine](#)



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TABLE 54.3 Tricyclic Antidepressants Commonly Used for Pain Management

Generic name	Trade name	Adult dosage range (mg/day)
Amitriptyline	Elavil	10–100
Clomipramine	Anafranil	25–200
Desipramine	Norpramin	10–200
Doxepin	Sinequan	10–200
Imipramine	Tofranil	10–200
Nortriptyline	Pamelor	10–150

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Duloxetine

The most common reported side effects of duloxetine were **nausea**, somnolence, dizziness, decreased appetite, and constipation. Hot flashes and erectile dysfunction were also reported infrequently.

Because nausea is common, patients are encouraged to take the drug on a **full stomach**. Duloxetine should **not be taken with other serotonin or norepinephrine uptake inhibitors** but can be combined with anticonvulsant therapy.

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Venlafaxine

Dosages evaluated varied considerably based on etiology of chronic pain, but efficacy has been shown for many conditions in the range of **75-225 mg/day**; onset of relief may occur in 1-2 weeks, or take up to 6 weeks for full benefit

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Anticonvulsants

- Compared with placebo, [pregabalin](#) treatment at total daily doses of 150, 300, and 600 mg resulted in a statistically significant reduction in the mean pain score, the primary end point of all included studies.
- The median time to a sustained one point improvement in pain score for pregabalin (at 150 mg, 300 mg, and 600 mg) and placebo was 13, 5, 4, and 60 days, respectively.

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Capsaicin cream

Anesthetic drugs

Alpha-lipoic acid



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