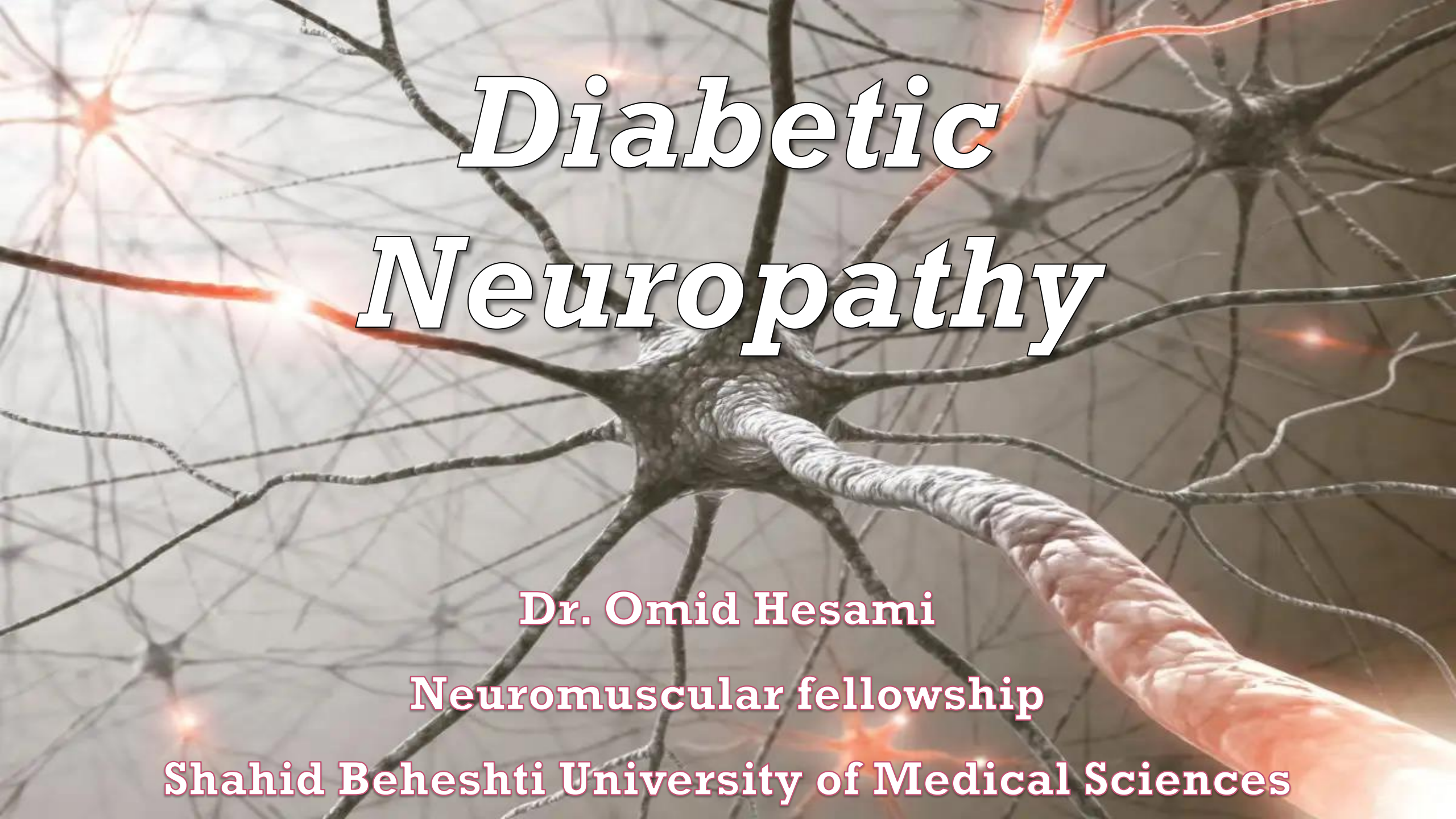

Diabetic Neuropathy

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Neuromuscular fellowship

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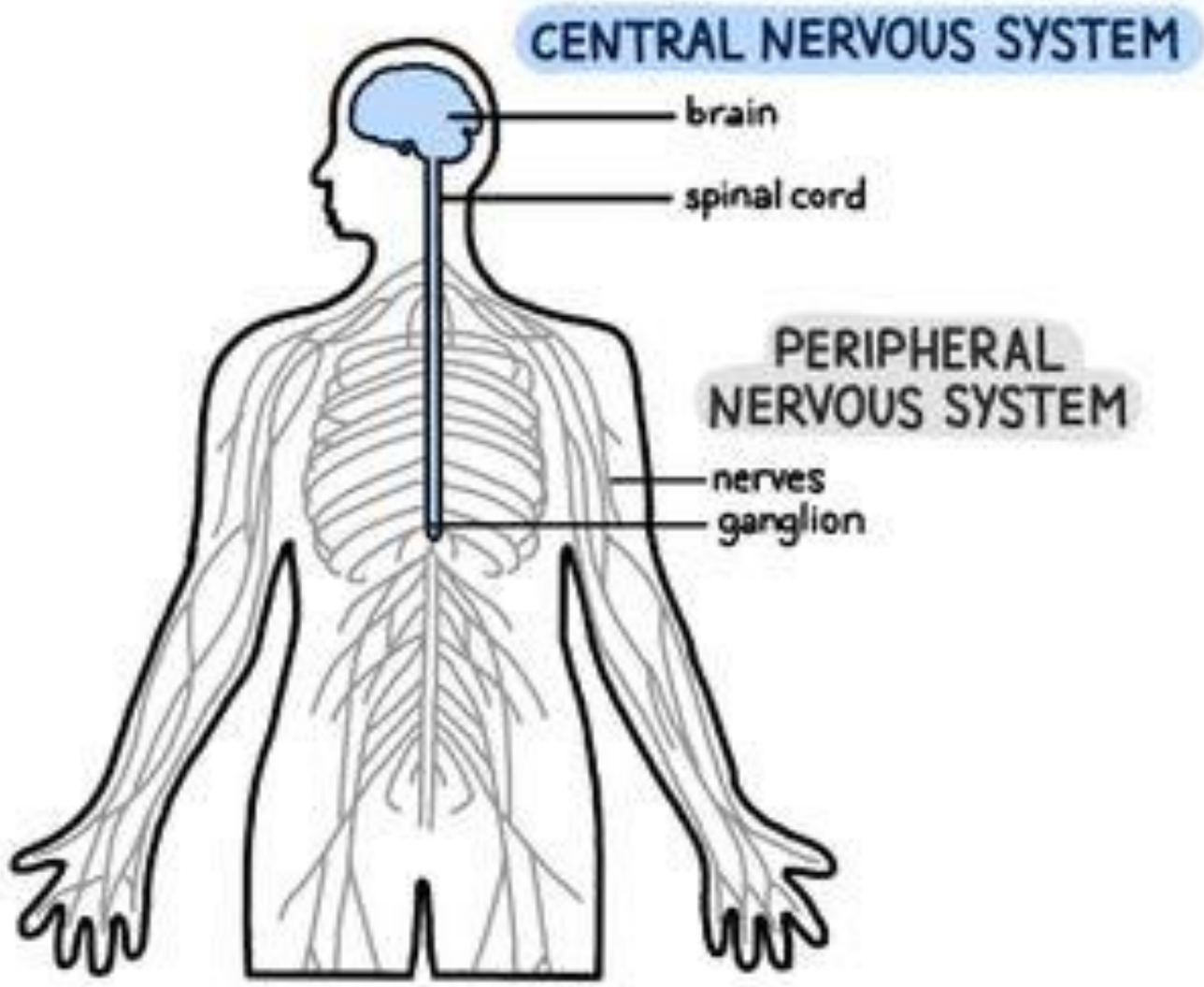
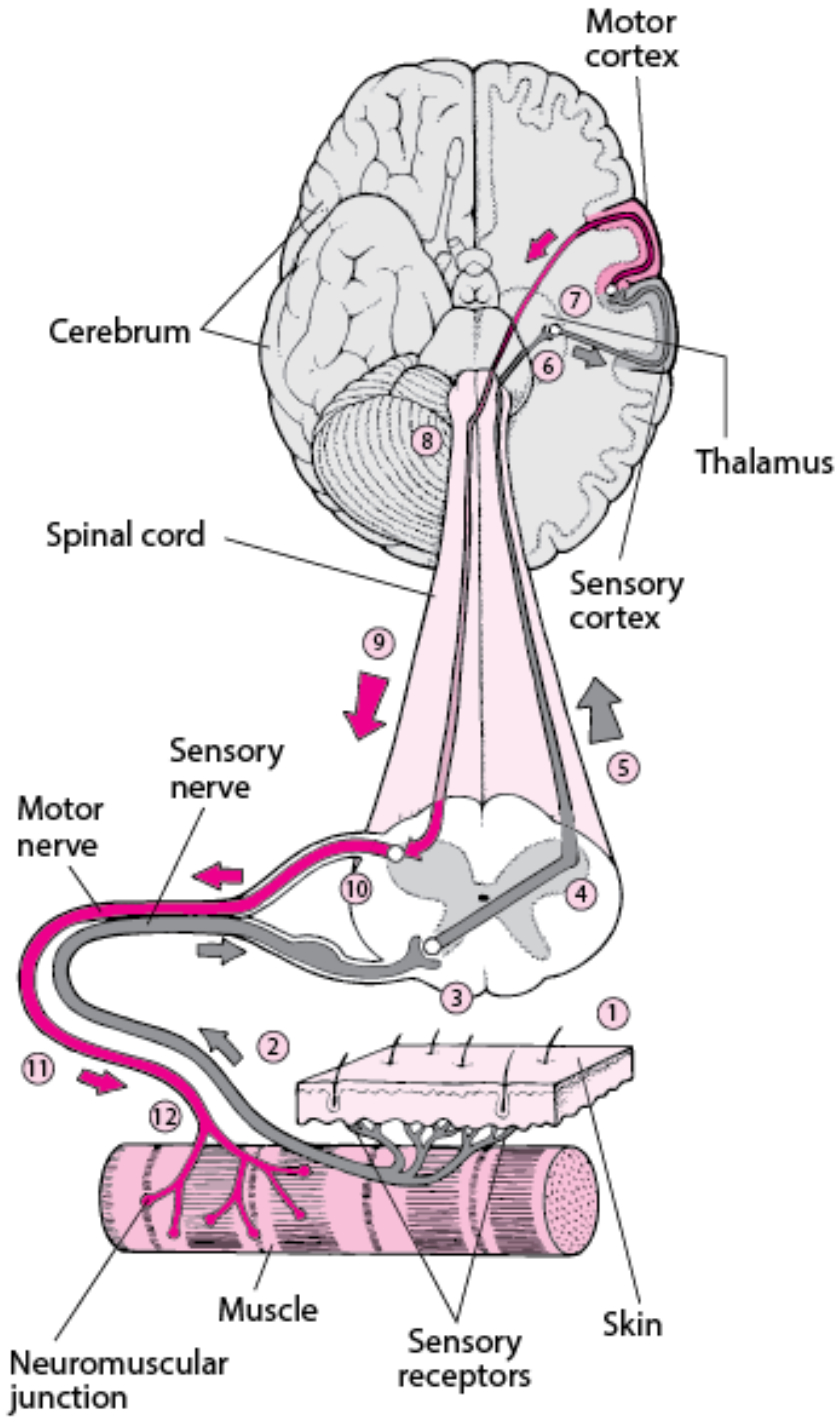
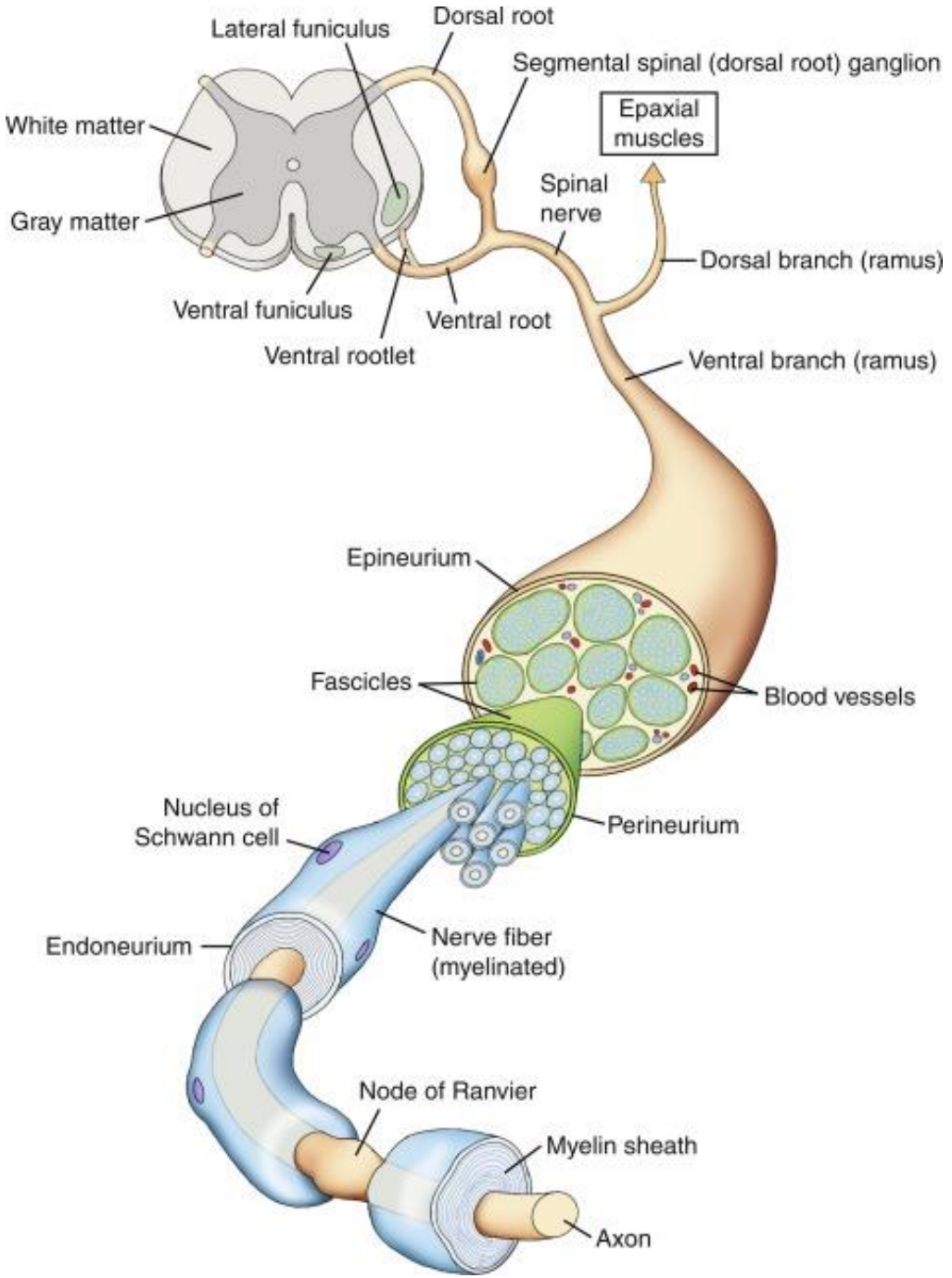
Outline

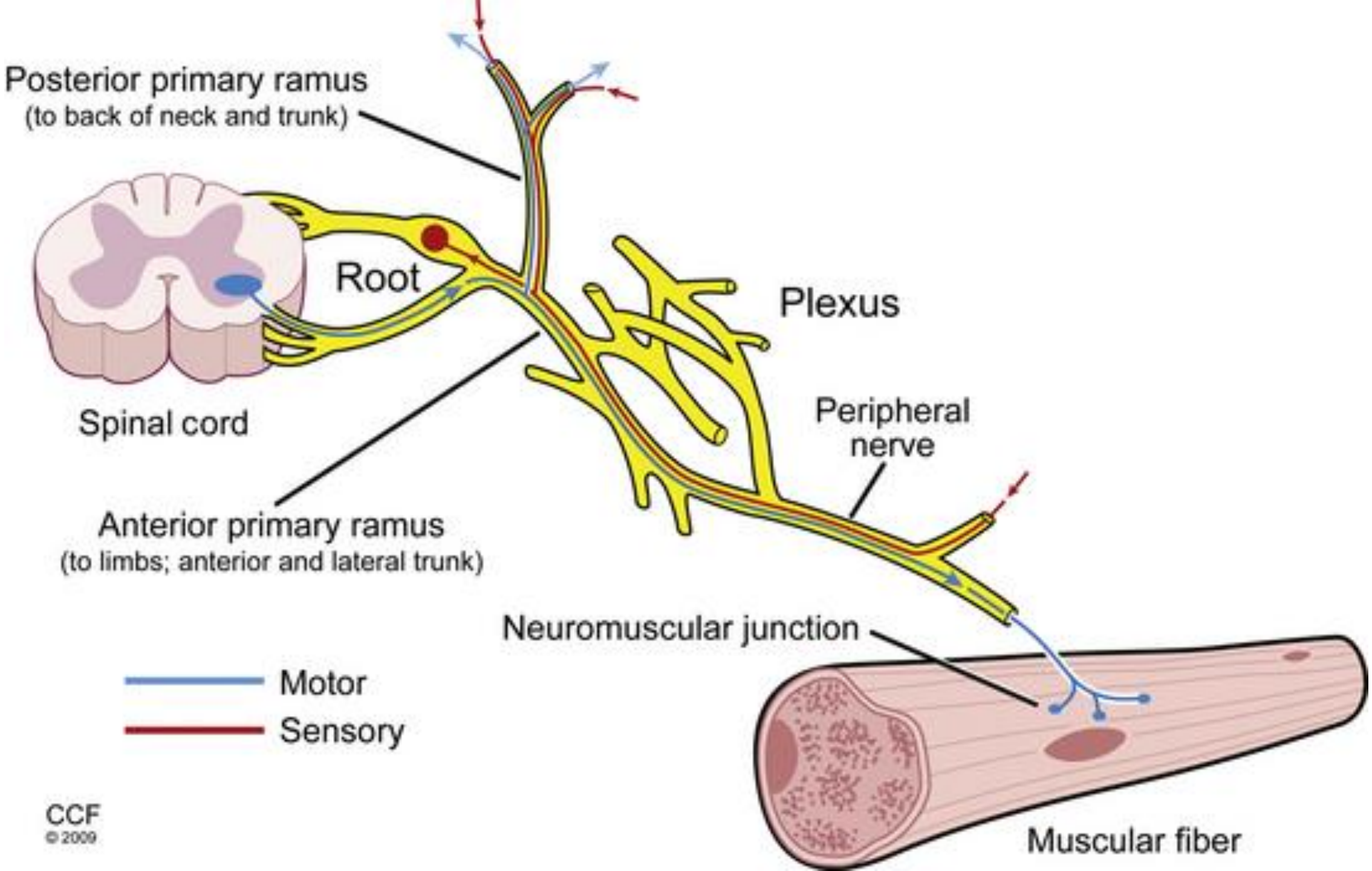
1. Definition
2. Pathophysiology
3. Epidemiology
4. Clinical Features
5. Conclusion


CENTRAL NERVOUS SYSTEM
brain
spinal cord
PERIPHERAL NERVOUS SYSTEM
nerves
ganglion


Motor cortex
Cerebrum
Thalamus
Spinal cord
Sensory cortex
Sensory nerve
Motor nerve
Muscle
Sensory receptors
Skin
Neuromuscular junction
1
2
3
4
5
6
7
8
9
10
11
12

- The peripheral nerve is a cable-like structure containing bundles of both unmyelinated and myelinated fibers and their supporting elements.




Posterior primary ramus
(to back of neck and trunk)
Root
Plexus
Spinal cord
Peripheral nerve
Anterior primary ramus
(to limbs; anterior and lateral trunk)
Neuromuscular junction
Motor
Sensory
CCF
© 2009
Muscular fiber

Peripheral nerve disorders

- Peripheral nerve disorders are common neurological problems caused by dysfunction of peripheral motor, sensory, or autonomic nerves.
- The causes of neuropathies are disparate and their clinical presentations highly variable.
- The main causes of neuropathy are entrapment, systemic diseases (DM), inflammatory and autoimmune disorders, inherited disorders, ischemic settings, paraneoplastic conditions, deficiency states, infections, and toxins.
- A logical systematic diagnostic approach to peripheral neuropathies consists of a detailed history, comprehensive physical and neurological examinations, detailed electrodiagnostic (EDX) studies, and possibly additional ancillary testing (such as autonomic testing,

Diabetic neuropathy

- Diabetic neuropathy is defined as the presence of symptoms and signs of peripheral nerve dysfunction in individuals with diabetes after the exclusion of other causes (vitamin B_{12} deficiency and endocrine neuropathies).
- In general, the diagnosis of a definite diabetic neuropathy should be based on clinical symptoms, objective neurological signs, and EDX confirmation.
- Diabetic neuropathies result in significant physical and psychological morbidity, including disabling pain, depression, and worse quality of life, as well as increased medical costs.

Pathophysiology of diabetic neuropathy

- The etiology is most likely multifactorial.
- Derangements of normal metabolic homeostasis.
- Autoimmunity.
- Microvascular insufficiency.

Pathophysiology

- Neuropathy related to type 1 diabetes is directly linked to glycemic control.
- Optimal glycemic control in type 1 diabetes reduces the relative risk of neuropathy development by 78% and improve EDX and vibratory threshold testing results among individuals with existing DN.
- In contrast, hyperglycemia is much less important in the pathogenesis of neuropathy in type 2 diabetes.
- In type 2 diabetes, intensive glycemic control only reduces the risk of neuropathy by 5% to 9%.
- Increasing evidence indicates that individual components of the metabolic syndrome, including hypertriglyceridemia, hypertension, abdominal obesity, low levels of high-density lipoproteins, and tobacco use, are important determinants of neuropathy risk and progression in type 2 diabetes.

Prevalence

- Both type 1 and type 2 diabetes carry a high risk of neuropathy development.
- The prevalence of neuropathy in the population of individuals with diabetes is similar between those with type 1 and type 2 diabetes, ranging from 10% to 50%.
- 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.

Prevalence

- In a population cohort of diabetic patients, two-thirds of diabetics had objective evidence of some type of neuropathy, but only about 15% had symptomatic degrees of polyneuropathy.

- Electrophysiological studies demonstrate subclinical conduction abnormalities in most patients with IDDM after 5 to 10 years of diabetes.

Diabetic neuropathy

- 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.

BOX 107.14 Classification of Diabetic Neuropathies

GENERALIZED SYMMETRICAL POLYNEUROPATHIES

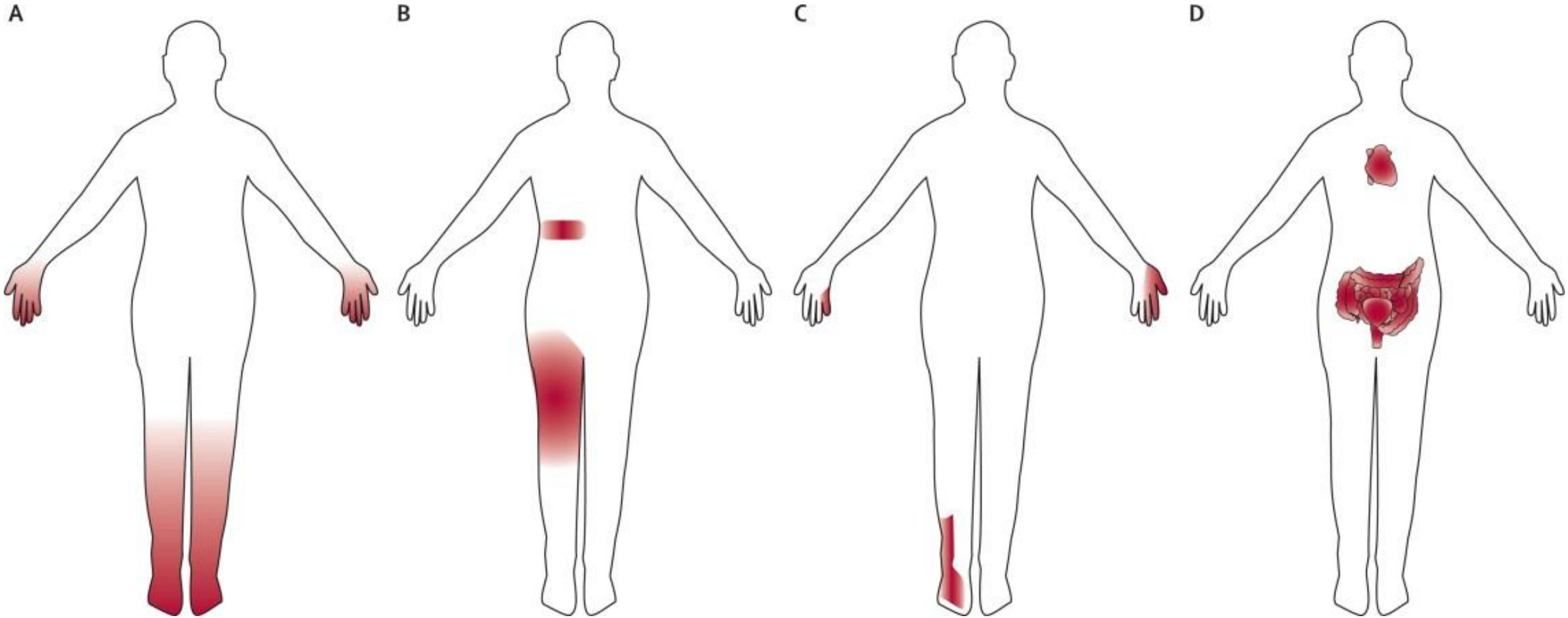
Distal sensory or sensorimotor polyneuropathy
Small-fiber neuropathy
Autonomic neuropathy
Large-fiber sensory neuropathy

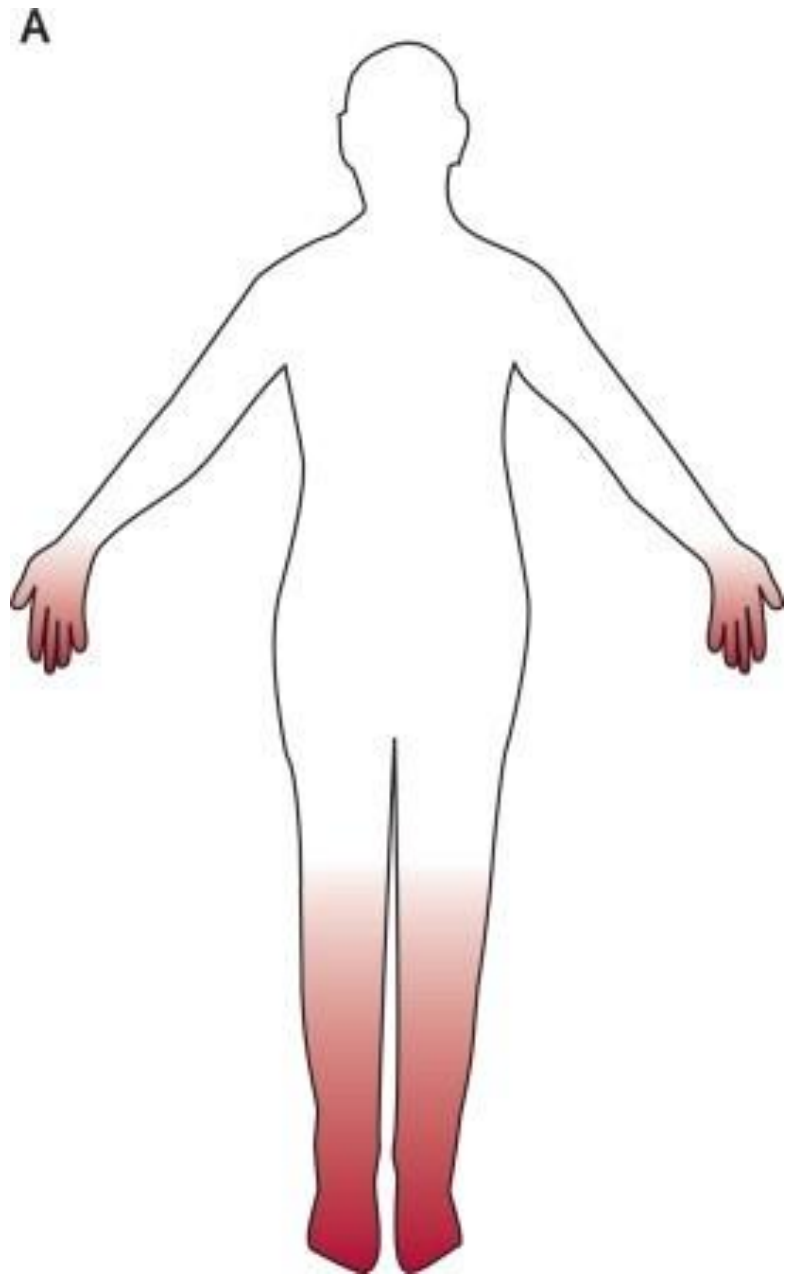
FOCAL AND ASYMMETRICAL NEUROPATHIES

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

COMBINATIONS

Polyradiculoneuropathy
Diabetic neuropathic cachexia


A
B
C
D


A

Distal Symmetric Polyneuropathy

- The most common clinical presentation of neuropathy in diabetes.
- Accounting for roughly 50% to 75% of cases of diabetic neuropathy.
- Risk factors: disease duration, disease severity and comorbid medical conditions (in particular metabolic syndrome).
- DSPN may be subclassified further into two major subgroups, depending on the nerve fiber type most involved: large-fiber and small-fiber variants.
- Diabetic neuropathy frequently forms a continuous spectrum ranging between these two polar types.

Small-fiber neuropathy

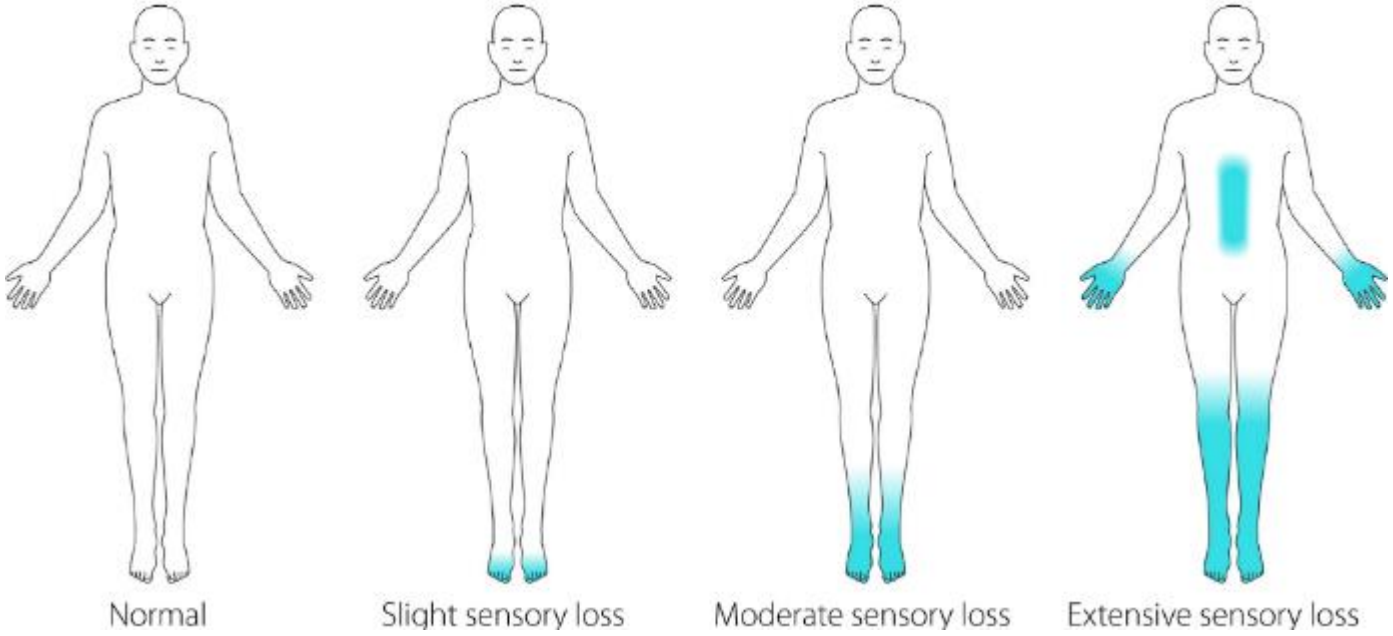
- Early DSPN in type 2 diabetes (or even prediabetes) preferentially involves small unmyelinated axons, frequently causing neuropathic pain, and gradually progresses to more involvement of large myelinated axons over time.
- Pain of a deep, burning, stinging, aching character, often associated with spontaneous 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.

Large-fiber neuropathy

- Large-fiber involvement is often asymptomatic, but sensory deficit may be detected by careful examination.
- The large-fiber neuropathy variant presents with painless paresthesia 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.

Distal Symmetrical Polyneuropathy

- Sensory deficits predominate.
- Sensory disturbances have a stocking-glove distribution following a length-dependent pattern.
- Most patients will develop only a minor motor involvement affecting the distal muscles of the lower extremities.
- Autonomic symptoms usually correlate with the severity of the neuropathy.
- Patients with neuropathic pain in the setting of DSPN typically present much earlier in the disease course than those without pain.



- 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.

Diagnosis

- The diagnosis of DSPN in diabetes is based on history, clinical examination findings, and nerve conduction studies in select cases.
- The appropriate clinical evaluation for DSPN includes, but is not limited to, examination of muscle strength, deep tendon reflexes, and sensation (vibration, proprioception, thermal, pain, and light touch sensation).
- The presence of atypical features such as significant asymmetry, an acute onset, or early motor involvement suggests a different neuropathy type or diagnosis and should prompt further diagnostic evaluation, including nerve conduction studies and EMG.
- Although DSPN is generally symmetric (by definition), symptoms may initially be reported in one limb and then

Management

- No disease-modifying therapies.
- Education about the underlying problem.
- To improve glycemic control.
- Pain management.
    1) Gabapentinoids: Gabapentin-Pregabalin
    2) SNRIs: Duloxetine-Venlafaxine
    3) TCAs: Amitriptyline
    4) Sodium channel blockers: Oxcarbazepine-Lamotrigine
    5) Also, Topical medications: Capsaicin
- Opioids (Tramadol) are not recommended.

Management

- Treatment of modifiable risk factors.
  1) To more aggressively manage lipids and blood pressure.
  2) To counsel on tobacco cessation.
  3) Weight loss through dietary modification.
- Advocating for an increase in exercise.
- Should be counseled on foot care.
  1) Should always wear hard-soled shoes.
  2) Should make sure to check their feet at least once daily.
  3) Should have a very low threshold for seeking medical attention in the setting of a foot injury.

Neuropathy associated with metabolic syndrome and prediabetes

- Prediabetes (impaired fasting glucose or impaired glucose tolerance) may precede the diagnosis of type 2 diabetes by several years.
- A hemoglobin A1c level of 5.7% to 6.4%.
- The prevalence of neuropathy in prediabetes is approximately 10%.
- Symptoms, EDX abnormalities, and intraepidermal nerve fiber density reduction consistent with a predominantly small-fiber neuropathy that may be either painful or painless.
- Although with changes less pronounced than in their diabetic counterparts.
- A growing body of literature links metabolic syndrome with

Impaired glucose tolerance neuropathy

- A smaller number of patients may present with autonomic dysfunction, primarily manifesting as reduced cardiovagal function with a resting tachycardia and reduced exercise tolerance.
- Among individuals with otherwise “idiopathic” neuropathy, the presence of prediabetes is approximately 25%.
- The implication for clinical practice is that patients with undiagnosed painful peripheral neuropathy should undergo OGTT.
- Early diagnosis followed by improved lifestyle may result in reversal of impaired glucose tolerance and neuropathy.

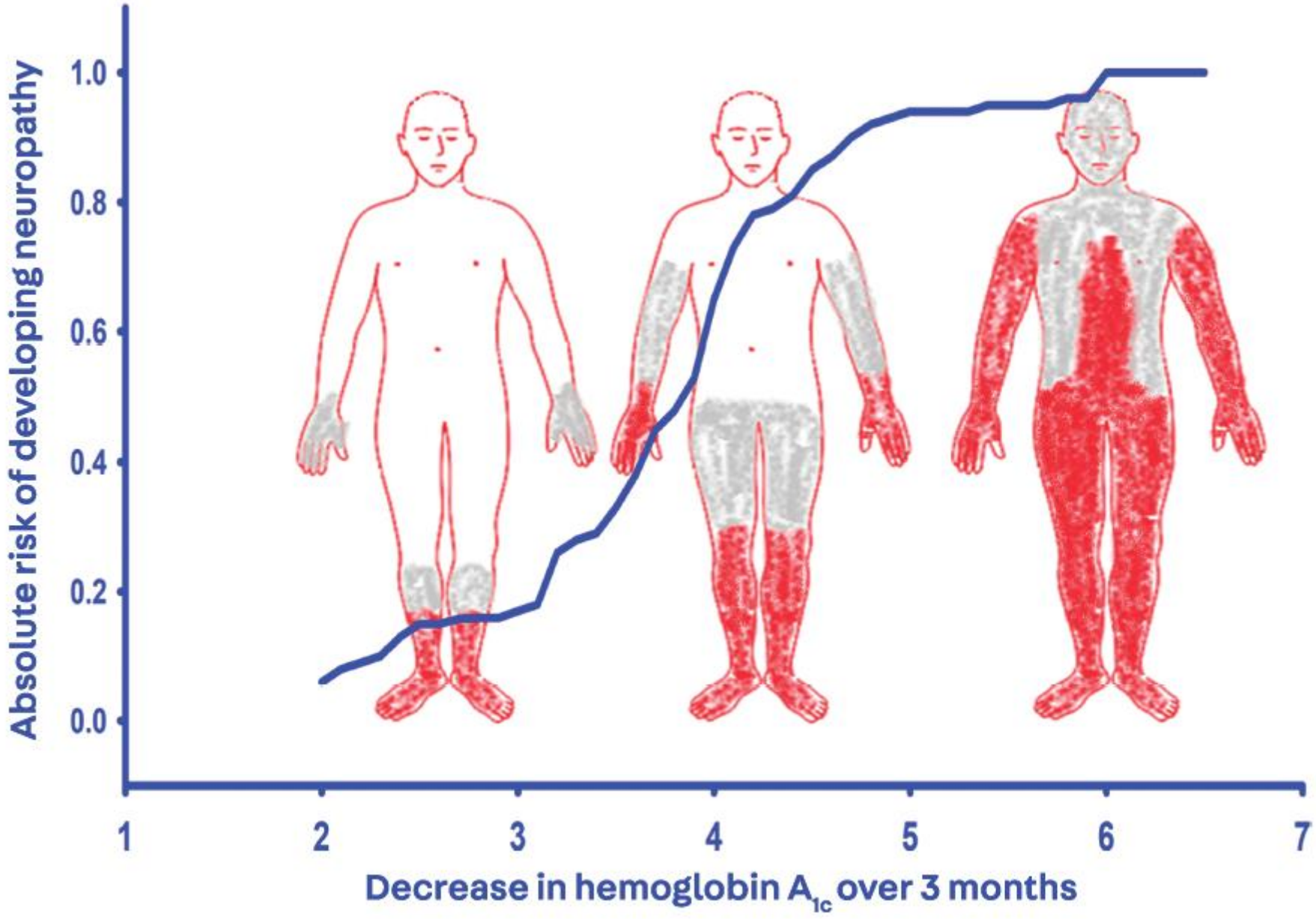
Treatment-Induced Neuropathy of Diabetes

- Previously known as insulin neuritis, or acute painful neuropathy.
- Develops suddenly following rapid improvement in glycemic control in the setting of chronic hyperglycemia.
- Most commonly seen after a significant treatment change in individuals with type 1 diabetes who have had chronic hyperglycemia or in individuals with newly discovered type 2 diabetes with an unknown period of hyperglycemia combined with an aggressive lowering of the hemoglobin A1c.
- The neuropathy predominantly involves small fiber sensory and autonomic nerve fibers.
- Characterized by the acute onset of neuropathic severe burning pain in a length-dependent or generalized distribution, often with accompanying autonomic symptoms.

Treatment-Induced Neuropathy of Diabetes

- Symptoms typically begin 2 to 8 weeks after the change in glucose control.
- Pain persists for weeks or up to several months, with spontaneous resolution to follow.
- Autonomic symptoms are sometimes prominent, including orthostatic intolerance or hypotension, hyperhidrosis or anhidrosis, early satiety, and erectile dysfunction, but they are frequently overlooked given the severity of the neuropathic pain.
- The severity of neuropathy in treatment-induced neuropathy of diabetes is tied to the magnitude and rate of the change in hemoglobin A_{1c}.

- Individuals with the largest changes in glucose control have the largest region of body involvement, the most severe pain, and the greatest symptoms of autonomic dysfunction.



Treatment-Induced Neuropathy of Diabetes

- In addition to the development of neuropathy, individuals who develop treatment-induced neuropathy of diabetes also frequently have renal and retinal involvement simultaneously.
- The majority of individuals with treatment-induced neuropathy of diabetes have significant progression of proliferative retinopathy over a period of 12 months.
- Renal function may decline, although increased microalbuminuria is the most common manifestation.

Management

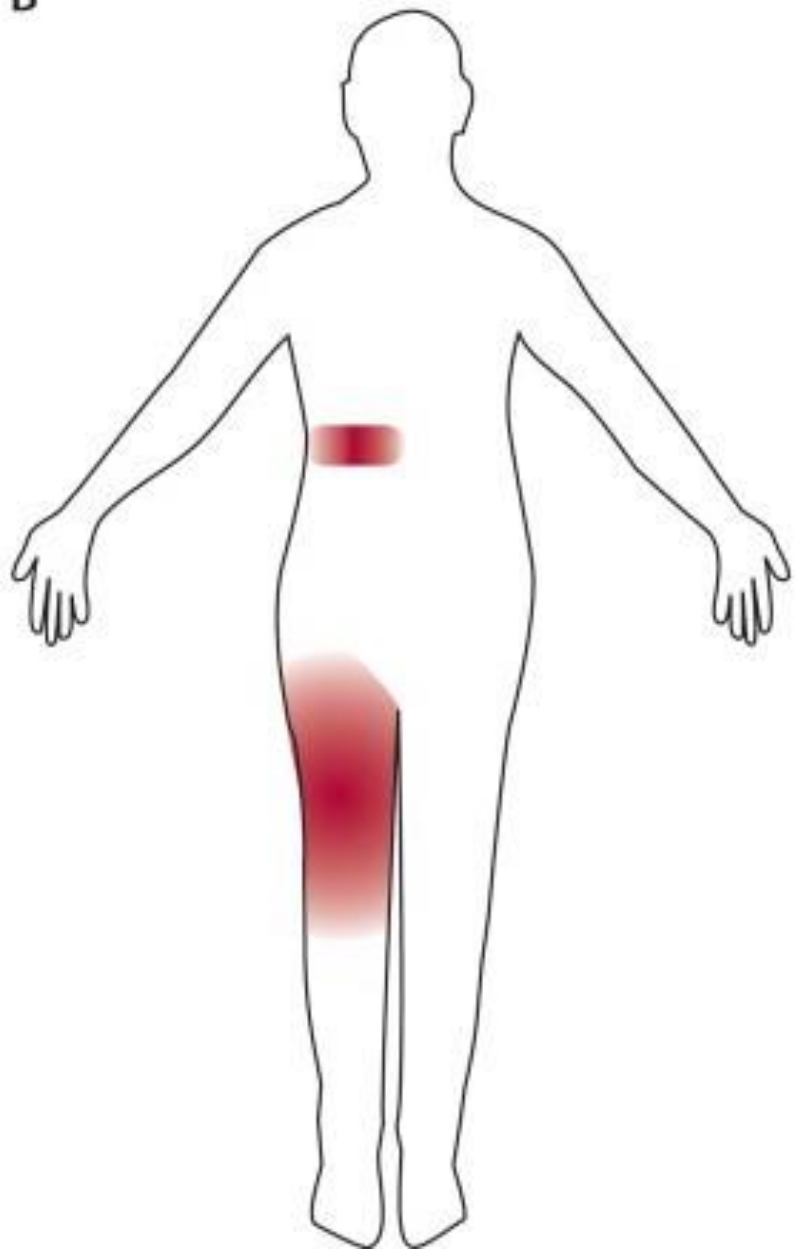
- Focused on preventing neuropathy progression, managing symptoms and preventing recurrence.

1. Often improve with stable glucose control => Encouraging glucose stabilization at the current hemoglobin A1c level until symptoms begin to improve.
2. Two and even three agents may be necessary for pain control (TCAs should be used cautiously as they may worsen orthostatic symptoms).
3. Avoiding dramatic improvements in hemoglobin A1c levels in individuals with chronic hyperglycemia is recommended (limiting change to 1% reduction in the hemoglobin A1c per month).

Diabetic neuropathic cachexia

- An acute and severe painful diabetic neuropathy associated with precipitous severe weight loss, depression, insomnia, and impotence in men.
- The syndrome is more common in men with poor glucose control.
- Improved glucose control and weight gain often result in recovery and improvement of EDX abnormalities.
- The reason for profound weight loss, severe pain, and spontaneous recovery remains obscure.

B



Diabetic Lumbosacral Radiculoplexus Neuropathy

- Different presentations of the same basic involvement of multiple nerve roots or proximal nerve segments. : Diabetic amyotrophy, thoracolumbar radiculopathy, and proximal or diffuse lower extremity weakness.
- The incidence to be approximately 4.2 per 100,000 per year.
- Most common in middle-aged (older than 50 years) patients with type 2 diabetes.
- Is more common in men than in women.
- The disorder is rare in young adults or children.
- The onset is unrelated to the duration of diabetes, and often have fairly well-controlled diabetes.
- Pathologic data suggest it is caused by a microvasculitis resulting in ischemic nerve injury.

Diabetic Lumbosacral Radiculoplexus Neuropathy

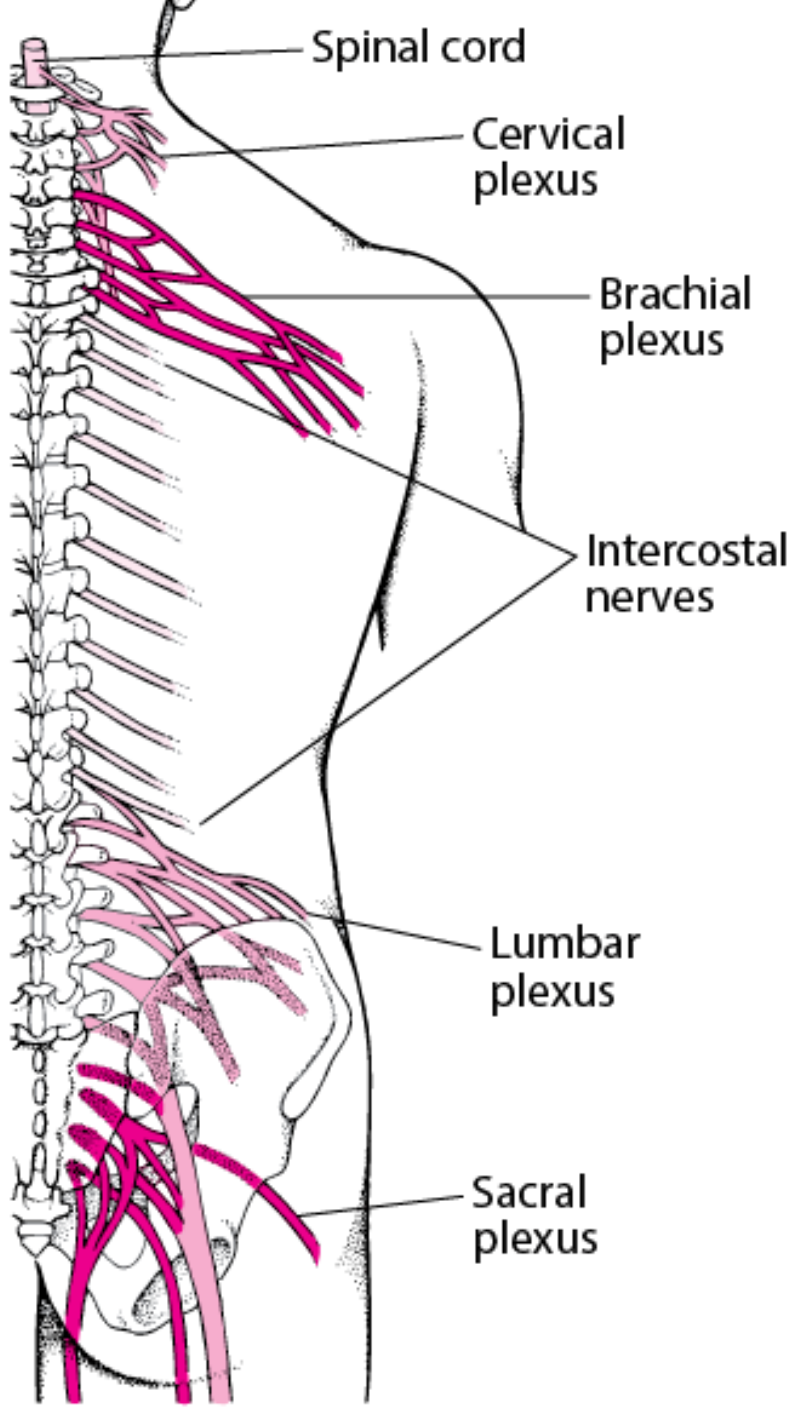
- Typically, unilateral severe pain in the lower back, hip, and anterior thigh heralds the onset of neuropathy.
- Within days to weeks asymmetrical weakness ensues, affecting proximal and, to a lesser extent, distal lower-extremity muscles (iliopsoas, gluteus, thigh adductor, quadriceps, hamstring, and anterior tibialis).
- Less commonly, patients may present with a symmetric motor-only form.
- 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.

Diabetic Lumbosacral Radiculoplexus Neuropathy

- The progression may be steady or stepwise and may continue for many months (in some cases as long as 18 months).
- 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.
- In some cases, the opposite leg becomes affected after a latency.
- Most patients require assistance with ambulation and aggressive pain management.

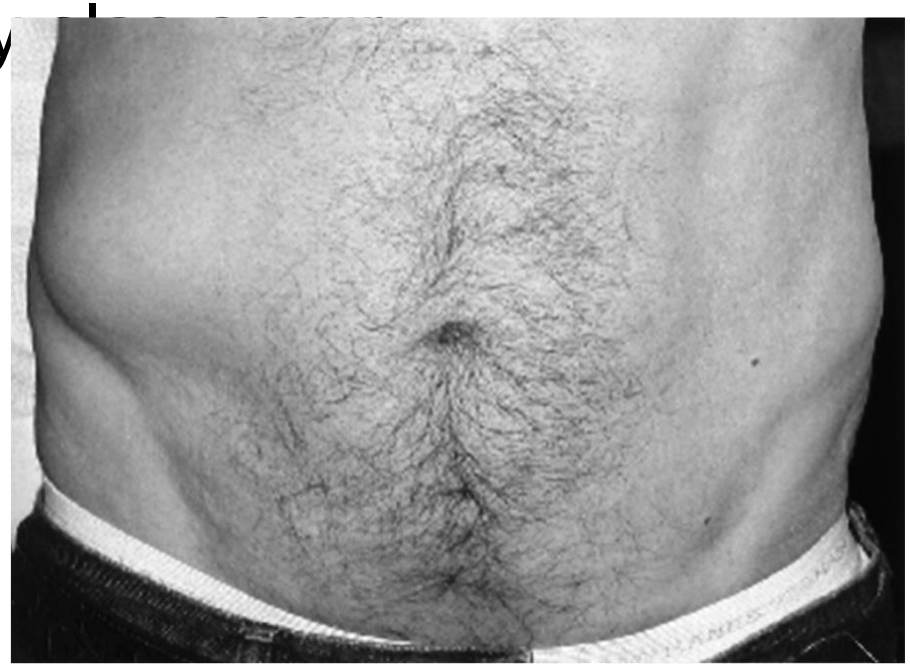
Management

- There are currently no effective disease-modifying treatments.
- The management is focused on pain management and adaptive devices to improve quality of life.
- Although a beneficial effect of immunomodulating therapies has been proposed, controlled studies have shown no positive effect for corticosteroids in enhancing the recovery of the motor deficit.
- A small randomized trial suggested that IV methylprednisolone may help neuropathic refractory pain associated with diabetic lumbosacral radiculoplexus neuropathy.


Spinal cord
Cervical plexus
Brachial plexus
Intercostal nerves
Lumbar plexus
Sacral plexus

Diabetic Truncal Neuropathy (thoracic radiculopathy)

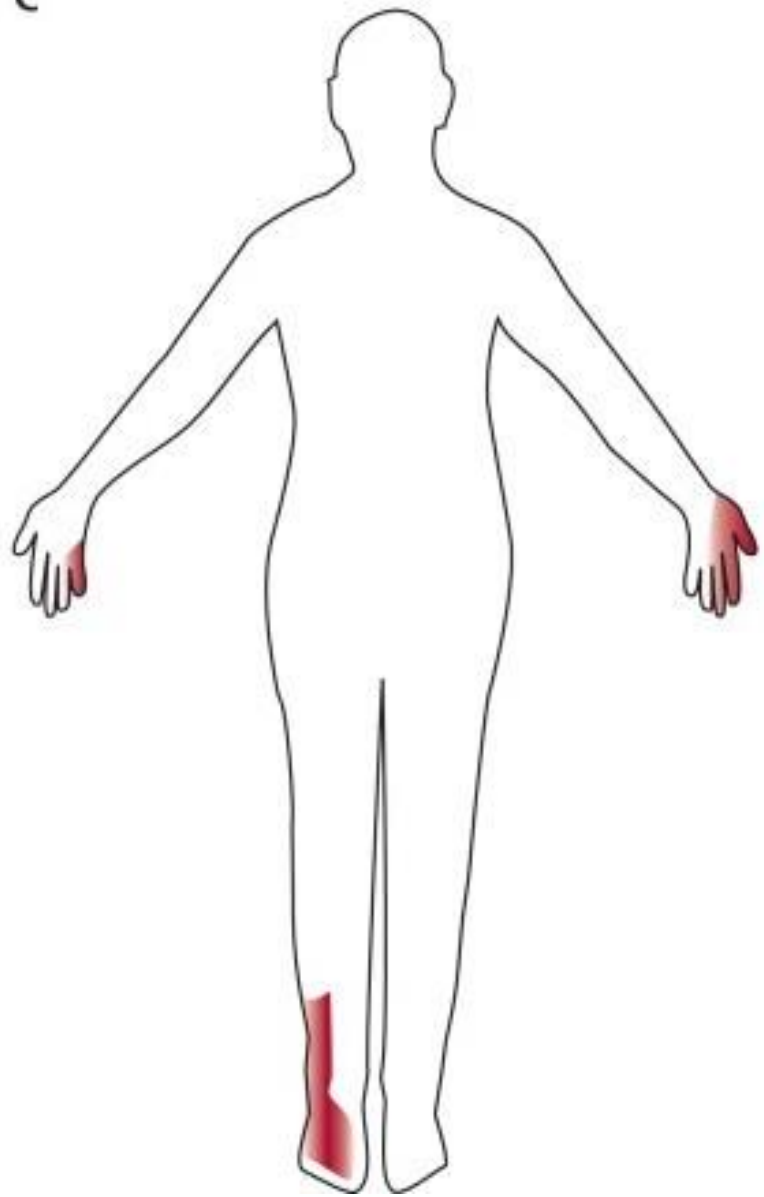
- Involving the T4 through T12 spinal nerve roots causes pain or dysesthesias in areas of the chest or abdomen, thereby producing diagnostic confusion.
- Bulging of the abdominal wall as a result of weakness of abdominal muscles may



Diabetic Truncal Neuropathy (thoracic radiculopathy)

- This unique truncal pain is seen in older patients with NIDDM.
- May occur either in isolation or together with the typical lumbosacral radiculoplexopathy.
- Contact with clothing can be very unpleasant.
- The onset may be either abrupt or gradual.
- In some patients preceded or accompanied by a profound weight loss.
- The symptoms may persist for several months before gradual and spontaneous resolution within 4 to 6 months.

C



Limb Mononeuropathy

- Caused by 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.
- Mononeuropathies due to nerve entrapment are more common than nerve infarctions.
- Entrapment neuropathies, including median mononeuropathy at the wrist (carpal tunnel syndrome), ulnar mononeuropathy at the elbow (cubital tunnel syndrome), and fibular (peroneal)mononeuropathy at the fibular head are more prevalent in individuals with diabetes.

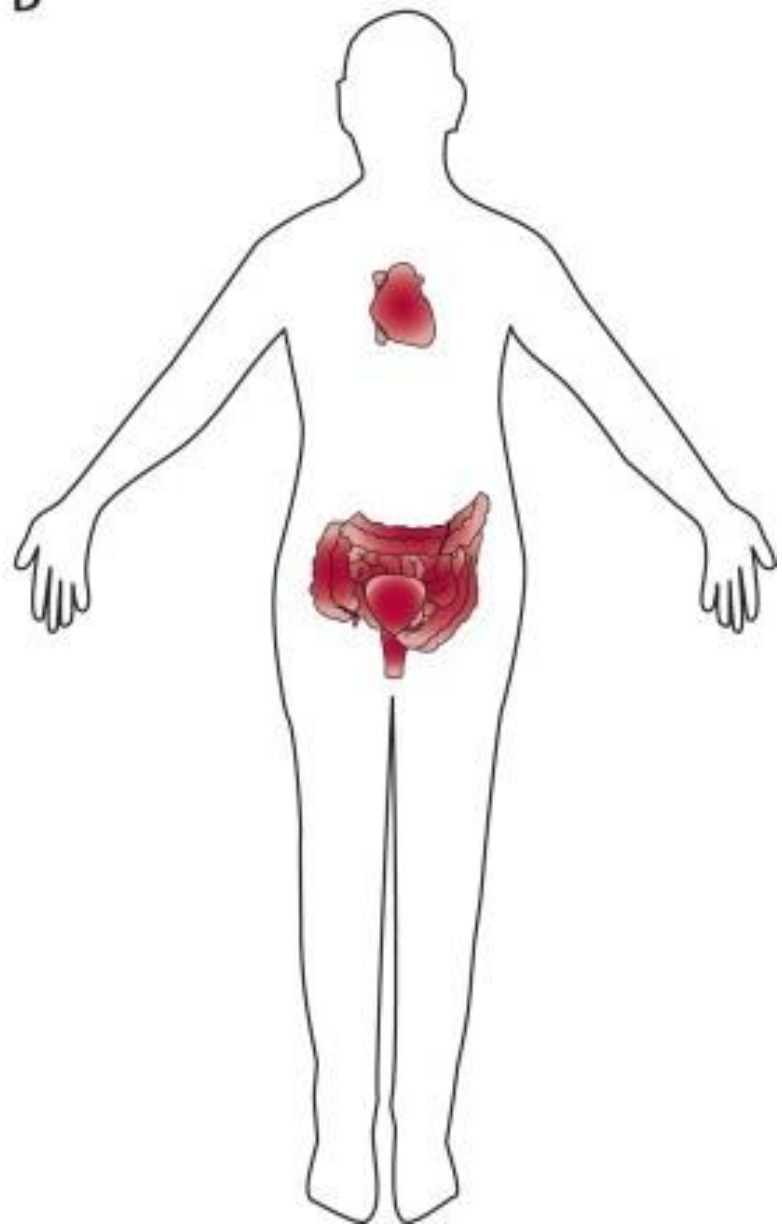
Limb Mononeuropathy

- Diabetes mellitus is a risk factor for single or multiple entrapment neuropathies.
- Diabetes is found in 8% to 12% of patients presenting with CTS.
- The risk for CTS is more than twofold for patients with diabetes than in the general population.

Cranial Mononeuropathies

- 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 freque
  nerves are also affecte

D



Autonomic Neuropathy

- In one study, autonomic impairment was present in 54% of IDDM and 73% of NIDDM.
- Diverse spectrum of clinical manifestations because of the different organ systems involved.
- 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.
- Patients may not notice the symptoms of cardiovascular autonomic neuropathy for several years, and late diagnosis increases the risk of mortality.

Diabetic Cardiovascular Autonomic Neuropathy

- Prolonged hyperglycemia is the primary risk factor.
- Decreased heart rate variability has also been reported in up to 38% of individuals with prediabetes.
- Among individuals with NIDDM, traditional cardiovascular risk factors (hypertension, dyslipidemia) are also associated with DCAN.
- DCAN is associated with a significant increase in both morbidity and mortality (cardiovascular events, including arrhythmia and MI).
- The American Diabetes Association recommends screening all patients with existing microvascular complication of diabetes (ie, DSPN, retinopathy, or nephropathy) for signs and symptoms of DCAN.

Diabetic Cardiovascular Autonomic Neuropathy

- Early sigs are from parasympathetic dysfunction of vagal nerve and include elevated resting heart rate and impaired heart rate variability which are often asymptomatic.
- As cardiovascular autonomic neuropathy becomes more severe, orthostatic hypotension (defined as a fall in blood pressure of >20mmHg systolic and >10 mm Hg diastolic when going from lying to sitting or sitting to standing after 3 minutes) develops, which is the most severe and debilitating form of cardiovascular autonomic neuropathy.
- Patients with diabetes who have orthostatic hypotension in the setting of cardiovascular autonomic neuropathy have a 5- to 10-year mortality range between 27% and 56%.

Diabetic Cardiovascular Autonomic Neuropathy

- At present, no treatment exists for the underlying disease.
- As a consequence, the primary goal is prevention of disease development and progression with glycemic control and aggressive management of other features of metabolic syndrome.
- Among patients with orthostatic hypotension, symptomatic management should also be considered.

Nonpharmacologic Interventions for Orthostatic Hypotension

In conjunction with a patient's primary care provider, review the existing medication list and discontinue medications that may be contributing to hypotension; offending agents may include antihypertensive medications, antidepressants, and dopaminergic medications for Parkinson disease

Increase intravascular volume

- Increase fluid intake (up to 1.5-3 L/d)
- Liberalize salt intake (up to 6-10 g/d of sodium)
- Waist-high compression stockings to reduce vascular pooling, increase venous return, and increase blood pressure (at least 15-20 mm Hg pressure), although the effect may be limited because of pooling in the splanchnic vasculature

Modify behavior

- Arise slowly, particularly in the morning when orthostatic tolerance is the lowest
- Elevate the head of the bed 30 to 45 degrees to avoid supine hypertension and nocturnal diuresis
- Avoid triggers: eg, Valsalva-like maneuvers, overheating, large carbohydrate-rich meals
- Continue a modified exercise regimen since deconditioning can worsen orthostatic hypotension; focus on recumbent activities

TABLE 5-2

Pharmacologic Interventions for Orthostatic Hypotension

Medication and mechanism of action	Dosing	Potential adverse effects
Fludrocortisone Synthetic mineralocorticoid, expands volume by increasing sodium and water reabsorption	0.1-0.2 mg/d administrated as 1 or 2 doses; start with 0.05 mg/d	Hypokalemia, supine hypertension, peripheral edema, renal failure; use cautiously in patients with congestive failure
Midodrine Direct α_1-adrenergic receptor agonist	2.5-10 mg 3 times a day administered every 3-4 hours during daytime hours	Severe supine hypertension, piloerection, urinary retention; do not use within 4 hours of bedtime; use cautiously in patients with congestive heart failure and chronic renal failure
Droxidopa Synthetic norepinephrine precursor	100-600 mg, 3 times a day, the last dose needs to be administered at least 3 hours before sleep	Headache, supine hypertension, nausea, fatigue; use cautiously in patients with congestive heart failure and chronic renal failure
Pyridostigmine Acetylcholinesterase inhibitor	Start with a 30-mg test dose; if well tolerated, increase to 60 mg, can be administered up to 3 times daily; rarely use more than 120 mg per dose	Wheezing, abdominal pain, diarrhea, hyperhidrosis

Gastroparesis

- Causes delayed transit of food (solids or liquids) from the stomach into the small intestine.
- It is present in up to 50% of individuals with diabetes.
- Many patients report postprandial fullness, nausea, bloating, or vomiting, although some patients may be asymptomatic.
- It further complicates glycemic control by causing a mismatch between glucose absorption and administration of insulin.
- Objective assessment of gastroparesis severity is recommended.
- A separate and potentially reversible component is directly related to hyperglycemia.

Treatments

- Having patients eat smaller, more frequent meals. (this strategy can further complicate glycemic control)
- Avoiding dietary fiber and fat is recommended.
- Removal of any offending medications (such as opioids, clonidine, tricyclic antidepressants, calcium channel blockers, dopamine agonists, muscarinic cholinergic receptor antagonists, glucagonlike peptide 1 [GLP-1] agonists, phenothiazines, and cyclosporine)
- Metoclopramide (duration of therapy beyond 5 days is not recommended)

Constipation

- Up to 60% of patients affected.
- The patient's medication list should be closely investigated.
- Constipation due to colonic hypomotility is more common than diarrhea.
- Treatment:
    1. food and dietary change (eating fiber-rich foods)
    2. more exercise
    3. bulking agents such as psyllium
    4. osmotic laxatives such as lactulose

Diarrhea

- It is typically a profuse and watery diarrhea that usually presents during sleep.
- It is more common in individuals with type 1 diabetes.
- Often associated with fecal incontinence.
- Associated weight loss or malabsorption is rare.
- Reported in up to 20% of individuals with diabetes.
- It may alternate with constipation or may persist as diarrhea for hours at a time.
- Loperamide, codeine, combination diphenoxylate and atropine, or tincture of opium.

Bladder dysfunction

- Reported in up to 50% of individuals with diabetes.
- The symptoms of urinary autonomic dysfunction develop insidiously and progress slowly.
- One of the initial symptoms of autonomic neuropathy involving the bladder is impaired sensation of fullness.
- As neuropathy severity increases, bladder atony leads to prolonged intervals between voiding, gradually increasing urinary retention, and finally overflow incontinence.
- Patients with diabetes who have neurogenic bladder should be encouraged to void routinely every few hours to prevent urinary retention (or bethanechol).
- Medications that impair detrusor activity include anticholinergic agents, tricyclic antidepressants, and calcium channel antagonists.

Sexual dysfunction

- Diabetic neuropathy leads to dysfunction of vaginal exocrine glands, resulting in dryness and tissue irritation, further compounding painful intercourse; with the frequency of 70% in women with type 2 diabetes.
- Erectile dysfunction is highly prevalent in men with diabetes, noted in up to 75% of male patients; the underlying pathophysiology is a combination of vascular, neurologic, and psychological factors.
- The other complication is retrograde ejaculation.
- Although a number of medications (sildenafil and vacuum-erection device) exist to treat erectile dysfunction, they become less effective as neuropathy and vascular disease worsen.

Sudomotor Function

- Necessary for proper homeostatic thermoregulation as well as skin health.
- May present as the earliest clinical manifestation of neuropathy.
- Sudomotor abnormalities result in distal anhidrosis, typically presenting in a stocking-and-glove distribution.
- Patients do not present with symptoms related to distal anhidrosis but instead report proximal hyperhidrosis to maintain thermoregulation.
- Patients feel that they are sweating too much over their head and trunk.
- Another classic finding in diabetic neuropathy, although less common than distal anhidrosis, is gustatory sweating. Sweat will appear over the face, head, neck, shoulders, and chest after eating.
- Oral or topical glycopyrrolate may prove partially effective in some

TABLE 2-2

Impact of Medications and Other Agents on Autonomic Function

Autonomic Symptoms/Signs	Potentially Causative Agents
Orthostatic hypotension	Antidepressants, antihypertensive medications, α_1-adrenoreceptor antagonists, antiparkinsonian dopaminergic agents
Gastroparesis	Opioids, clonidine, tricyclic antidepressants, calcium channel blockers, dopamine agonists, muscarinic cholinergic receptor antagonists, glucagonlike peptide 1 (GLP-1) agonists, phenothiazines, cyclosporine
Constipation	Calcium channel antagonists, opioids, anticholinergic medications
Diabetic diarrhea	Metformin, sorbitol-containing foods
Bladder dysfunction	Anticholinergic agents, tricyclic antidepressants, calcium channel antagonists (impair detrusor activity); α_1-adrenoreceptor agonists (increase urethral sphincter tone), α_1-adrenoreceptor antagonists (decrease urethral sphincter tone)
Sexual dysfunction	Antidepressants, antihypertensive medications, statins, antihistamines

Conclusion

- Unfortunately, once the diabetic neuropathy is established, the existing damage is largely irreversible.

- The cornerstone in the treatment of diabetes and its complications is prevention of disease development and progression with glycemic control and aggressive management of other features of metabolic syndrome, and symptom management including pain treatment.


THANK YOU ☺