Diabetic Neuropathy

N.Beladi Moghadam.MD

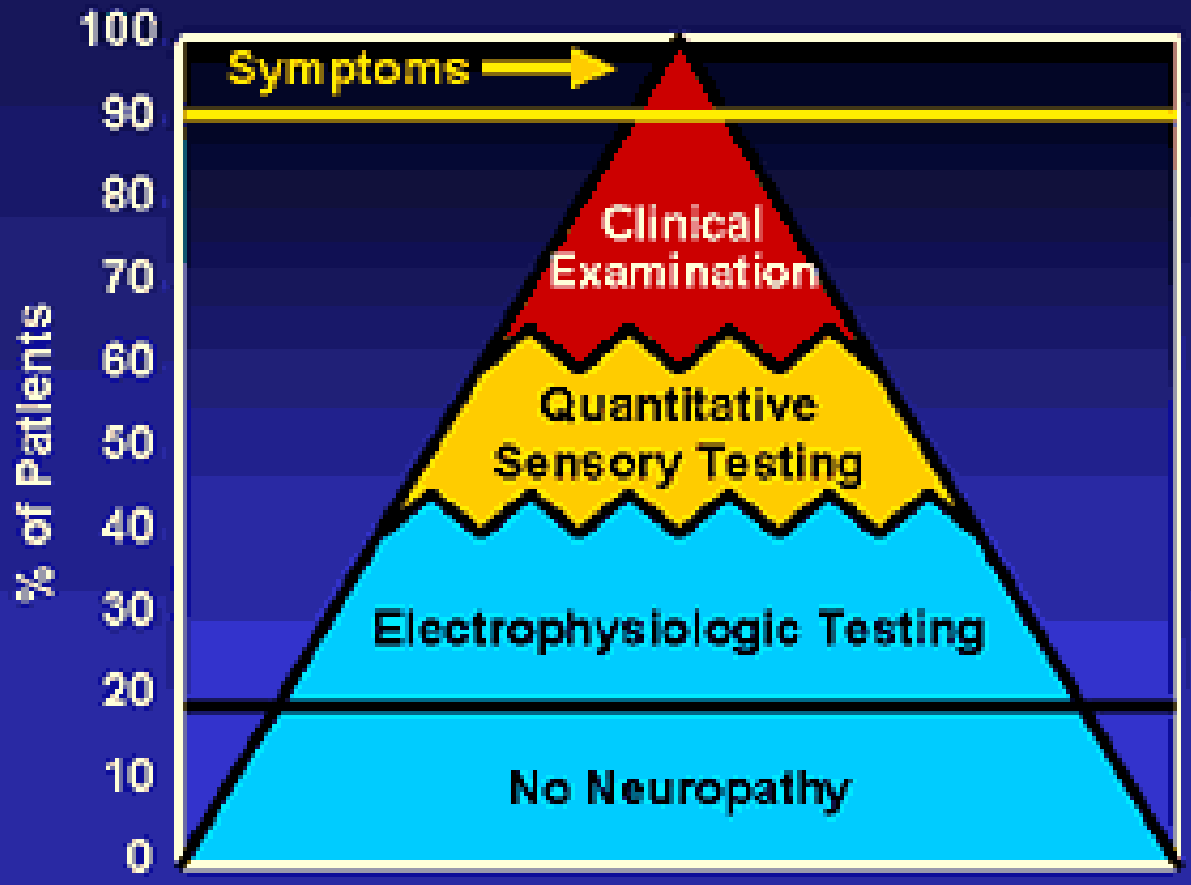
Shahid Beheshti University of Medical Science

Diabetes Care 2017

- Up to 50% of diabetic peripheral neuropathies may be asymptomatic.

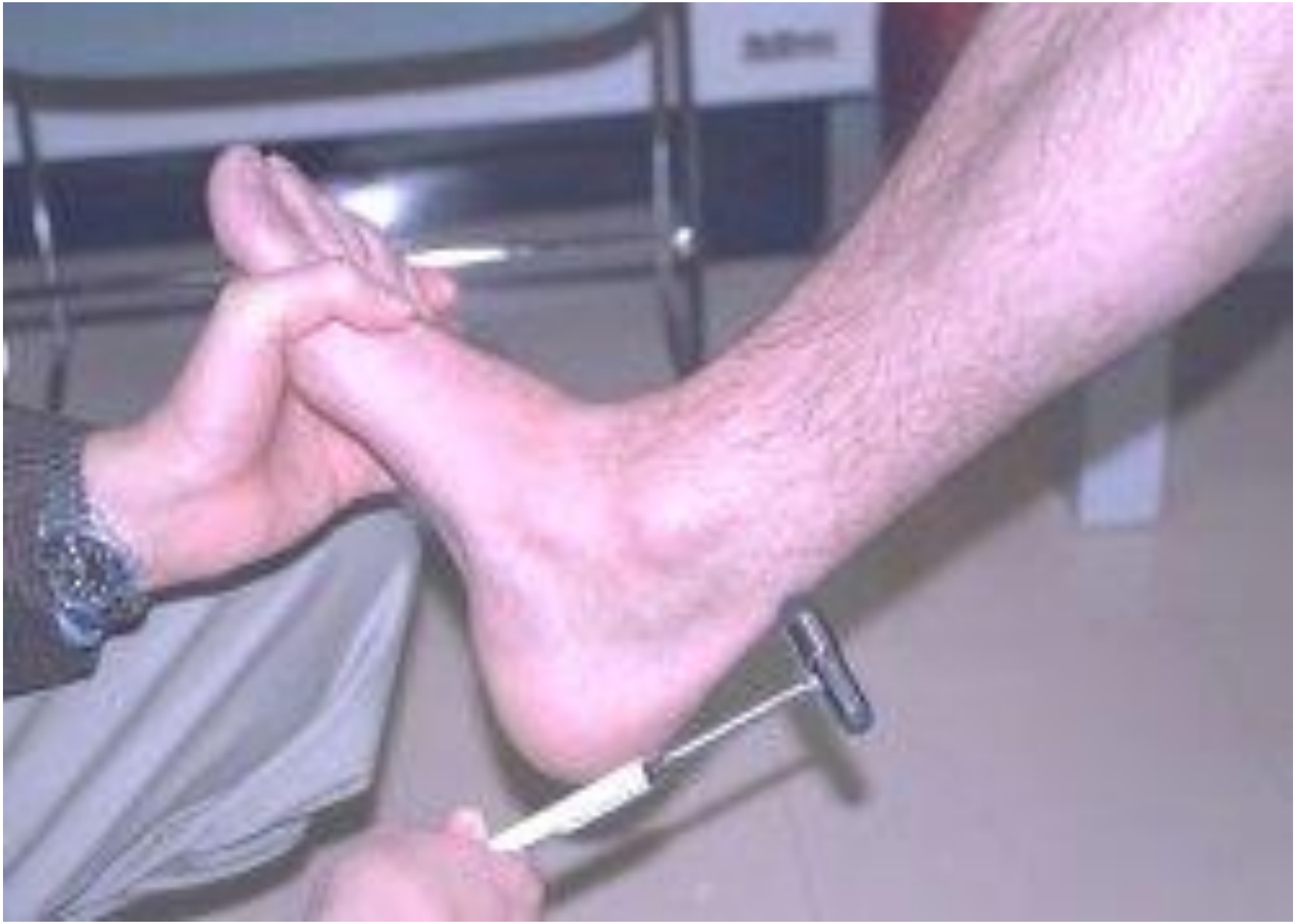
- If not recognized and if preventive foot care is not implemented, patients are at risk for injuries to their insensate feet.

The Extent of Diabetic Neuropathy



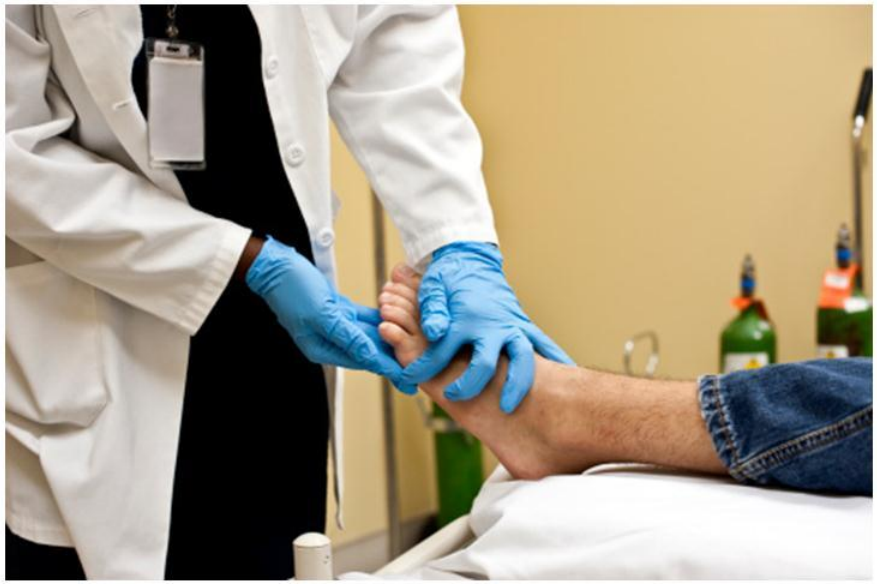
Semiology of neuropathyies

- **1-Motor symptoms & signs:**
- Weakness:distal muscles
- (occasionally: proximal+distal,such as GBS,Diabet,CIDP,…) – May be accompanied with cranial neuropathies so related cranial muscles weakness is added.
- Atrophy+decreased or absent reflexes
- **2-Sensory symptoms & signs:**
  Paresthesia+Numbness+Dysesthesia+Burning pain
- Stocking & gloves pattern sensory impairment
- Proprioceptive & vibration impairment (-Romberg sign)



“Take Off Your Shoes”

- The healthcare provider should examine feet at each office visit.
- Tell the patient to take off his or her shoes and socks when they are in the exam room.

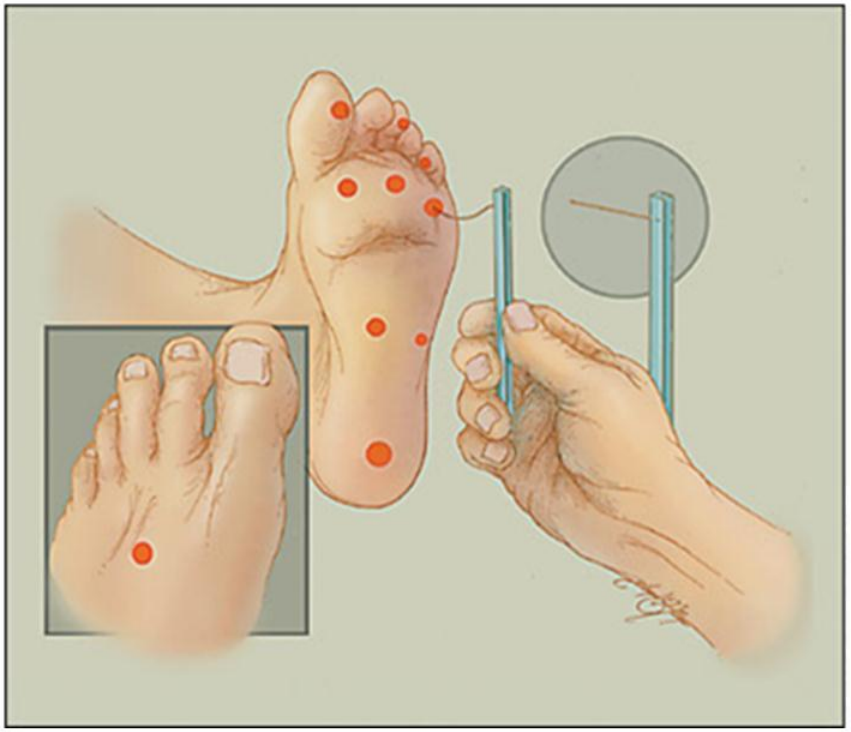


Atrophy of Leg Muscles

- Motor weakness occurs late in the clinical course.
- Atrophy of foot muscles can result in toe abnormalities (clawing, hammering).

Anderson H, et al.[7]

Diagnostic Tools for DPN: Large-fiber



5.07 Semmes-Weinstein Monofilament

Calibrated Tuning Fork

Boulton AJ, et al.[4]

Table 2—Symptoms and signs of DSPN

	Large myelinated nerve fibers	Small myelinated nerve fibers
Function	Pressure, balance	Nociception, protective sensation
Symptoms§	Numbness, tingling, poor balance	Pain: burning, electric shocks, stabbing
Examination (clinically diagnostic)**	Ankle reflexes: reduced/absent Vibration perception: reduced/absent 10-g monofilament: reduced/absent Proprioception: reduced/absent	Thermal (cold/hot) discrimination: reduced/absent** Pinprick sensation: reduced/absent**

§To document the presence of symptoms for diagnosis; **Documented in symmetrical, distal to proximal pattern.

Standards of Care: Comprehensive Annual Foot Examination

- Inspection
- Palpation of dorsalis pedis and posterior tibial pulses
- Evaluate for presence/absence of patellar and Achilles reflexes
- Determine proprioception, vibration, and monofilament sensation

ADA.[1]

Classification of neuropathies:

- **1-By duration**: Acute-subacute-chronic
- **2-By type of involved nerves** :sensory-motor-sensorymotor
- **3-By pathology**:Axonal-Demyelinatig-Mixed axonal & Demyelinatig.
- **4-Cranial or Peripheral nerves involvement or both**
- **5-By distribution of involvement** :
- Mononeuropathy such as CTS
- Asymmetric involvement of 2 or more nerves : Mononeurit multiplex
- Symmetric involvement of peripheral nerves in 4 limbs: Polyneuropathy
- **Diabetic neuropathy could be presented in all above forms**

A useful **classification** divides the diabetic neuropathies into

symmetrical polyneuropathies

versus

focal or multifocal neuropathies

However, there is significant overlap between these syndromes.

Classification of Diabetic Neuropathies

SYMMETRICAL POLYNEUROPATHIES

Distal sensory or sensorimotor polyneuropathy

Small-fiber neuropathy

Autonom ic neuropathy

Large-fiber neurop athy

ASYMMETRICAL NEUROPATHIES

Cranial neuropathy (single or multiple)

Truncal neuropathy (thoracic radiculopathy)

Limb mononeuropathy (single or multiple)

Lumbosacral radiculoplexopathy (asymmetrical proximal motor neuropathy)

Entrapment neuropathy

COMBINATIONS

Polyradiculoneuropathy

Diabetic neuropathic cachexia

Symmetrical polyneuropathies

Classification for diabetic neuropathies

- **A. Diffuse neuropathy**
- **DSPN**
- Primarily small-fiber neuropathy
- Primarily large-fiber neuropathy
- Mixed small- and large-fiber neuropathy (most common)
- **Autonomic**
- Cardiovascular
- Reduced HRV
- Resting tachycardia Orthostatic hypotension
- Sudden death (malignant arrhythmia)
- **Gastrointestinal**
- Diabetic gastroparesis (gastropathy)
- Diabetic enteropathy (diarrhea)
- Colonic hypomotility (constipation)
- **Urogenital**
- Diabetic cystopathy (neurogenic bladder)
- Erectile dysfunction
- Female sexual dysfunction
- **Sudomotor dysfunction**
- Distal hypohydrosis/anhidrosis,
- Gustatory sweating
- Hypoglycemia unawareness
- Abnormal pupillary function

Classification for diabetic neuropathies

- **B. Mononeuropathy (mononeuritis multiplex) (atypical forms)**
- Isolated cranial or peripheral nerve (e.g., CN III, ulnar, median, femoral, peroneal)
- Mononeuritis multiplex (if confluent may resemble polyneuropathy)
- **C. Radiculopathy or polyradiculopathy (atypical forms)**
- Radiculoplexus neuropathy (lumbosacral polyradiculopathy, proximal motor
- amyotrophy)
- Thoracic radiculopathy
- **Nondiabetic neuropathies common in diabetes**
- Pressure palsies
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Radiculoplexus neuropathy
- Acute painful small-fiber neuropathies (treatment-induced)

Large-fiber involvement is often **asymptomatic.**

In advanced cases, significant ataxia

Symptoms and Signs of DPN

Symptoms (Small-fiber)	Signs (Large-fiber)
Numbness or loss of feeling (asleep or "bunched-up sock under toes" sensation)	Diminished vibratory perception
Prickling/tingling	Decreased knee and ankle reflexes
Aching pain	Reduced protective sensation, such as pressure, hot and cold, pain
Burning pain	Diminished ability to sense position of toes and feet
Lancinating pain	Pain is deep, aching, or cramping
Allodynia	
Defective thermal sensation	
Decreased sweating	

Boulton AJ, et al.[3]

Diabetic neuropathy is **defined** as :

The presence of symptoms and signs of peripheral or cranial nerve dysfunction in individuals with diabetes *after the exclusion of other causes*.

Table 3—Differential diagnosis of diabetic neuropathies

- Metabolic disease
  - Thyroid disease (common)
  - Renal disease
- Systemic disease
  - Systemic vasculitis
  - Nonsystemic vasculitis
  - Paraproteinemia (common)
  - Amyloidosis
- Infectious
  - HIV
  - Hepatitis B
  - Lyme
- Inflammatory
  - Chronic inflammatory demyelinating polyradiculoneuropathy
- Nutritional
  - B_{12}*
  - Postgastroplasty
  - Pyridoxine
  - Thiamine
  - Tocopherol
- Industrial agents, drugs, and metals
  - Industrial agents
    - Acrylamide
    - Organophosphorous agents
  - Drugs
    - Alcohol
    - Amiodarone
    - Colchicine
    - Dapsone
    - Vinka alkaloids
    - Platinum
    - Taxol
  - Metals
    - Arsenic
    - Mercury
- Hereditary
  - Hereditary motor, sensory, and autonomic neuropathies

*B_{12} deficiency is more commonly associated with malabsorption rather than nutritional deficiency.

Neuropathy : To confirm and approach

Symptoms & signs

Lab Tests :

EMG – NCS :

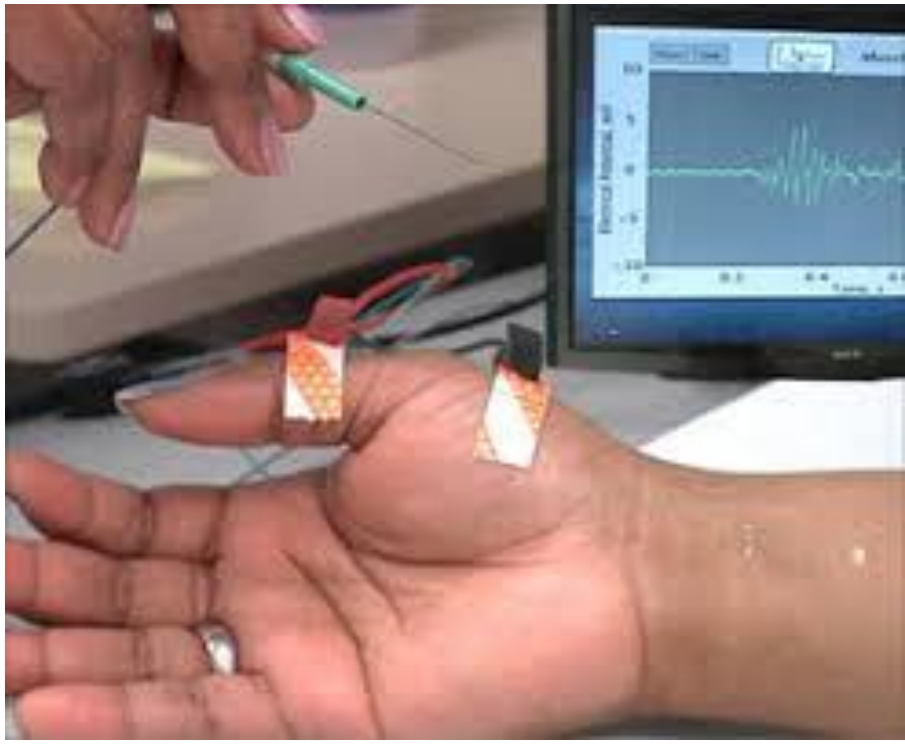
(Distal latency-CMAP Amplitude-NCV)

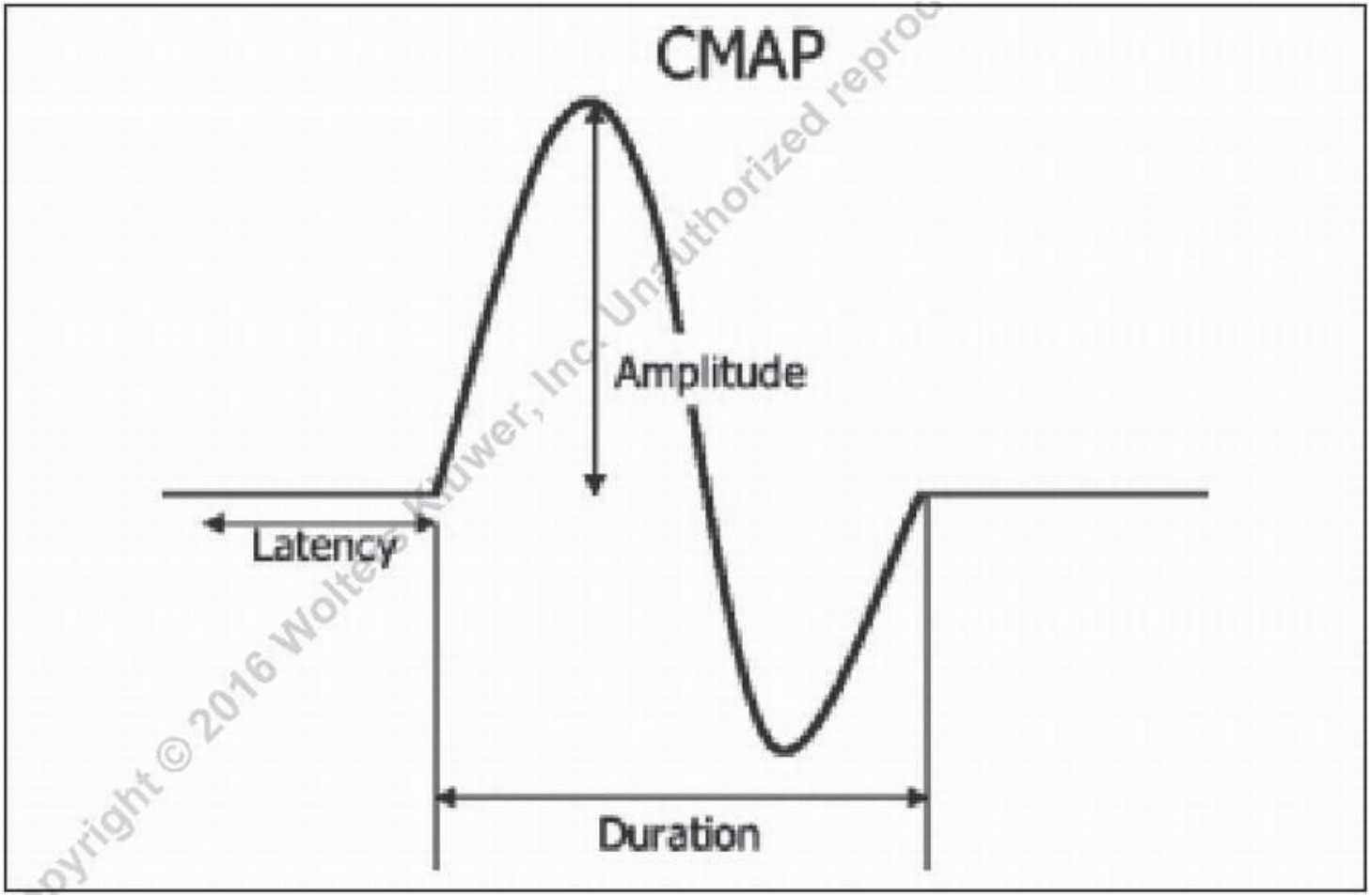
CSF Study

Nerve Biopsy may be needed

Nerve Conduction Study

Electromyograghy





May coincide with

CIDP,

Vitamin Bl2 deficiency,

Alcoholic neuropathy,

Endocrine neuropathies.

Additional causes of polyneuropathy may be present in 10% and up to 55% of patients with diabetes mellitus .

May predispose to earlier development and more severe symptoms of neuropathy, presumably by inducing vasoconstriction and nerve ischemia.

Longer duration of diabetes

Male gender

Consume excessive amounts of alcohol.

Tobacco use

Height

Age

Poor glycemic control

.

Several recent studies have shown that 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.

These studies suggest that an axonal neuropathy may be the ***presenting*** or the earliest manifestation in diabetes.

Treatment-induced neuropathy

Burning pain and paresthesias develop in the distal lower extremities after the establishment of glucose control.

Pain persists for weeks or up to several months with spontaneous resolution.

Distal Symmetrical Polyneuropathy

Sensory deficits predominate, and autonomic symptoms usually correlate with the severity of the neuropathy.

Most patients will develop only a **minor motor involvement** affecting the distal muscles of the lower extremities.

Sensory disturbances have a **stocking-glove distribution following a length-dependent pattern.**

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

- DSPN is the most important cause of **foot ulceration,** and it is also a prerequisite in the development of **Charcot neuroarthropathy** .

- These late complications drive amputation risk and economic costs of diabetic neuropathy and are also predictors of mortality.

- DSPN is also a major contributor to **falls and fractures .**

Asymmetrical Proximal Diabetic Neuropathy or Lumbosacral Radiculoplexopathy (diabetic amyotrophy)

Clinically, asymmetrical weakness and wasting of pelvifemoral muscles may occur either **abruptly** or in a **stepwise** progression in individuals with diabetes who are older than 50 years.

Most patients have type 2, but the onset is unrelated to the duration of diabetes .

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 .

Recovery takes up to 24 months ,

Recommendations

- All patients should be assessed for distal symmetric polyneuropathy starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter. **B**
- Consider screening patients with prediabetes who have symptoms of peripheral neuropathy. **B**
- Assessment should include a careful history and either temperature or pinprick sensation (small-fiber function) and vibration sensation using a 128-Hz tuning fork (large-fiber function). All patients should have an annual 10-g monofilament testing to assess for feet at risk for ulceration and amputation. **B**
- Electrophysiological testing or referral to a neurologist is rarely needed for screening, except in situations where the clinical features are atypical, the diagnosis is unclear, or a different etiology is suspected. Atypical features include motor greater than sensory neuropathy, rapid onset, or asymmetrical presentation. **B**

Pathogenesis of Diabetic Neuropathy

Currently accepted hypotheses focus on the possibilities of metabolic and ischemic factors and their interactions in causing nerve injury .

Hyperglycemia increase endoneurial vascular resistance and reduce nerve blood flow.

Hyperglycemia also causes depletion of nerve myoinositol.

Persistant hyperglycemia enhances the polyol pathway in nerve tissue through the enzyme aldose reductase, which leads to the accumulation of sorbitol and fructose in nerve and enhancement of nonenzymatic glycosylation of structural nerve proteins.

Pathology

Cranial and limb mononeuropathy

and multiple mononeuropathies are thought to be caused by small-vessel occlusive disese.

In multiple lumbar roots, plexus, or proximal nerve segments: Whether ischemic or inflammatory lesions?

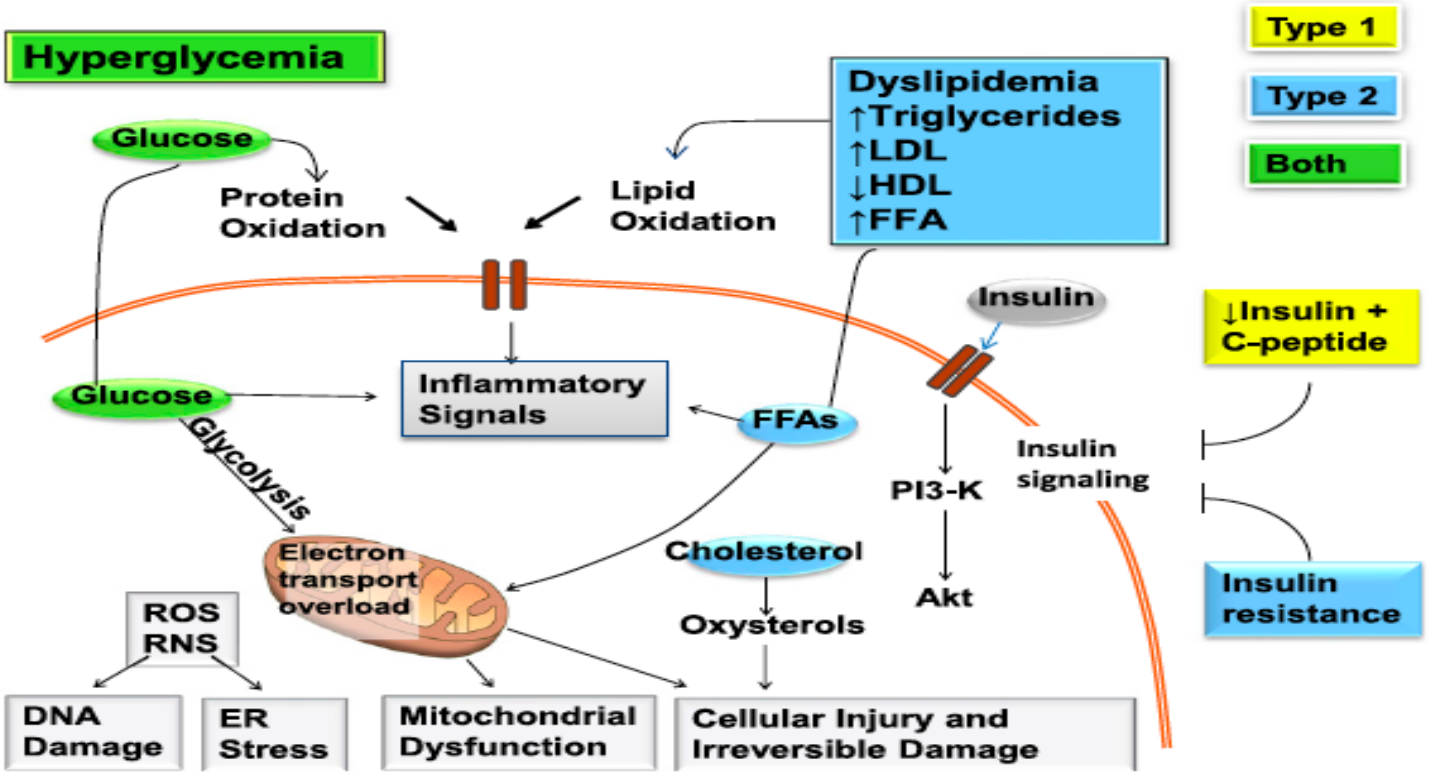


Figure 1—Mechanisms of diabetic neuropathy. Factors linked to type 1 diabetes (yellow), type 2 diabetes (blue), and both (green) cause DNA damage, endoplasmic reticulum stress, mitochondrial dysfunction, cellular injury, and irreversible damage. The relative importance of the pathways in this network will vary with cell type, disease profile, and time. ER, endoplasmic reticulum; FFA, free fatty acids; PI3-K, phosphatidylinositol-3 kinase; RNS, reactive nitrogen species; ROS, reactive oxygen species. Adapted and reprinted from Callaghan et al. (20), with permission from Elsevier.

Asymmetric Leg Weakness and Diabetes

- A 56-year-old diabetic woman developed gait difficulty over a 7-month period.
- She had pain & had occasional hand numbness. There was a medical history of hypertension.
- **PHYSICAL EXAMINATION**. Cranial nerves and cerebellar and sensory function were normal.
- There was isolated weakness and atrophy of the left quadriceps. **DTRs were active and symmetric, except** for absence of the left knee jerk and ankle jerks. Plantar responses were normal.

- **1-Where is the lesion?**
- UMN?-LMN?(Ant horn cell?-Radiculopathy?-Plexopathy?-Neuropathy?)-NMJ ?-Myopathy?)
- **2. What are the neurological complications of diabetes?**
- **3-Comment on the syndrome of diabetic amyotrophy.**

- **Plan**
- Screen for polyneuropathy.
- Delineate the pattern of abnormality.

Electrodiagnostic Examination:EMG-NCS

- **NCS**:

Motor Conduction :

- **Tibial :**No response-**peroneal:**NCV: slow-**Femoral**:No response

Sensory Nerve Action: Median: Low amplitude SNAPS-

absent SNAPS in lower limbs-

- **EMG(Electromyography)**:The EMG reveals disproportionate denervation in the Left quadriceps-and also neurogenic in paravertebral,Ant.Tibialis –Gastrocnemious-Adductors-bilateral asymmetrically .
- **1-Does patient have a polyneuropathy?**
- **2. Patient was referred with a diagnosis of femoral neuropathy.**
- **Any Comment ?.**

- **Electrodiagnostic Interpretation**
- **Left $L_{2,3,4}$ radiculopathy**. This is superimposed on a **sensorimotor axonal polyneuropathy in a mononeuritis multiplex pattern.**

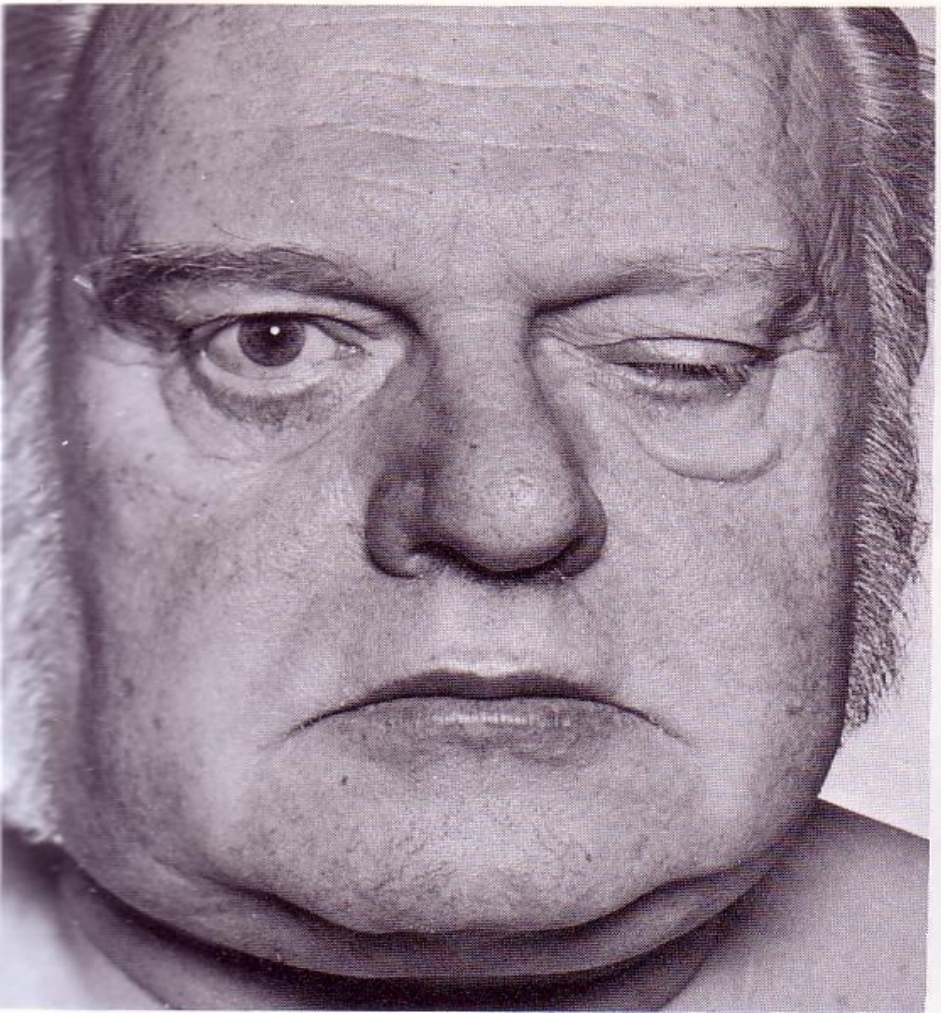
- **For 6 years, a 73-year-old woman experienced low back pain radiating into her right leg.**
- **She denied numbness, weakness, and bladder problems. Symptoms were not increased by Valsalva's maneuver. Medical history included** diabetes mellitus, hypertension, and removal of a benign colon tumor 4 years ago.
- **PHYSICAL EXAMINATION.** Cranial nerves and cerebellar function were normal. **No weakness or sensory deficit was found. DTRs were absent and Plantar responses flexor. There was no Lasegue's sign**

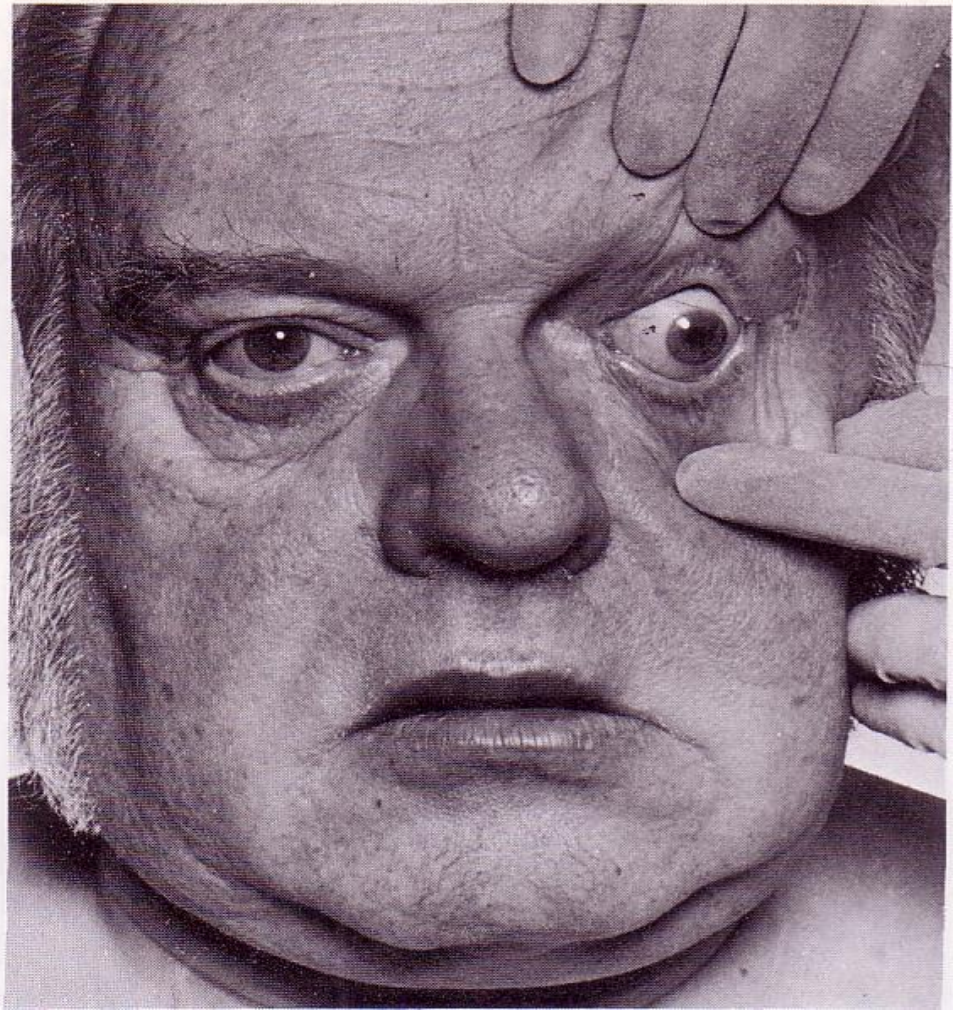
- **1. What do the patient's symptoms suggest?**
- The symptoms of low back pain with radiation to a leg are suggestive of lumbosacral radiculopathy.
- There was no supportive clinical evidence, such as Lasegue's sign, sensory deficit, or motor deficit, but this is often the case.
- **2. In view of the diabetes mellitus, what else has to be considered?**
- Diabetes can affect the peripheral nervous system in many patterns, including **(1) focal**, or multiple nerve lesions (mononeuritis multiplex) possibly on a vascular basis
- **; (2) diffuse symmetrical polyneuropathy** suggesting a metabolic process; or
- **(3) lesions of the proximal neuraxis (radiculopathy, or polyradiculopathy**). The last occurs in varying patterns depending on the roots involved (diabetic amyotrophy, thoracoabdominal neuropathy, truncal mono-neuropathy).
- **In this case, the global absence of DTRs (although of lesser significance with advancing age) can alert the examiner to a diffuse problem.**

Plan:Look for right-sided lumbosacral radiculopathy. (Screen for more diffuse problems

- **Motor NCS**: **Rt Tibial & Peroneal**:Low amplitude CMAPs-NCV slowing-and the same on **Left side**
- **Sensory NCS:Absent SNAPs in 4 limbs**
- **EMG:Neurogenic pattern in all paravertebral and lower limbs muscles**
- **Electrodiagnostic Interpretation :diffuse polyradiculoneuropathy**
- **1-Why were other limbs & lumbar paraspinal muscles sampled? 2-Are there any clues to suggest this diffuse pled?**
- **With what conditions is this diffuse pattern associated?** The polyradiculopathy pattern of diffuse paraspinal abnormalities is not specific to diabetes mellitus.
- /Other conditions noted in the literature associated with diffuse paravertebral muscle abnormalities include leptomeningeal carcinomatosis (metastatic cancer, leukemia), AIDS, Lyme disease, sarcoidosis, and eosinophilia-myalgia syndrome

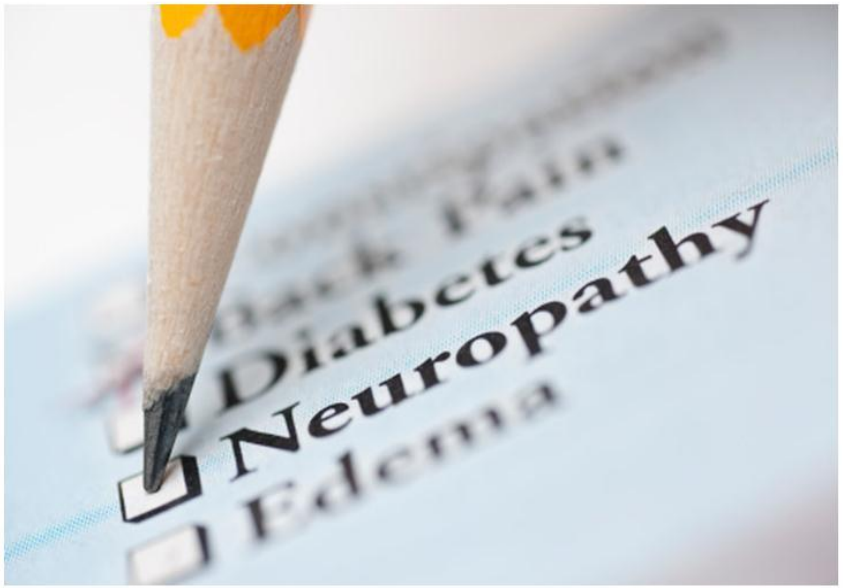
A 70 years old man with diabetes and acute left side ptosis + diplopia





Goals of Treatment

- Decrease pain
- Provide symptom relief, ultimately, to prevent ulceration
- Prescribe medications when necessary, focusing on efficacy and a minimization of side effects



ADA.[1]

Recommendations

- Tight glucose control targeting near-normal glycemia in patients with type 1 diabetes dramatically reduces the incidence of distal symmetric polyneuropathy and is recommended for distal symmetric polyneuropathy prevention in type 1 diabetes. **A**
- In patients with type 2 diabetes with more advanced disease and multiple risk factors and comorbidities, intensive glucose control alone is modestly effective in preventing distal symmetric polyneuropathy and patient-centered goals should be targeted. **B**
- Lifestyle interventions are recommended for distal symmetric polyneuropathy prevention in patients with prediabetes/metabolic syndrome and type 2 diabetes. **B**

Approved Medications

Pregabalin and duloxetine have received regulatory approval for the treatment of neuropathic pain in diabetes in the U.S., Europe, and Canada.

- Gabapentin may also be used as an effective initial approach, taking into account patients' socioeconomic status, comorbidities, and potential drug interactions. **B**
- Although not approved by the U.S. Food and Drug Administration, tricyclic antidepressants are also effective for neuropathic pain in diabetes but should be used with caution given the higher risk of serious side effects. **B**
- Given the high risks of addiction and other complications, the use of opioids, including tapentadol or tramadol, is not recommended as first- or second-line agents for treating the pain associated with DSPN. **E**

Anticonvulsant

- **Gabapentin (Neurontin)** has been reported to work excellently in the treatment of dysesthetic pain.
- **Carbamazepine (Tegretol)** has been used mainly for partial seizures and can be used in peripheral neuropathy as a **third-line** agent if all other agents fail to reduce or improve symptoms of diabetic neuropathy.
- **Pregabalin (Lyrica**) is approved for the treatment of pain due to generalized diabetic peripheral neuropathy and may be considered as a **first-line agent** in diabetic peripheral neuropathic pain.

Antidepressants

- **Tricyclic**
- For paresthetic pain, tricyclic antidepressants such as imipramine (Tofranil), nortriptyline (Pamelor, Aventyl), and amitriptyline (Elavil) have been shown to be useful as analgesics for paresthetic pain,
- **Selective Serotonin/norepinephrine Reuptake Inhibitor (ssnri)**
- Duloxetine (Cymbalta) was the first medication to be approved specifically for the treatment of diabetic neuropathy. Venlafaxine (Effexor) has been recommended by the AAN/AANEM/AAPMR guidelines for consideration in diabetic neuropathy pain management.
- **Serotonin Reuptake Inhibitor**
- Paroxetine-- Citalopram
- **Tetracyclic**
- Desipramine

Diabetic Neuropathic Pain Management

- **Topical therapy** with **capsaicin** or **transdermal lidocaine** may be useful in some patients, **especially those with more localized pain or those in whom interactions with existing oral medications is a concern**.

Challenges With Current Treatments

Treatment	Side Effect
Pregabalin	Weight gain
Duloxetine	Nausea and vomiting Worsen glycemic control
Tricyclic antidepressants*	Weight gain Blood pressure
Opioids*	Gastroparesis

*FDA-approved therapies that deviate from FDA recommendations.
Boulton AJ, et al.[3]

Homocysteine

- Metformin contributes to the severity of DPN by inhibiting absorption of B12[a]
- Link between high homocysteine levels and cardiovascular disease[b]
- Folates and other B vitamins have homocysteine-lowering effects[b]
- Deficiency in folates and B vitamins increase homocysteine levels[b]
- Methylmalonic acid test

a. Wile DJ, et al.[12]
b. Perna AF, et al.[13]

Metanx®

- L-methylfolate: 3 mg
- Methylcobalamin: 2 mg
- Pyridoxal 5'-phosphate: 35 mg

Fonseca VA, et al. [15]

Symptomatic treatment for autonomic manifestations

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

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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 0z/day) and **salt ingestion** (10 to 20 g/day). **Elastic body stockings** may be beneficial by reducing the venous capacitance in bed but are poorly tolerated by many patients. Plasma volume expansion can be achieved by **fludrocortisone** (0.1 to 0.6 mg/day)

Treatment of Autonomic Dysfunction

Erectile dysfunction from diabetic neuropathy is a very difficult condition to treat. All other causes of impotence must be excluded. Once the diagnosis has been confirmed, the oral agent **sildenafil Viagra) and related phosphodiesterase type 5 (PDE5) inhibitors** can be used (if not contraindicated in the patient). Older methods such as **vacuum devices or intracavernosal papaverine** injections may be tried. Referral to a urologist is suggested.

Gustatory sweating: **Glycopyrrolate** is an antimuscarinic compound that can be used for the treatment for diabetic gustatory sweating. When applied topically to the affected area, it results in a marked reduction in sweating while eating a meal

Diabetic Gastroparesis

- **Erythromycin, cisapride, and metoclopramide** are used to treat diabetic gastroparesis. Additionally, MiraLax (**polyethylene glycol**) is gaining increasing popularity as the first-line agent for severe constipation and lower motor unit bowel.
- A newer agent, **tegaserod** (Zelnorm), may be helpful in patients with chronic ileus. In early 2010, however, tegaserod marketing was suspended because of a meta-analysis showing an excess number of serious cardiovascular adverse events, including angina, myocardial infarction, and stroke, in those taking tegaserod compared with placebo. Tegaserod is currently available only on an emergency basis

Surgical Treatment

- **Charcot foot** can be treated with bracing or special boots. In some cases, surgery is used to correct the deformity.
- **Pancreatic Surgery** is indicated in patients with infected foot ulcers when the infection cannot be controlled medically. Aggressive debridement or amputation may be necessary if signs of necrosis or infection do not improve with IV antibiotics
- **Jejunostomy** may be performed in patients with intractable gastroparesis (ie, severe nausea and vomiting, severe weight loss). This will allow patients to be fed enterally, bypassing the paralytic stomach.
- When impotence is a continual problem, the patient may pursue the option of a **penile prosthesis**.
- Pancreatic transplantation in patients with diabetes and end-stage renal disease can stabilize neuropathy and in some instances improve motor, sensory, and autonomic function for as long as 48 months after uremia plateaus

Experimental Therapies

- **Aldose reductase inhibitors**(eg, alrestatin, sorbinil, tolrestat, epralrestat) Aldose reductase inhibitors block the rate-limiting enzyme in the polyol pathway that is activated in hyperglycemic states.
- Epralrestat is currently marketed only in Japan. Epalrestat reduces intracellular sorbitol accumulation, which has been implicated in the pathogenesis of late-onset complications of diabetes mellitus. Epalrestat 150 mg/day for 12 weeks improved motor and sensory nerve conduction velocity and vibration threshold compared with baseline and placebo in patients with diabetic neuropathy. Subjective symptoms, including pain, numbness, hyperesthesia, coldness in the extremities, muscular weakness, dizziness, and orthostatic fainting, were also improved
- **Alpha-lipoic acid**
- **Actovegin**
- **Spinal cord stimulators and other therapies**

Dietary Supplements

- Vitamin supplementation is being studied to see if that can have an impact.
- One study of zinc sulfide showed improvement in glycemic control in 60 patients.
- Certain B vitamins are often prescribed in an attempt to reduce paresthesias

Pain Control in Pregnancy

- At the end of the third trimester, the physician can prescribe **amitriptyline, gabapentin,** and other medications as indicated if the benefit clearly outweighs the risk to the fetus.

Intravenous methylprednisolone therapy for patients with diabetic lumbo sacral radiculoplexopathy showed no beneficial effect in the weakness and atrophy but some lessening of pain and positive neuropathic symptoms.

Use of **high-dose intra venous immunoglobulin or methylprednisolone** has been reported to benefit patients with progressive deficits and biopsy evidence of inflammation in uncontrolled studies.