

Metabolic, Hormonal, and Nutritional Neuropathies

Peripheral nerve pathology · pathogenesis, morphology, and clinical patterns

Diabetes

Renal and thyroid disorders

Nutritional deficiency

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Learning objectives

Recognize common anatomic patterns of acquired peripheral neuropathy.

Explain the interacting mechanisms of diabetes-associated nerve injury.

Interpret characteristic nerve pathology and clinical consequences.

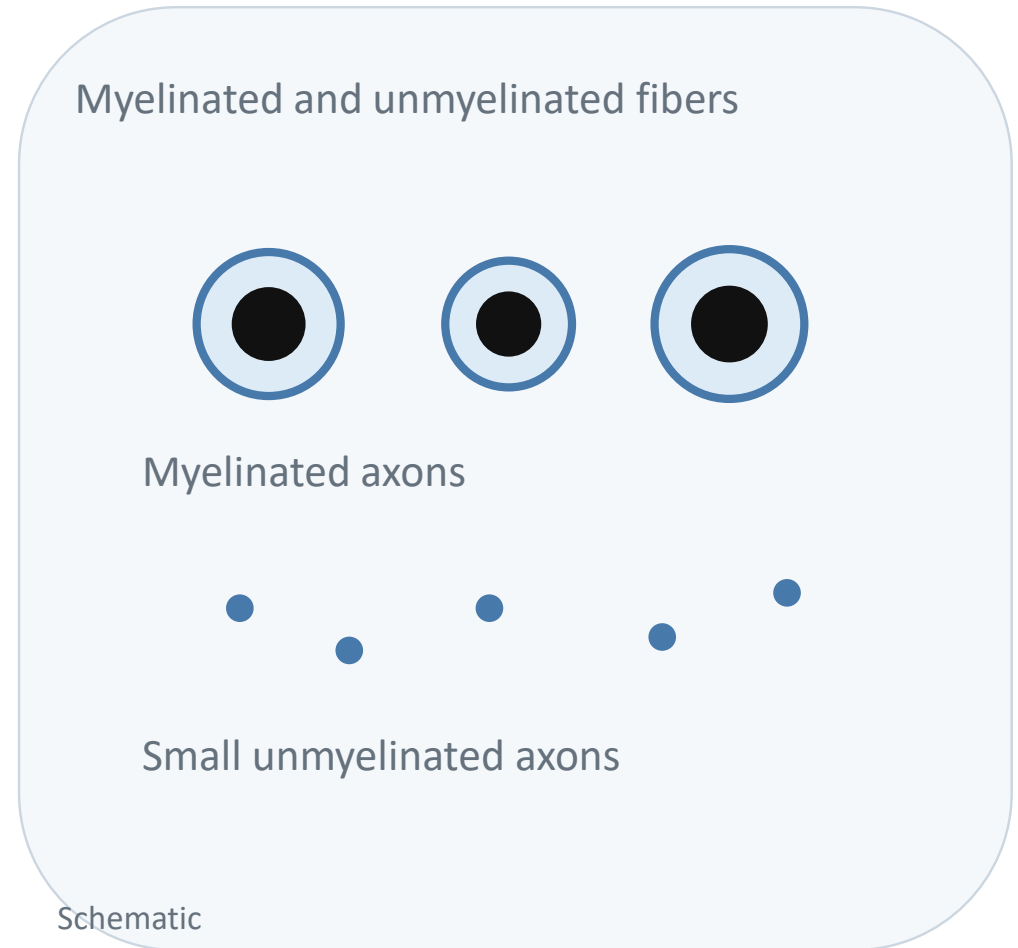
Contrast uremic, thyroid-related, and nutritional neuropathies.

Peripheral nerve: Vulnerable structures

Axons carry sensory, motor, and autonomic signals over long distances.

Schwann cells support axons and form myelin around larger fibers.

Small unmyelinated fibers convey pain, temperature, and autonomic signals.



Axonal versus myelin-predominant injury

Axonal injury causes fiber dropout with secondary myelin degeneration.

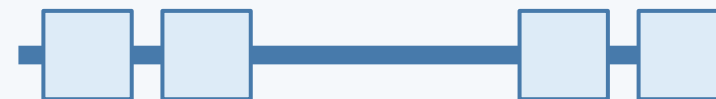
Demyelination primarily affects the Schwann-cell myelin sheath.

Metabolic neuropathies in this chapter usually show an axonal pattern.

Schematic patterns of injury



Axonal disruption



Segmental myelin loss

Schematic

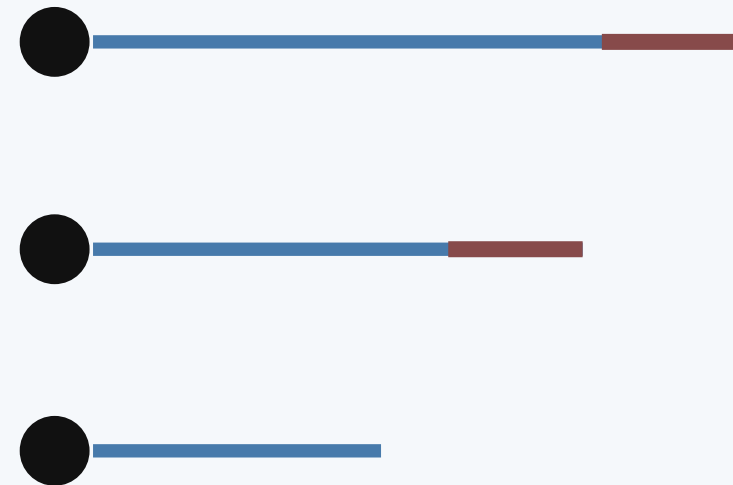
Why distal axons are vulnerable

An axon may extend from a proximal cell body to a distant skin or muscle target.

Long fibers are especially susceptible to sustained toxic or metabolic stress.

Length-dependent axonal degeneration produces a distal “dying-back” pattern.

Long fibers show distal-first injury



Cell bodies

Distal fiber injury

Schematic

Distribution is a diagnostic clue

Polyneuropathy: Multiple nerves, typically symmetric and distal.

Mononeuropathy: Deficit localized to one named peripheral nerve.

Radiculoplexus neuropathy: Asymmetric involvement of a nerve-root/plexus region.

Anatomic / functional patterns

Distal symmetric

Focal nerve

Plexus / roots

Autonomic

Schematic

How to classify these neuropathies

First determine the anatomic pattern and dominant fiber type.

Then consider axonal loss versus primary demyelination.

Finally relate the phenotype to metabolic, hormonal, or nutritional disease.

Anatomic / functional patterns

Distal symmetric

Focal nerve

Plexus / roots

Autonomic

Schematic

Diabetes: Principal metabolic cause

Diabetes as the most common cause of peripheral neuropathy.

Both type 1 and type 2 diabetes may be associated with neuropathy.

Several different clinicopathologic neuropathy patterns are recognized.

Anatomic / functional patterns

Distal symmetric

Focal nerve

Plexus / roots

Autonomic

Schematic

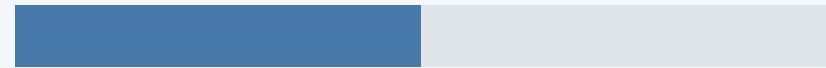
Neuropathy increases with disease duration

Evidence of neuropathy in up to 50% of all patients with diabetes.

For diabetes lasting more than 15 years, its quoted figure is up to 80%.

These are upper estimates reported by the source—not universal prevalence rates.

Upper estimates quoted



Overall: Up to 50%



Duration >15 years: Up to 80%

Schematic

Diabetic neuropathy is heterogeneous

The predominant phenotype is distal symmetric sensorimotor polyneuropathy.

Autonomic dysfunction commonly coexists with this phenotype.

Less common patterns include focal, cranial, and radiculoplexus neuropathies.

Anatomic / functional patterns

Distal symmetric

Focal nerve

Plexus / roots

Autonomic

Schematic

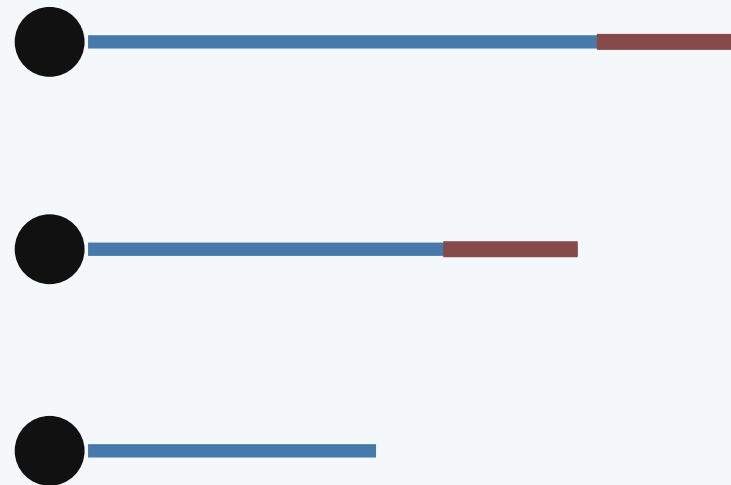
The canonical diabetic phenotype

Symptoms typically begin distally and extend proximally over time.

Sensory manifestations dominate; Motor involvement is less prominent.

Distribution is often bilateral and approximately symmetric.

Long fibers show distal-first injury



Cell bodies

Distal fiber injury

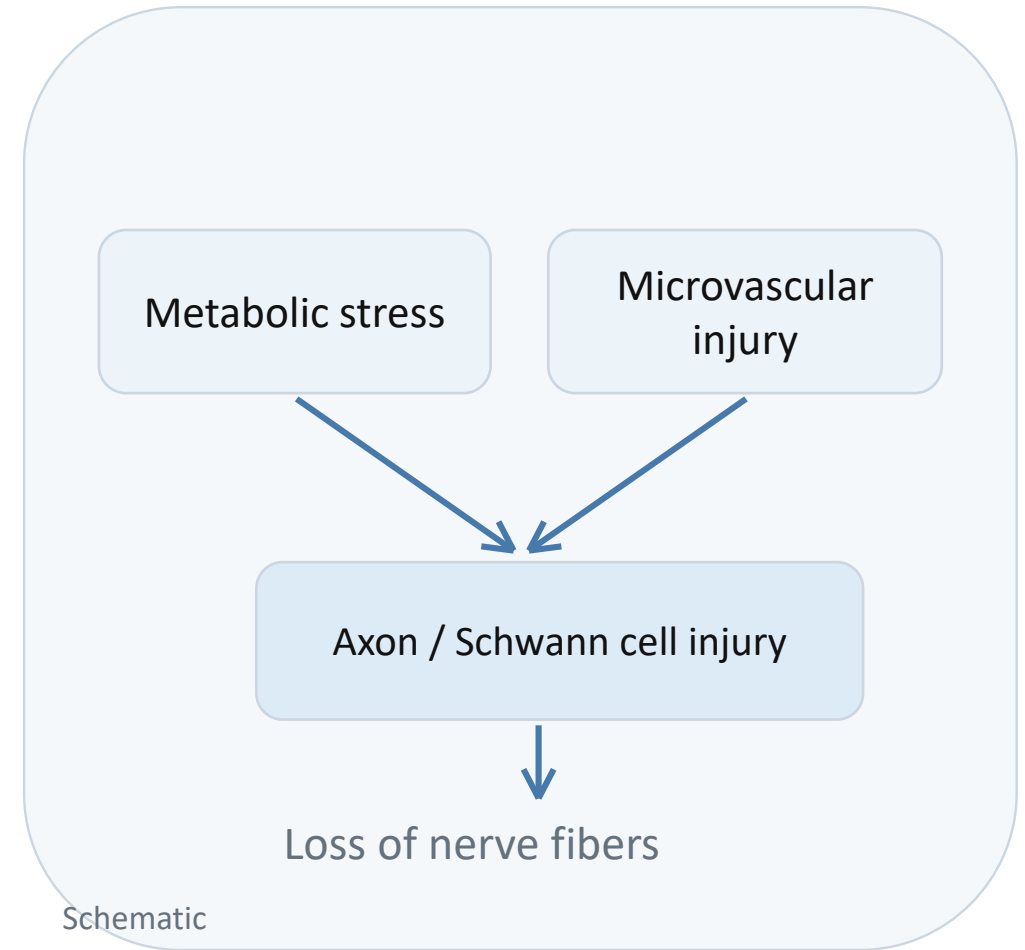
Schematic

Diabetic nerve injury is multifactorial

Metabolic disturbances act directly on axons and Schwann cells.

Microvascular injury can compromise nerve perfusion.

The combined mechanisms are incompletely defined.

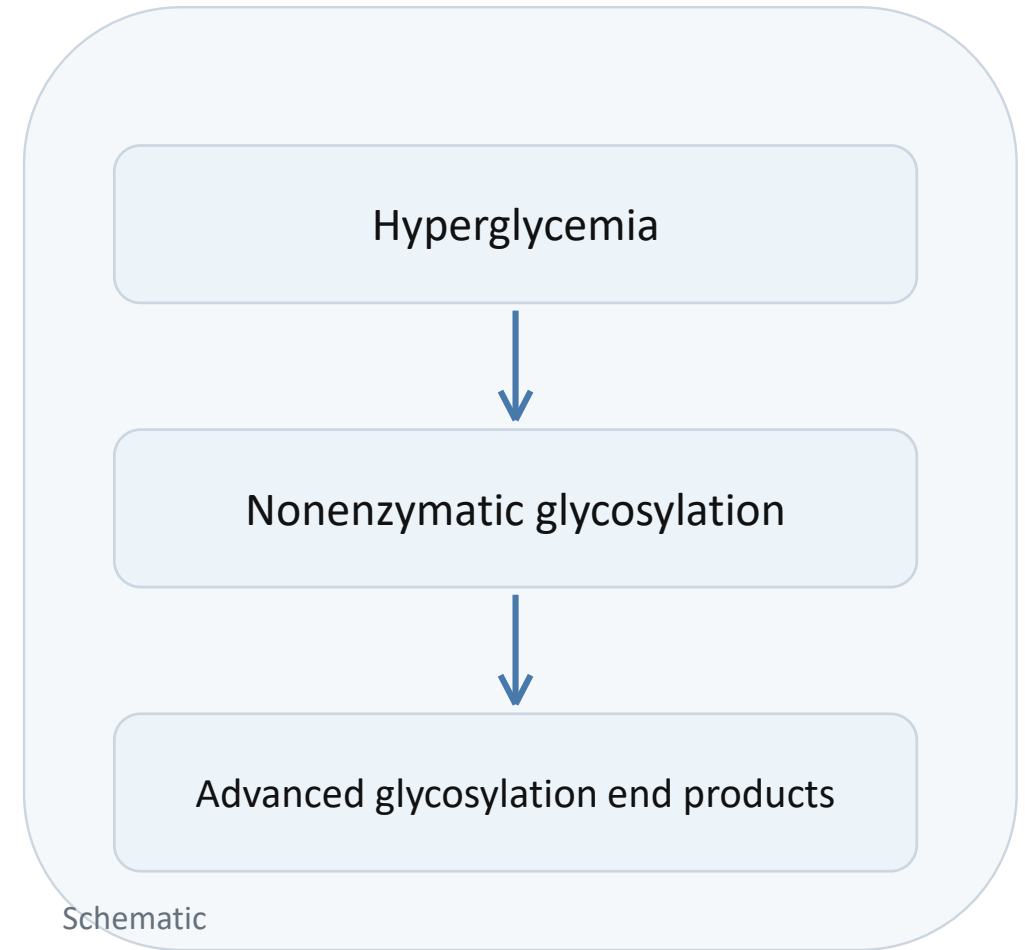


Hyperglycemia drives AGE formation

High glucose promotes nonenzymatic glycosylation of biomolecules.

Proteins, lipids, and nucleic acids can acquire advanced glycosylation end products.

AGE accumulation creates potential disturbances in normal molecular function.

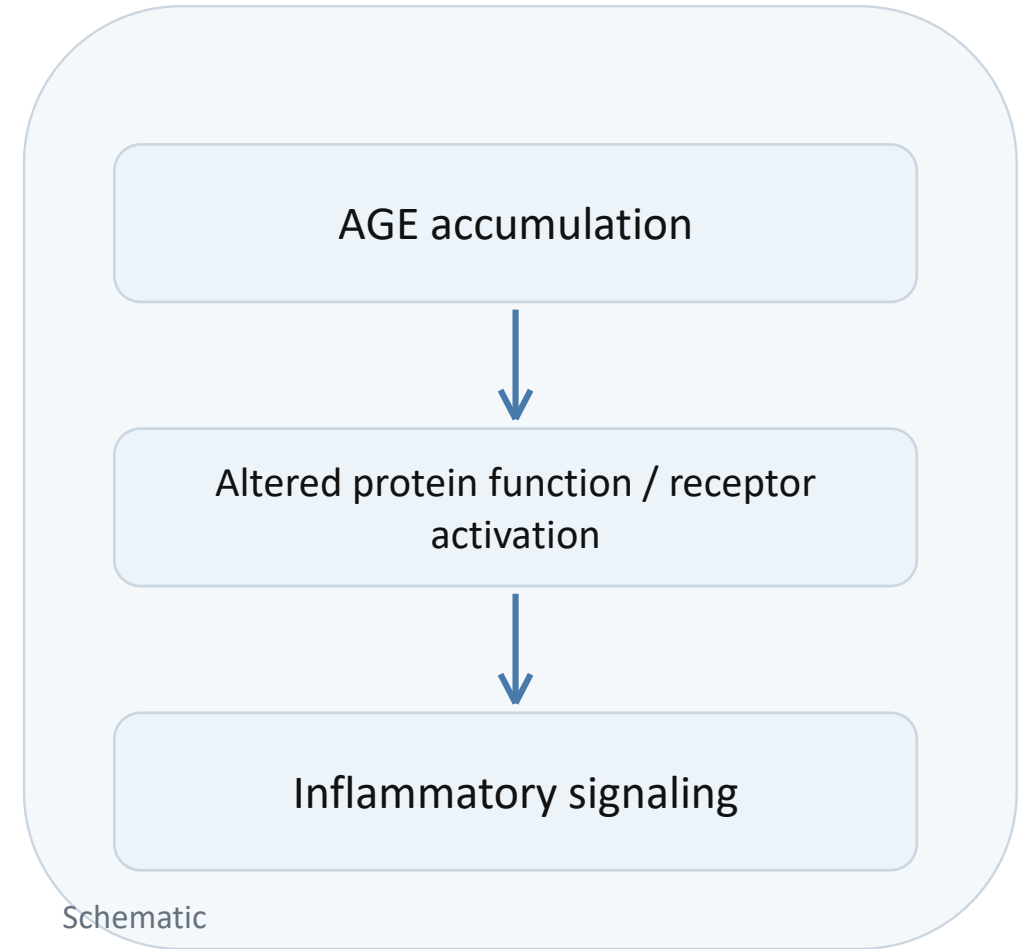


AGEs: Function and inflammatory signaling

AGE modification may interfere with normal protein activity.

AGE recognition by its receptor can activate inflammatory signaling.

This is one contributing pathway, not a complete explanation of neuropathy.

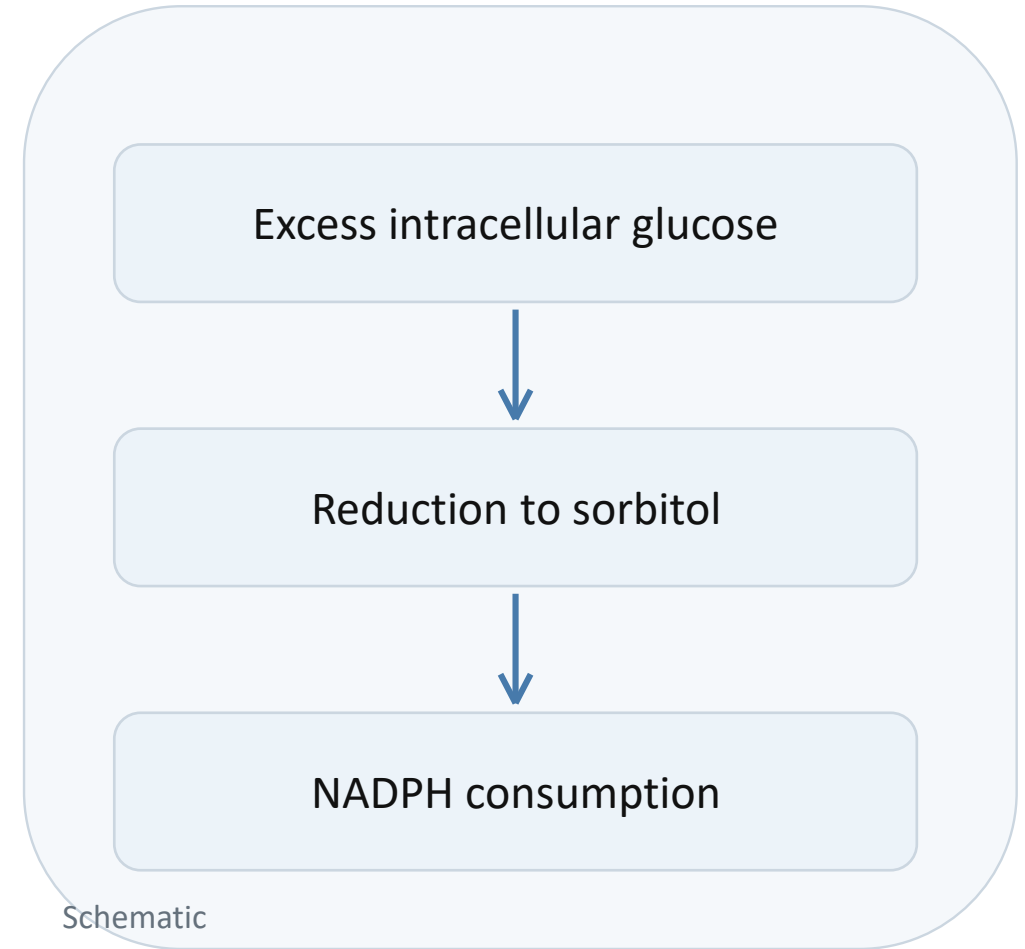


The polyol pathway diverts glucose

Within cells, excess glucose can be reduced to sorbitol.

This reaction consumes NADPH.

The pathway links persistent hyperglycemia to altered intracellular metabolism.

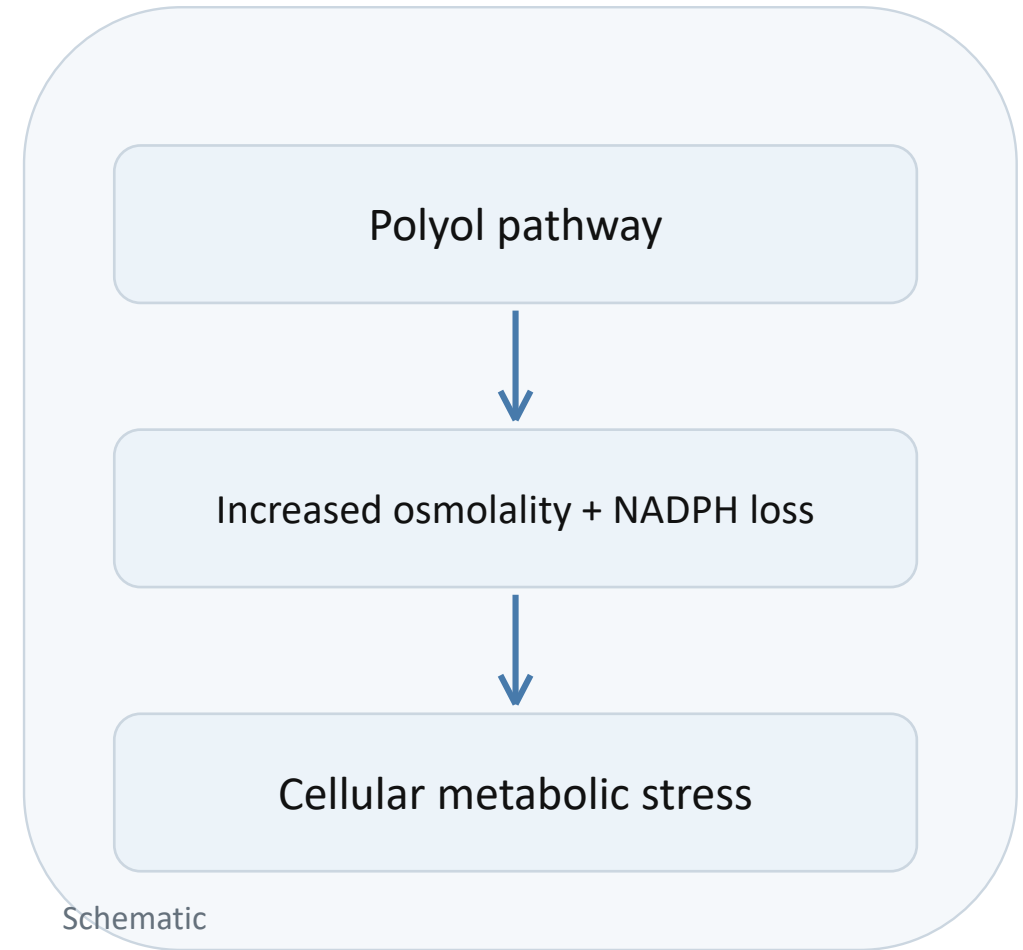


Polyol effects on cellular homeostasis

Sorbitol accumulation can increase intracellular osmolality.

NADPH depletion alters the cellular redox environment.

These changes add to other metabolic stresses affecting peripheral nerves.

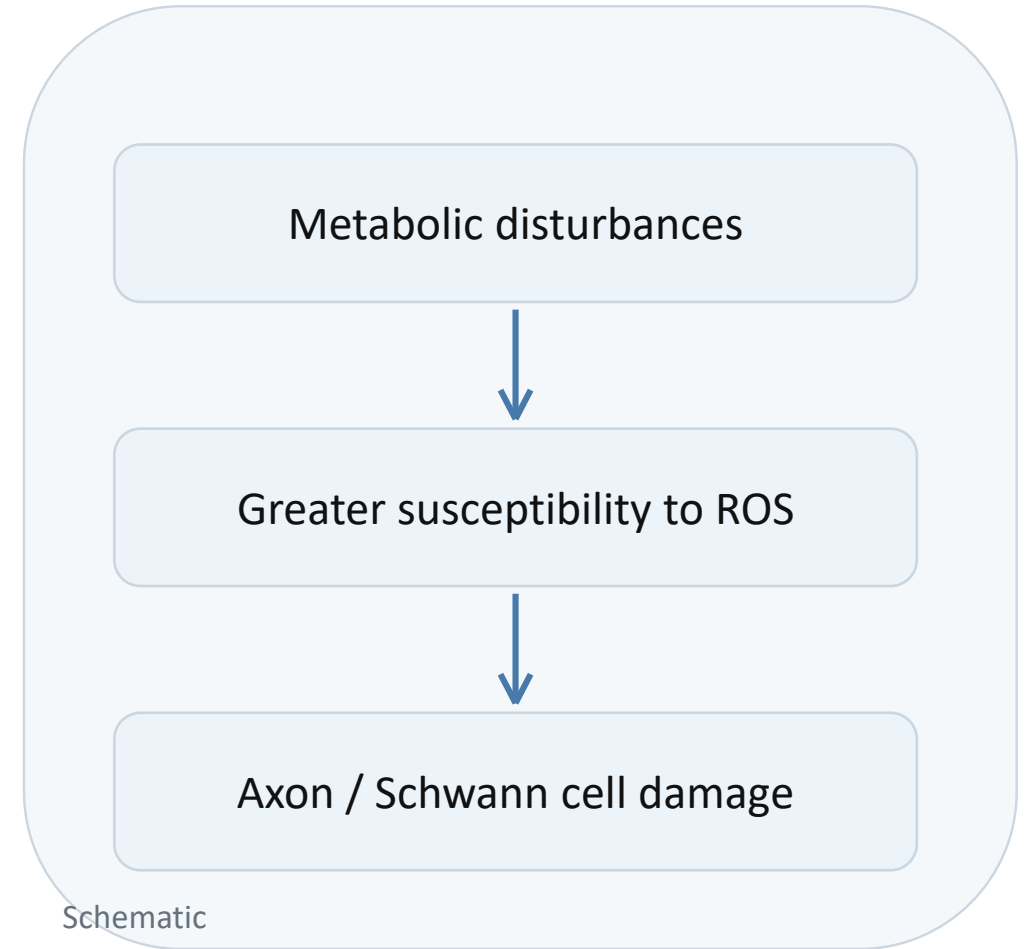


Oxidative injury connects metabolic pathways

Diabetes-associated metabolic disturbances increase susceptibility to reactive oxygen species.

Axons and Schwann cells may be injured through convergent metabolic stresses.

The source does not assign a single dominant molecular lesion.



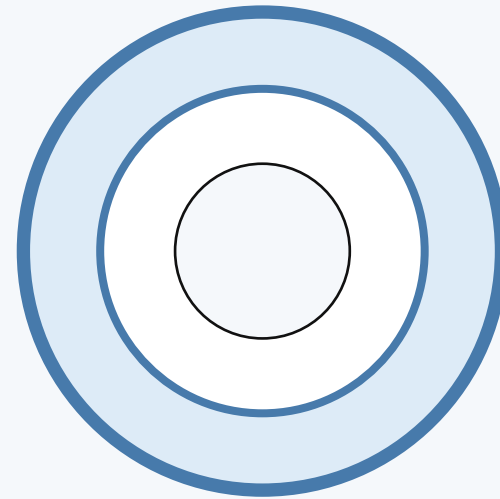
Chronic diabetes also injures nerve vessels

Hyperlipidemia and other metabolic alterations contribute to vascular disease.

Impaired microcirculation can produce ischemic nerve injury.

Metabolic and vascular pathways may act together.

Endoneurial arteriole — schematic



Thickened vessel wall

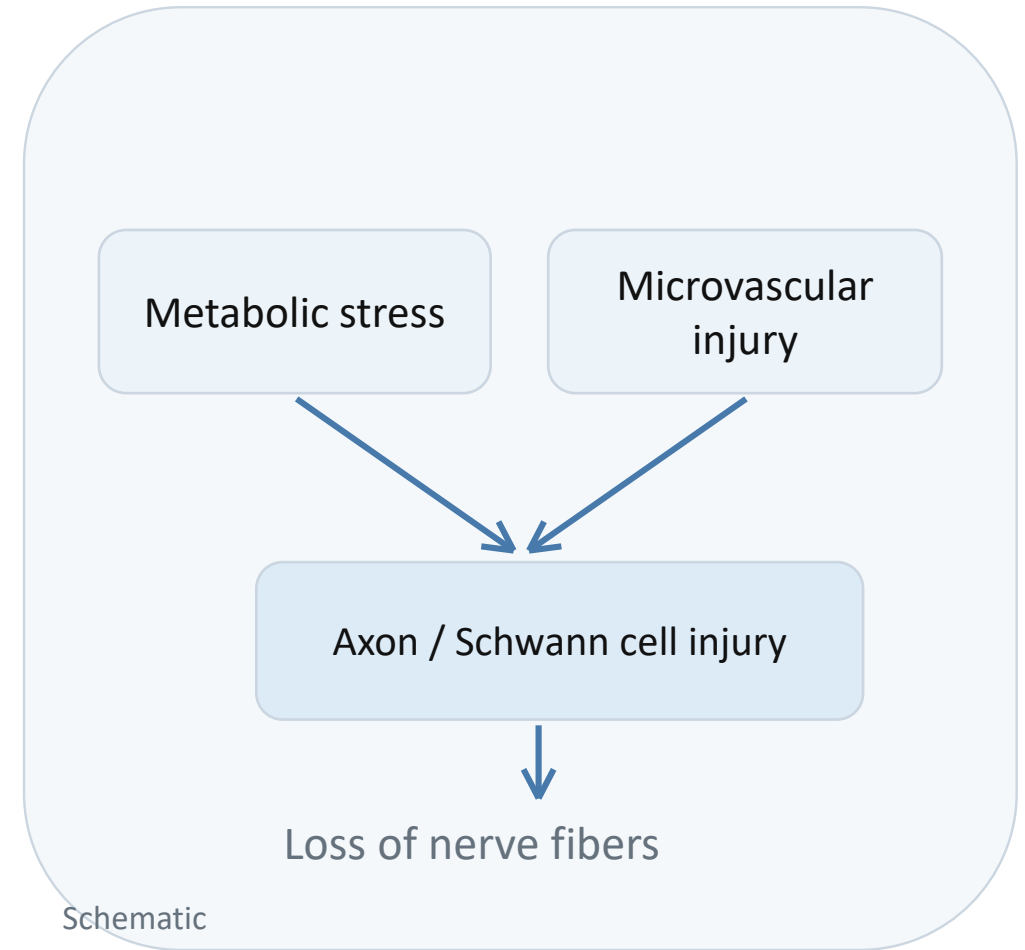
Schematic

Integrated pathogenesis of axonal loss

Hyperglycemia produces AGE- and polyol-associated stresses.

Vascular disease can reduce endoneurial perfusion.

Both streams converge on injury to axons and their supporting Schwann cells.



Relative vulnerability of fiber systems

Sensory axons are most prominently involved.

Autonomic axons are affected in a substantial subset of patients.

Motor axons are involved less often.

Relative involvement in diabetes

Sensory axons

Autonomic axons

Motor axons

Schematic

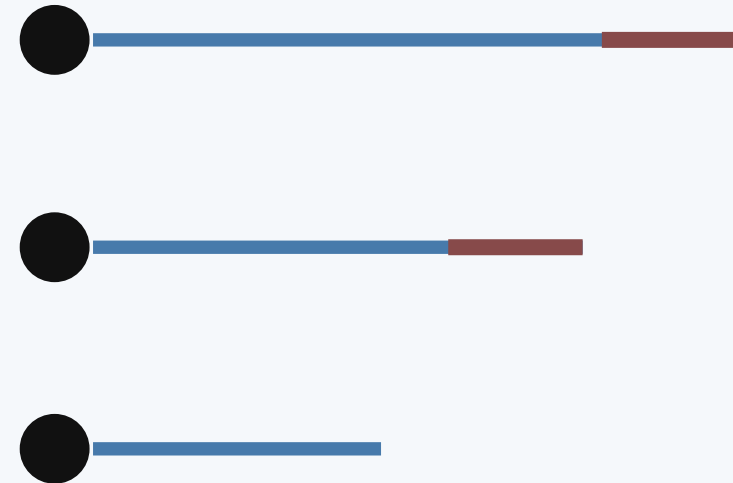
Length-dependent distal degeneration

Degeneration typically progresses backward from distal axonal regions.

Cell bodies are relatively preserved in the described diabetic phenotype.

Distal first involvement explains the ascending clinical distribution.

Long fibers show distal-first injury



Cell bodies

Distal fiber injury

Schematic

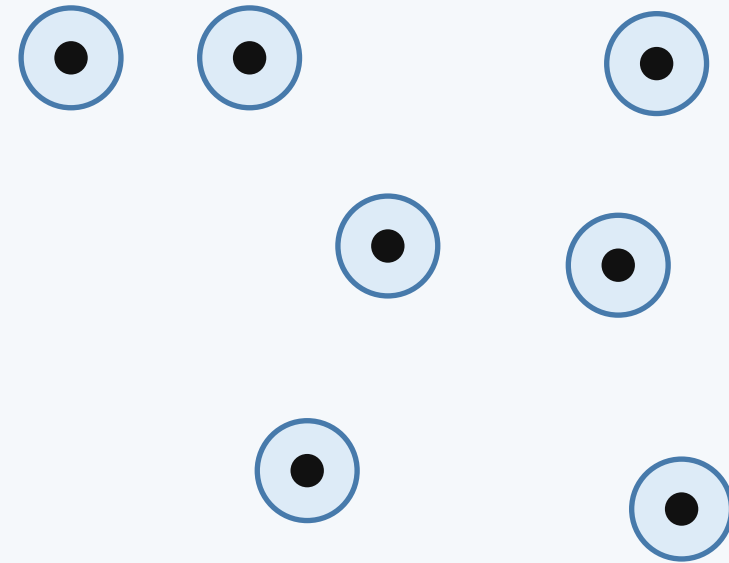
Nerve pathology: Axon loss dominates

Nerve biopsy generally shows reduced axon numbers.

The overall pattern is a predominantly axonal neuropathy.

Preserved fibers may coexist with axons at different stages of injury.

Nerve cross-section — schematic



Schematic

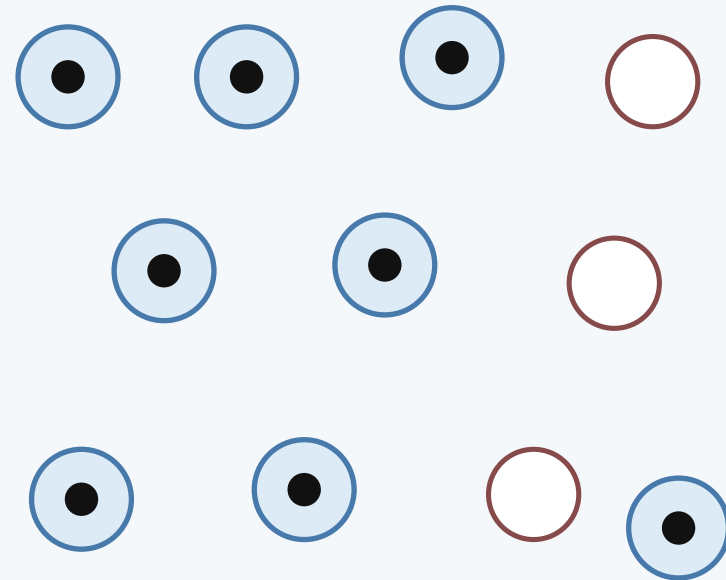
Ongoing degeneration leaves myelin debris

Degenerating axons are accompanied by deterioration of their myelin sheaths.

Degenerating myelin provides a morphologic clue to active injury.

This finding need not imply primary demyelinating disease.

Nerve cross-section — schematic



Schematic

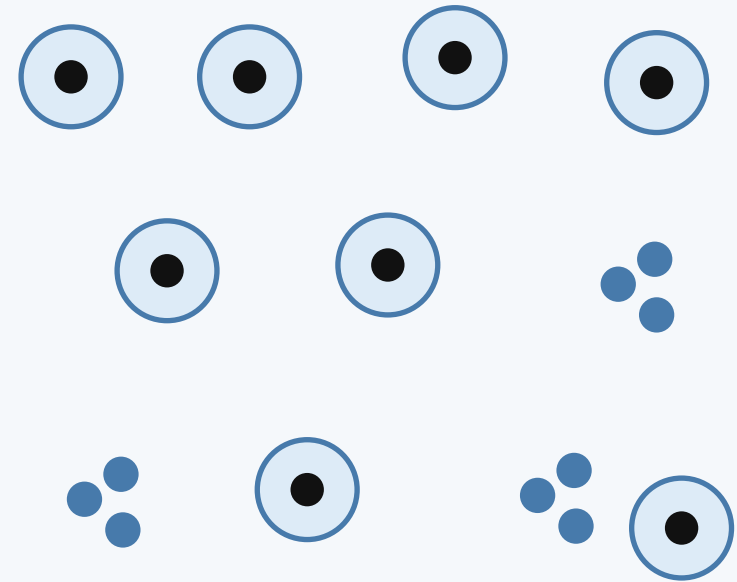
Regenerative clusters document attempted repair

Axonal sprouts may form clusters during regeneration.

Degeneration and regeneration can coexist in a chronically injured nerve.

The amount of repair does not necessarily match ongoing fiber loss.

Nerve cross-section — schematic



Schematic

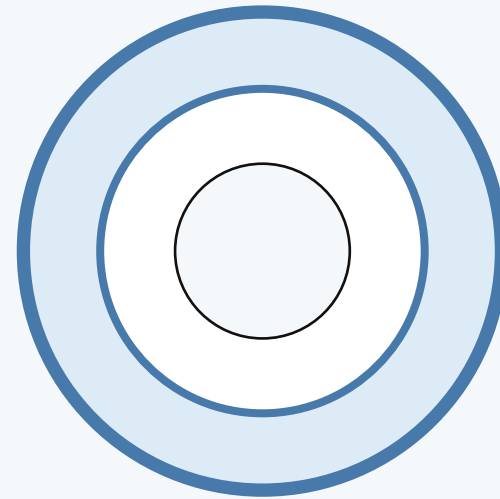
Small endoneurial vessels become thickened

Arterioles show prominent wall thickening and hyalinization.

These structural changes parallel the ischemic contribution to nerve injury.

The characteristic vessel alterations may accompany axonal depletion.

Endoneurial arteriole — schematic



Thickened vessel wall

Schematic

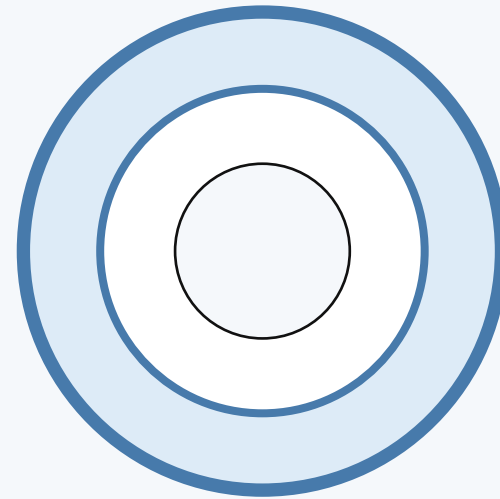
PAS staining highlights vascular injury

Endoneurial arteriole walls may stain intensely with periodic acid–Schiff.

Multiple basement-membrane layers may be seen.

These are microvascular findings within an axon-predominant neuropathy.

Endoneurial arteriole — schematic



Thickened vessel wall

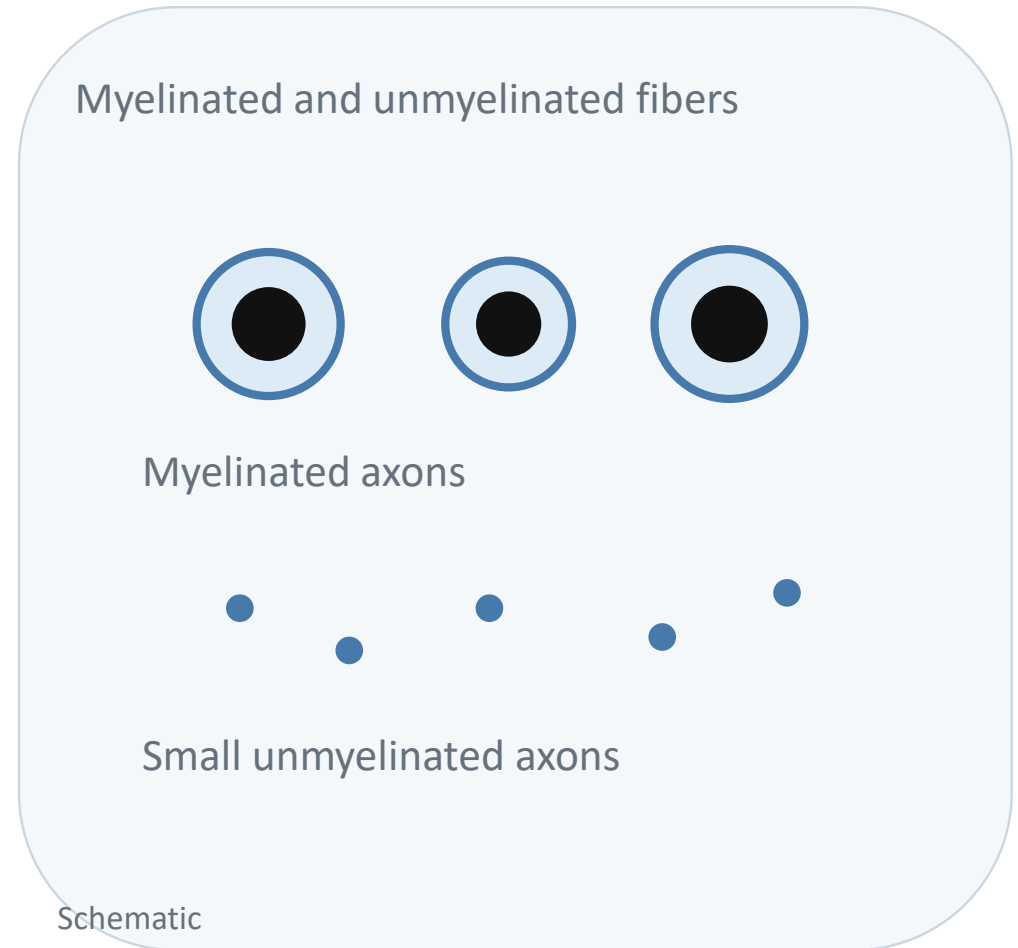
Schematic

Unmyelinated C-fiber loss matters

Small unmyelinated sensory fibers in skin may be extensively depleted.

Their loss correlates with clinical sensory symptoms.

Large myelinated-fiber pathology alone does not capture the whole phenotype.



Morphology: Read findings together

Compartment	Observed abnormality	Interpretation
Axons	Reduced fiber density	Predominant axonopathy
Myelin	Degenerating sheaths	Active axonal injury
Regeneration	Axonal clusters	Repair attempt
Endoneurial vessels	Thickened, hyalinized; PAS+	Microvascular pathology
Skin small fibers	C-fiber dropout	Sensory symptoms

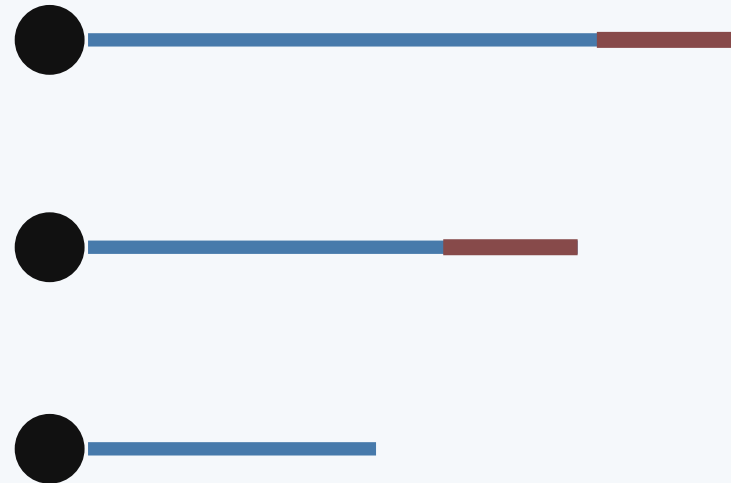
Why symptoms follow a stocking–glove map

Long sensory fibers innervating the feet are affected early.

Clinical loss ascends as axonal involvement extends to shorter fibers.

Hand symptoms typically become evident later in the length-dependent course.

Long fibers show distal-first injury



Cell bodies

Distal fiber injury

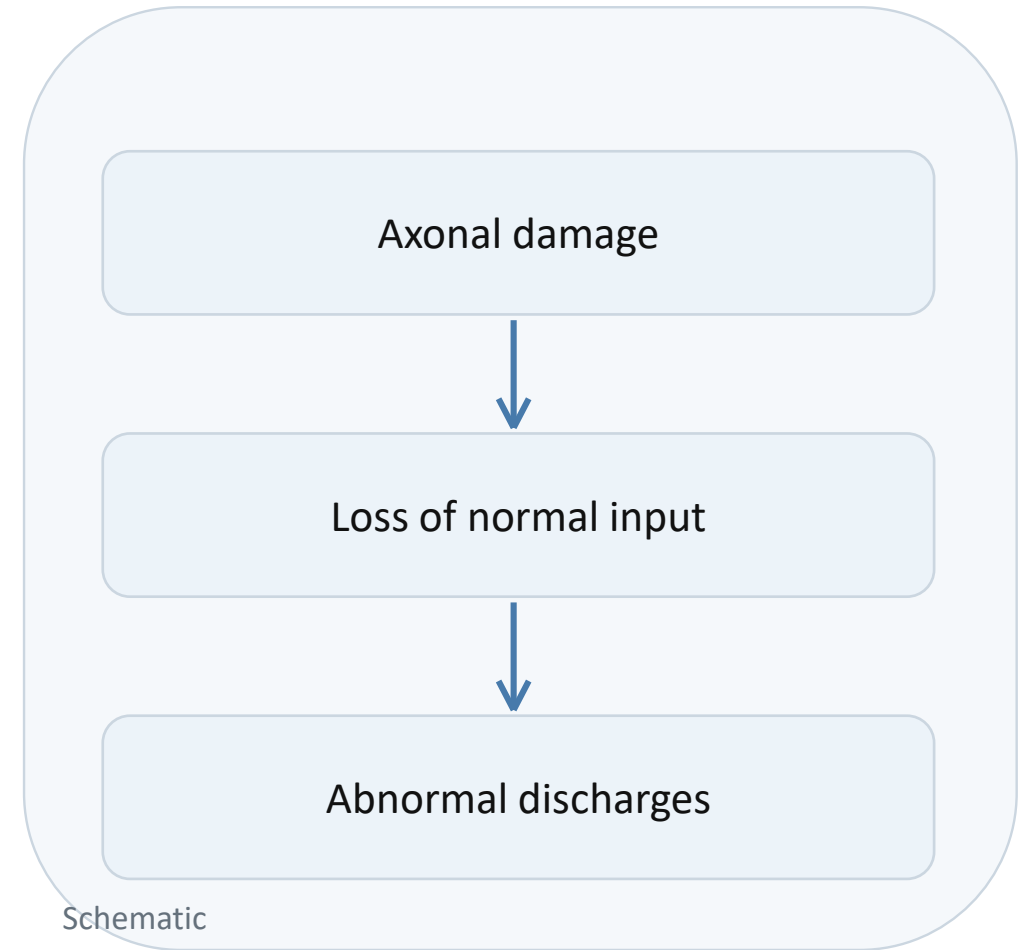
Schematic

Negative sensory symptoms

Numbness reflects loss of normal sensory function.

Reduced pain sensation diminishes protective feedback about injury.

Sensory loss can be functionally serious despite little reported discomfort.

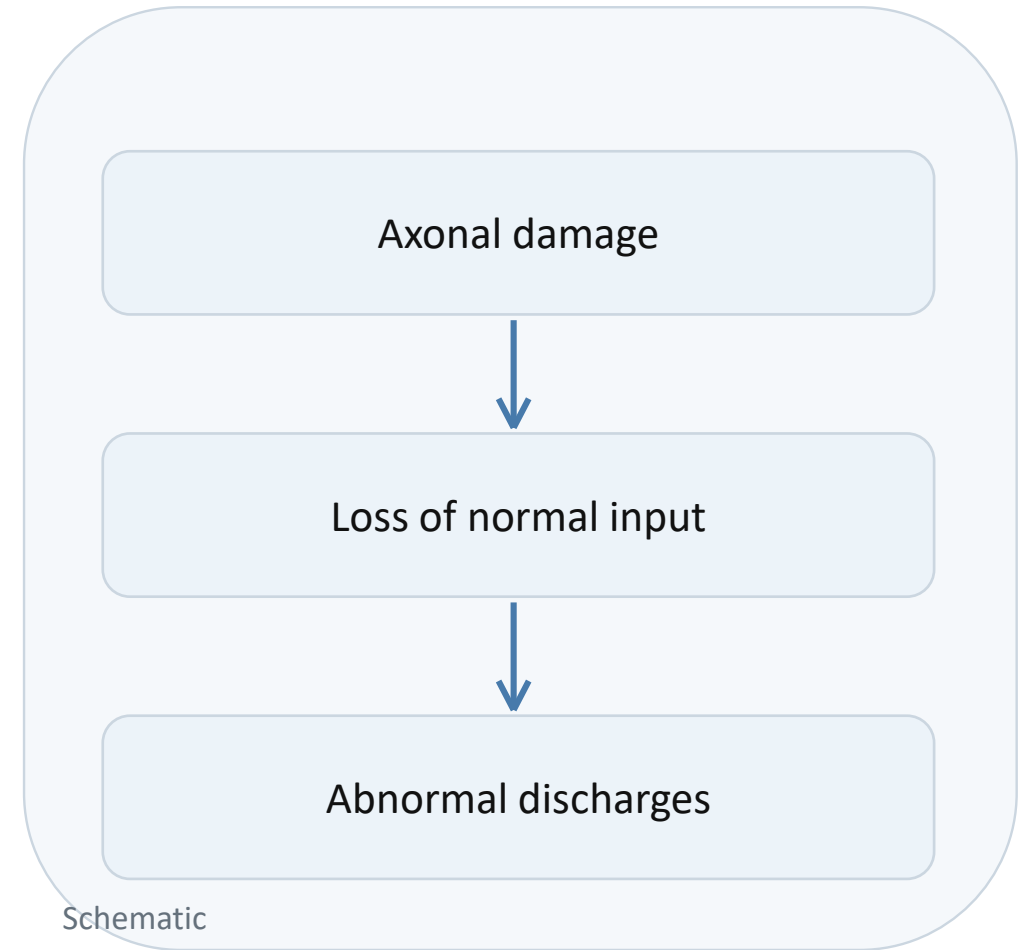


Positive sensory symptoms

Paresthesias are abnormal sensations such as tingling.

Dysesthesias are unpleasant abnormal sensations that may be painful.

Damaged nerves can generate abnormal discharges perceived as pain.

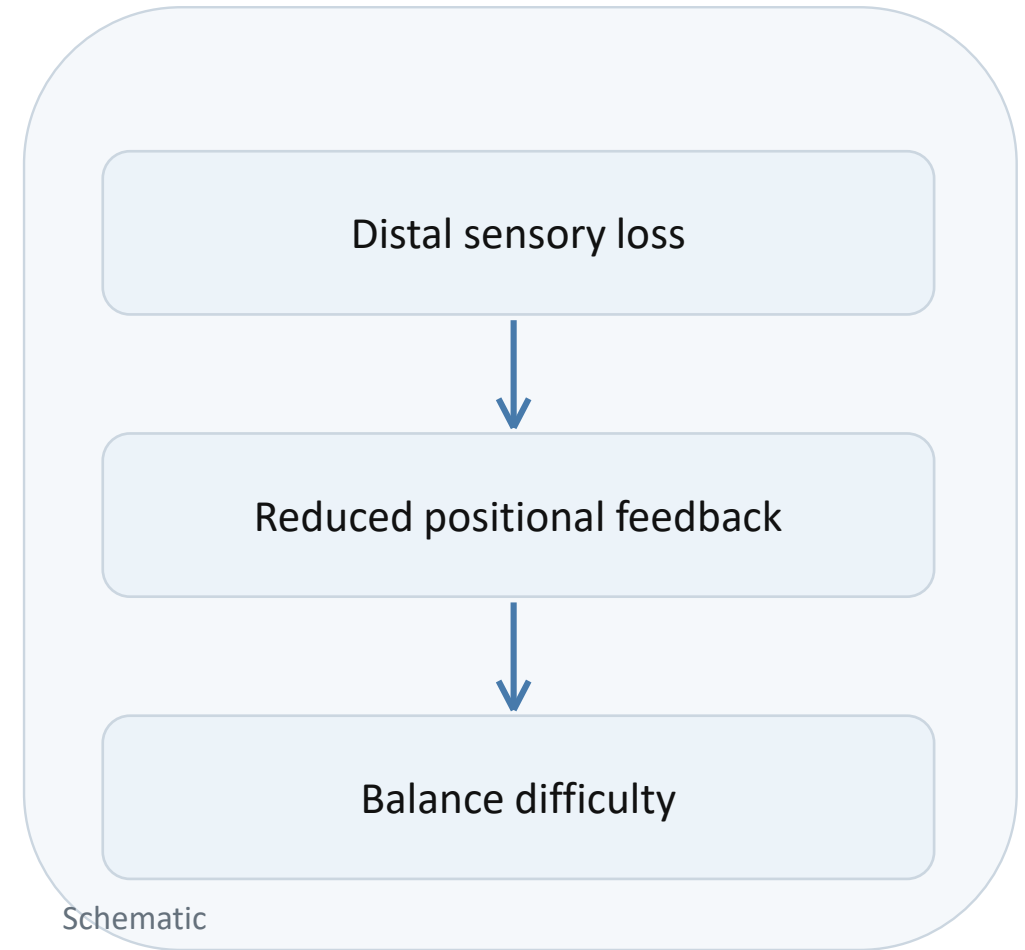


Loss of sensation affects balance

Distal sensory disturbance can impair the feedback used for stable posture.

Patients may report difficulty maintaining balance.

Balance difficulty should be interpreted with the accompanying sensory pattern.

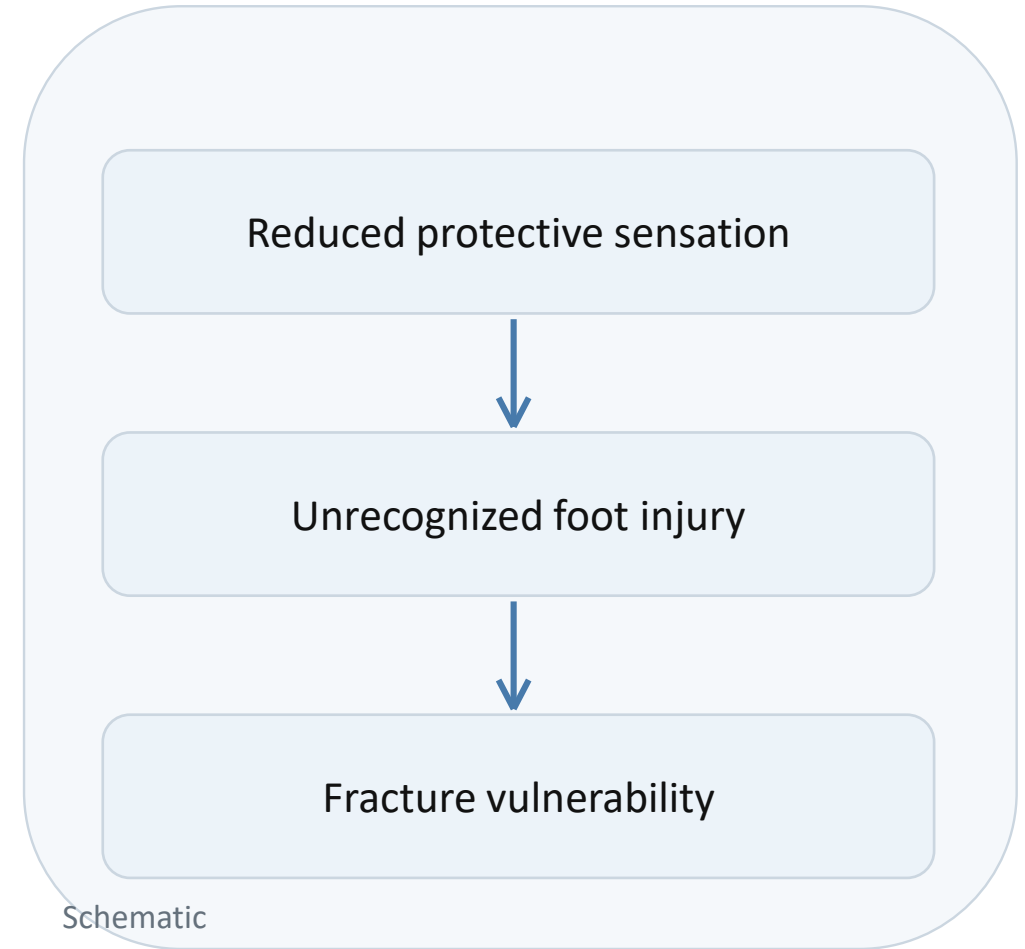


Skeletal injury is an important consequence

Diabetic peripheral neuropathy increases susceptibility to foot and ankle fractures.

Loss of protective sensation can allow injury to go unrecognized.

The nerve lesion has substantial morbidity beyond paresthesias.

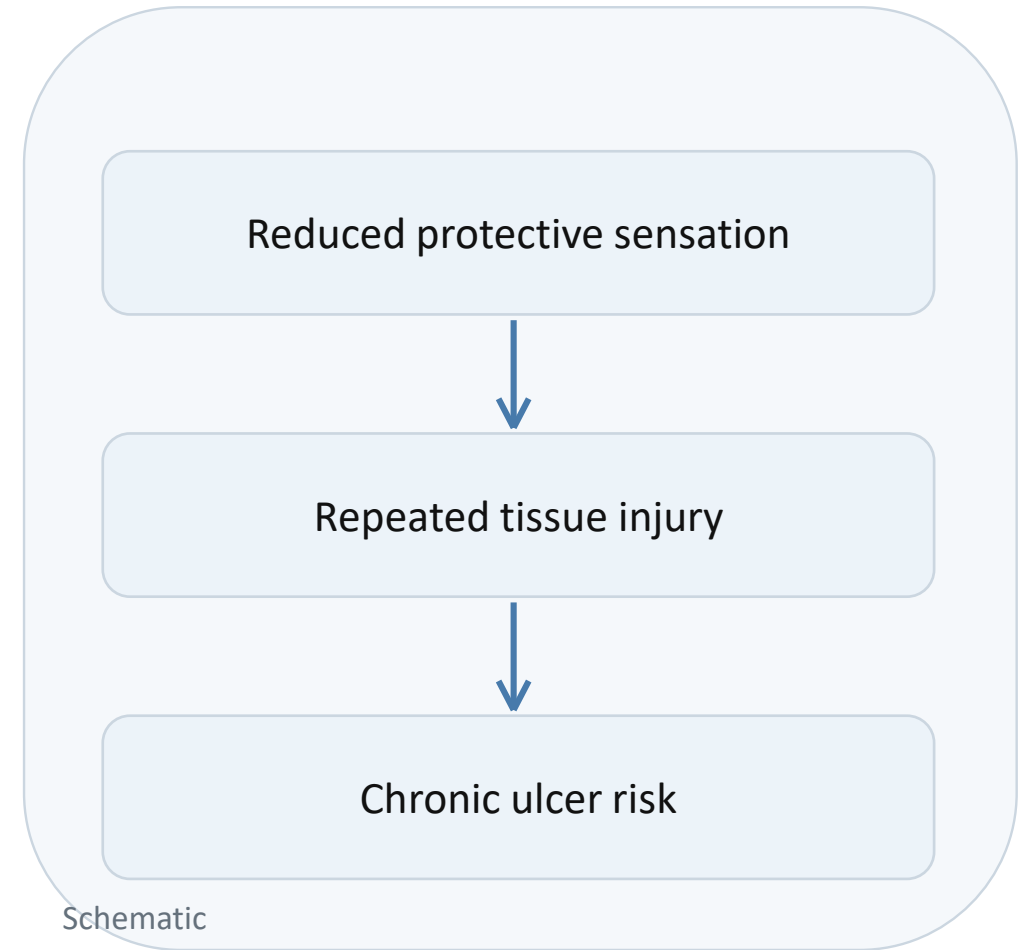


Chronic skin ulceration is consequential

Sensory loss increases vulnerability to repeated unrecognized tissue injury.

Chronic skin ulcers are a major manifestation associated with diabetic neuropathy.

Severe downstream consequences may culminate in amputation.

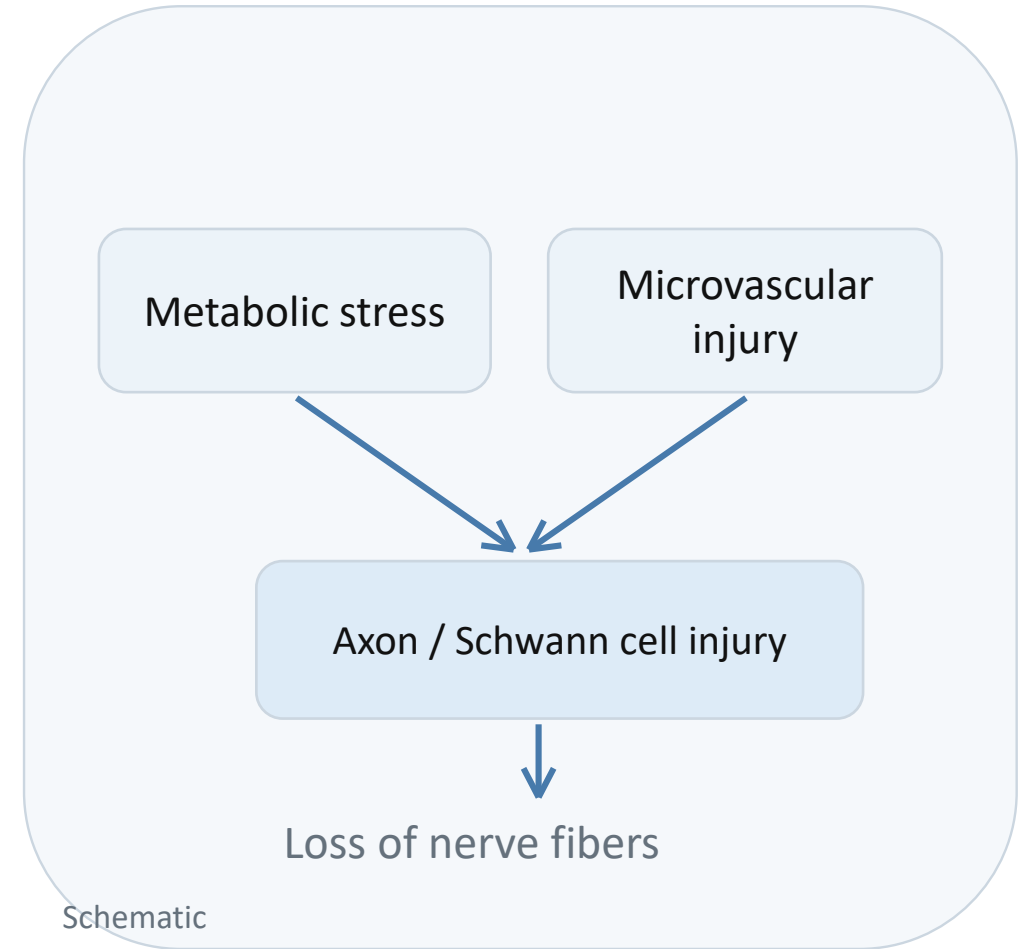


Clinical effect follows neural mechanism

Axonal loss reduces normal sensory signaling.

Abnormal discharges generate positive sensory symptoms.

Loss of protective sensation increases orthopedic and skin complications.



Autonomic neuropathy is common

Autonomic dysfunction in 20%–40% of individuals with diabetes.

It almost always accompanies distal sensorimotor polyneuropathy.

Its manifestations reflect dysfunction in involuntary neural control.

Relative involvement in diabetes

Sensory axons

Autonomic axons

Motor axons

Schematic

Autonomic feature: Postural hypotension

The autonomic nervous system contributes to postural circulatory adjustment.

Autonomic dysfunction can produce postural hypotension.

This is part of a broader diabetic neuropathy phenotype.

Relative involvement in diabetes

Sensory axons

Autonomic axons

Motor axons

Schematic

Autonomic feature: Bladder emptying

Impaired autonomic control can cause incomplete bladder emptying.

Urinary retention predisposes to recurrent infections.

A urinary complaint may therefore reflect a peripheral nerve complication.

Relative involvement in diabetes

Sensory axons

Autonomic axons

Motor axons

Schematic

Autonomic feature: Sexual dysfunction

Sexual dysfunction is among the recognized diabetic autonomic manifestations.

It may coexist with distal sensorimotor impairment.

This symptom extends neuropathy assessment beyond limb examination.

Relative involvement in diabetes

Sensory axons

Autonomic axons

Motor axons

Schematic

Autonomic and somatic disease coexist

Somatic sensory complaints may lead the presentation.

Autonomic disturbances may be present concurrently.

The two should not be treated as mutually exclusive phenotypes.

Relative involvement in diabetes

Sensory axons

Autonomic axons

Motor axons

Schematic

Diabetes can also cause focal neuropathy

Some patients develop asymmetric rather than distal symmetric disease.

Examples include mononeuropathy, cranial neuropathy, and radiculoplexus neuropathy.

The focal patterns are especially noted in older patients with long-standing diabetes.

Anatomic / functional patterns

Distal symmetric

Focal nerve

Plexus / roots

Autonomic

Schematic

Mononeuropathy has a restricted territory

The neurologic deficit follows the distribution of one affected peripheral nerve.

This differs from a symmetric length-dependent polyneuropathy.

Diabetes is among the disorders that may produce this focal phenotype.

Anatomic / functional patterns

Distal symmetric

Focal nerve

Plexus / roots

Autonomic

Schematic

Cranial neuropathy is another pattern

A cranial nerve deficit may occur in diabetes-associated peripheral neuropathy.

The distribution reflects the involved nerve, not a stocking–glove gradient.

An asymmetric presentation should not be forced into the common distal pattern.

Anatomic / functional patterns

Distal symmetric

Focal nerve

Plexus / roots

Autonomic

Schematic

Radiculoplexus neuropathy is often painful

This disorder involves brachial or lumbosacral plexus distributions.

The onset may be acute and painful, with asymmetry.

It often follows a monophasic course and may improve over months.

Anatomic / functional patterns

Distal symmetric

Focal nerve

Plexus / roots

Autonomic

Schematic

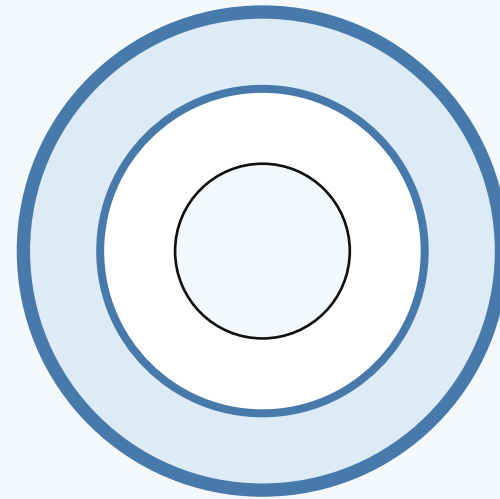
Microvascular involvement: A hypothesis

The source suggests microvascular disease may underlie asymmetric diabetic manifestations.

The proposed contribution differs from a proven single-cause explanation.

The mechanisms of diabetic neuropathy remain incompletely defined.

Endoneurial arteriole — schematic



Thickened vessel wall

Schematic

Compare common diabetic presentations

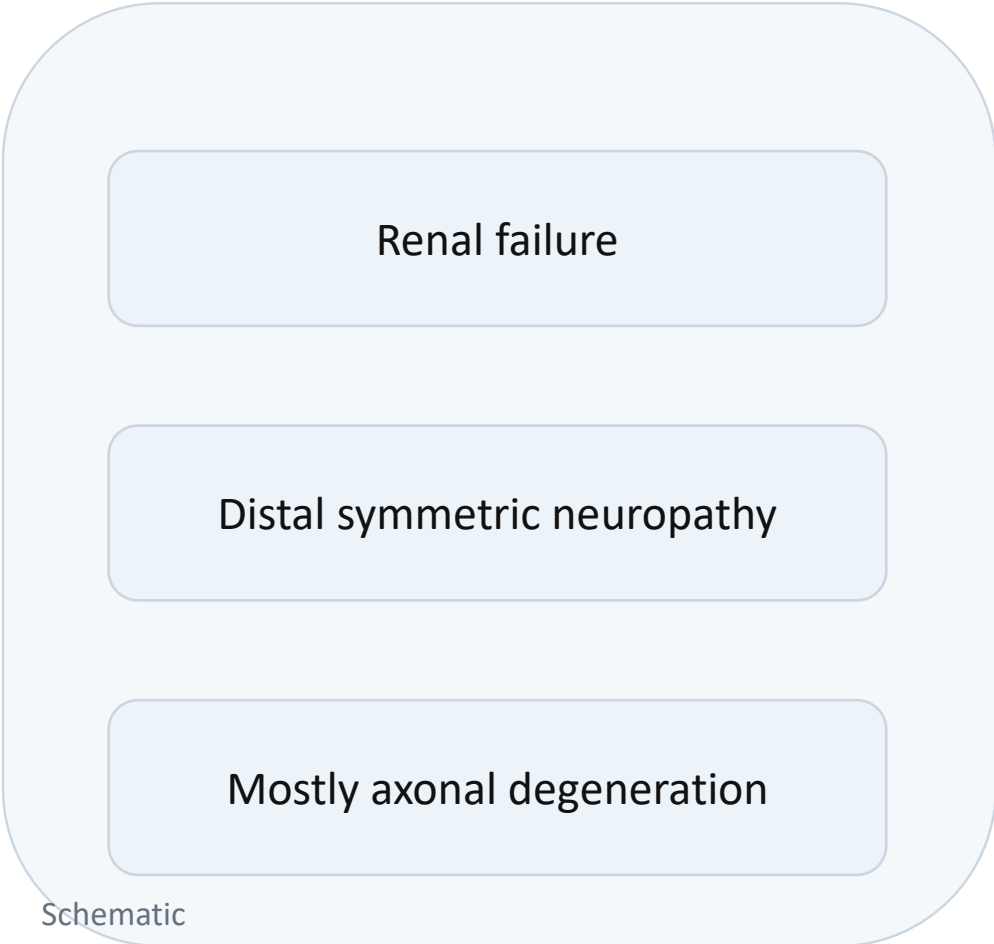
Feature	Distal symmetric	Autonomic	Asymmetric / focal
Distribution	Length-dependent limbs	Visceral / vascular control	One nerve or plexus territory
Dominant effects	Numbness; pain; balance	Postural, bladder, sexual	Focal deficits; plexus pain
Time course	Usually progressive	Often coexisting	Plexus may be monophasic
Pathology clue	Axonal loss	Autonomic axons	Possible microvascular role

Uremic neuropathy: Renal failure context

Peripheral neuropathy is common in people with renal failure.

The typical pattern is distal and symmetric.

Individuals may be asymptomatic despite the presence of neuropathy.



Renal failure

Distal symmetric neuropathy

Mostly axonal degeneration

Schematic

Uremic neuropathy: Clinical signs

Muscle cramps may be a presenting symptom.

Distal dysesthesias reflect sensory nerve involvement.

Deep tendon reflexes may be diminished.

Muscle cramps

Distal dysesthesias

Reduced tendon reflexes

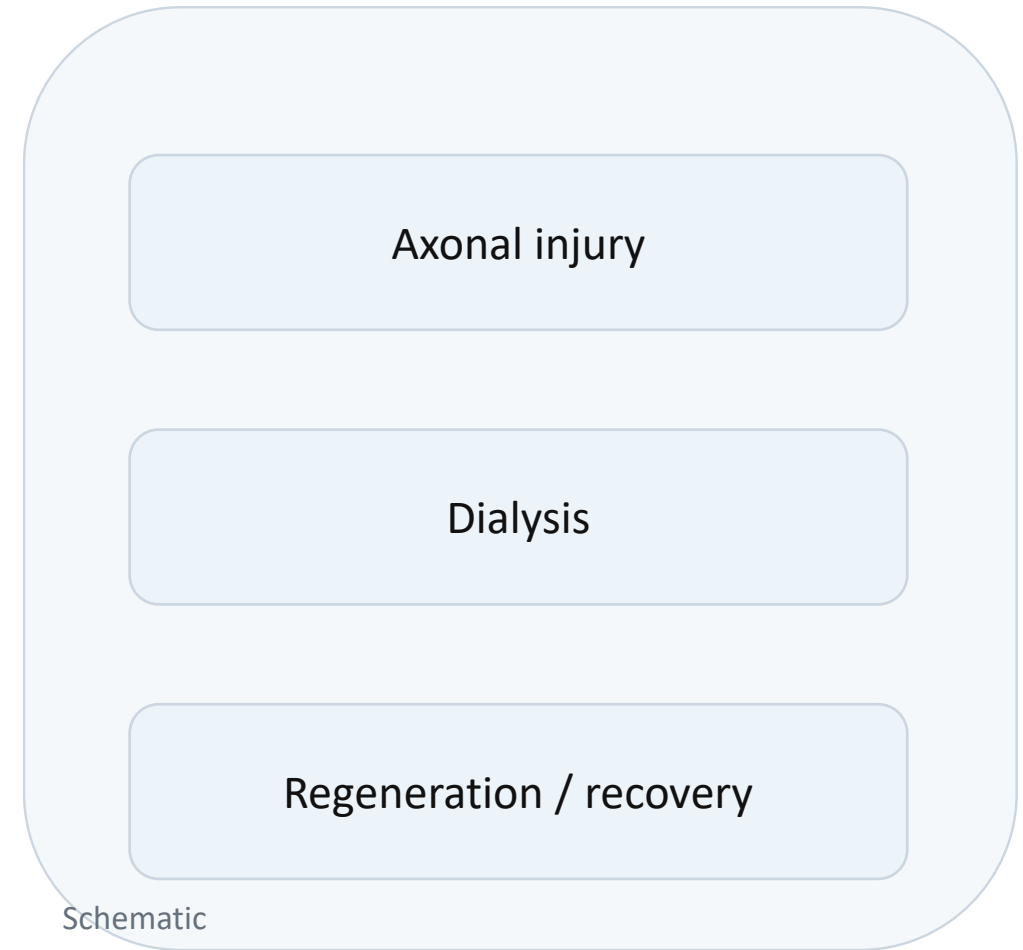
Schematic

Uremia: Axonal injury and possible recovery

Axonal degeneration is the primary morphologic event.

Secondary demyelination may occasionally accompany axonal damage.

Regeneration and recovery are common after dialysis.

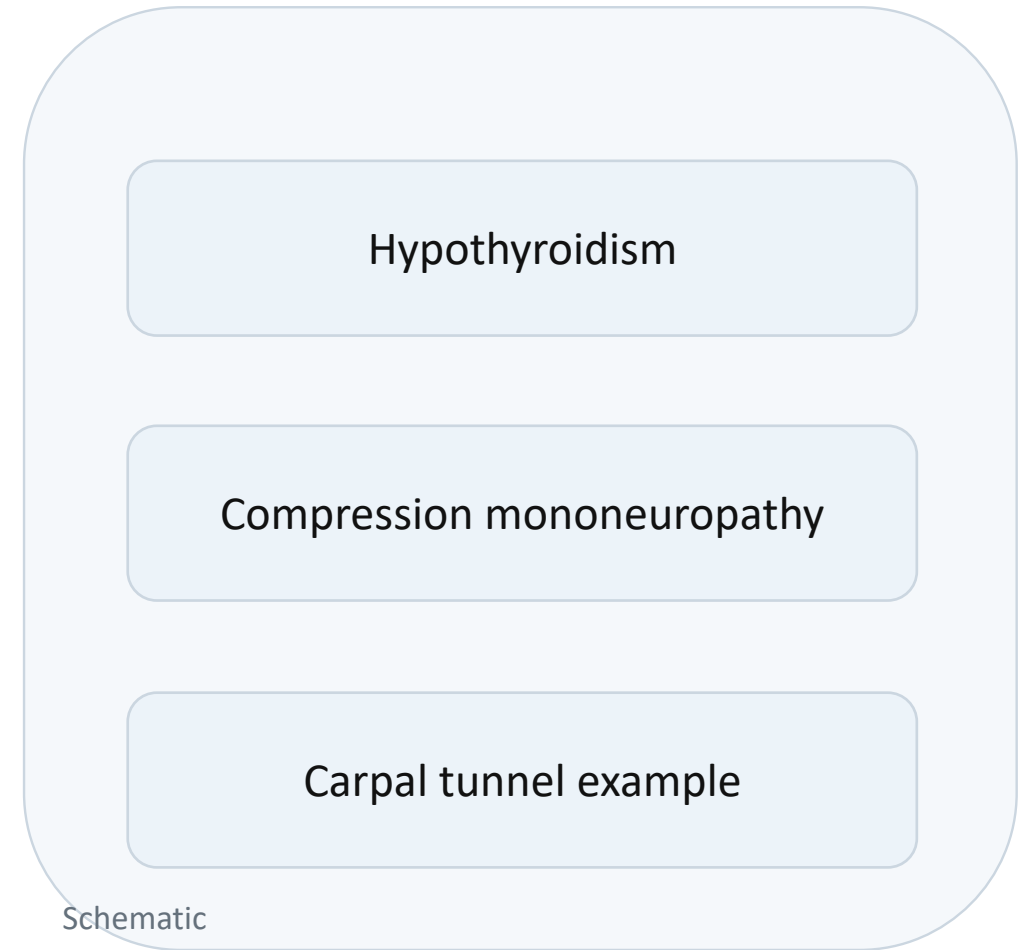


Hypothyroidism may cause entrapment

Compression mononeuropathies may occur in hypothyroidism.

Carpal tunnel syndrome is a characteristic example cited.

A focal distribution contrasts with length-dependent polyneuropathy.

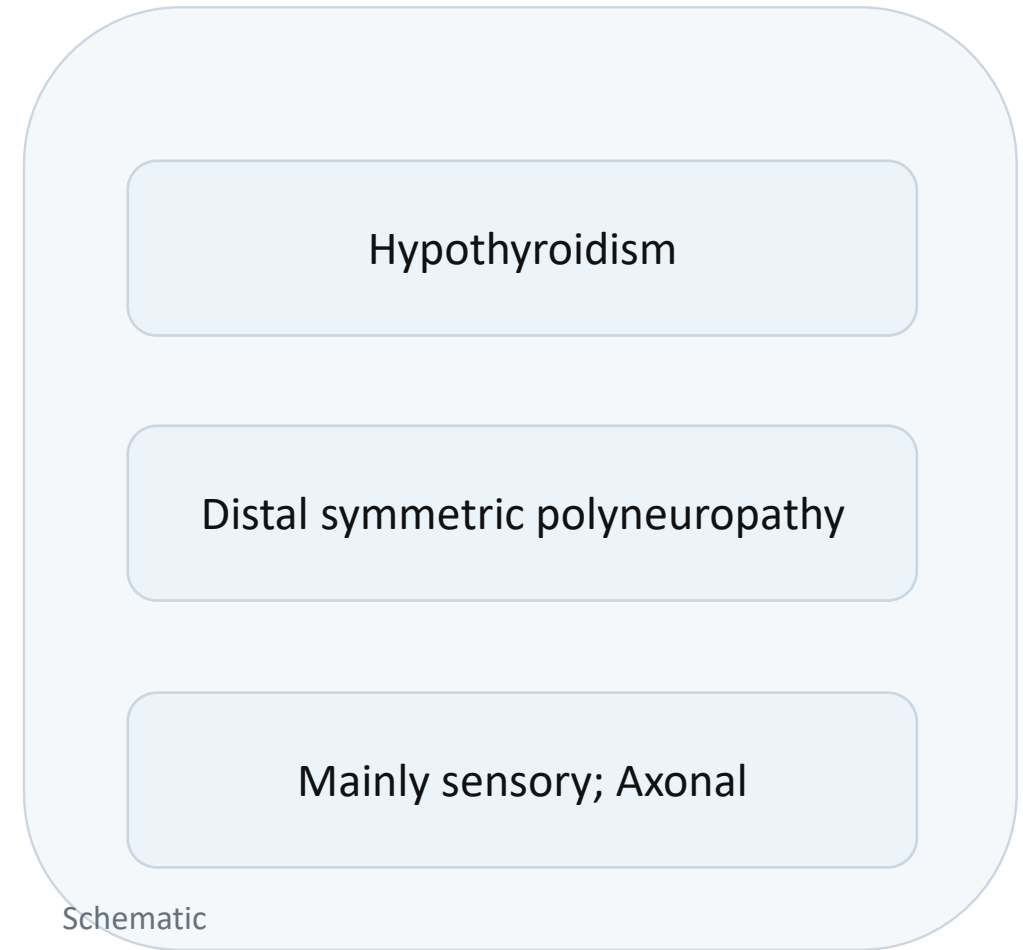


Hypothyroidism may also cause polyneuropathy

A distal symmetric neuropathy can develop with thyroid hypofunction.

Sensory impairment is usually predominant.

The pathologic pattern is described as axonal.

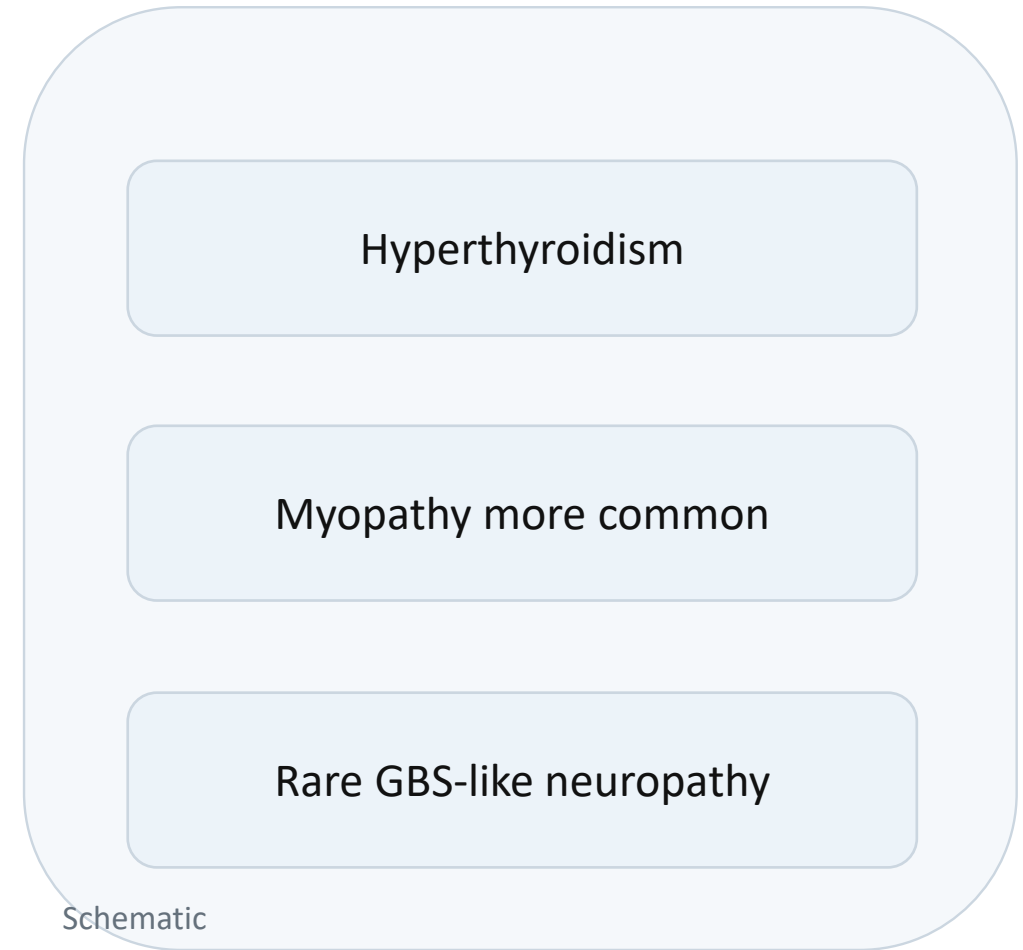


Hyperthyroidism: Uncommon nerve phenotype

Hyperthyroidism is much more often associated with myopathy.

Rare peripheral neuropathies can resemble Guillain–Barré syndrome.

The resemblance is a clinical description, not proof of an identical cause.

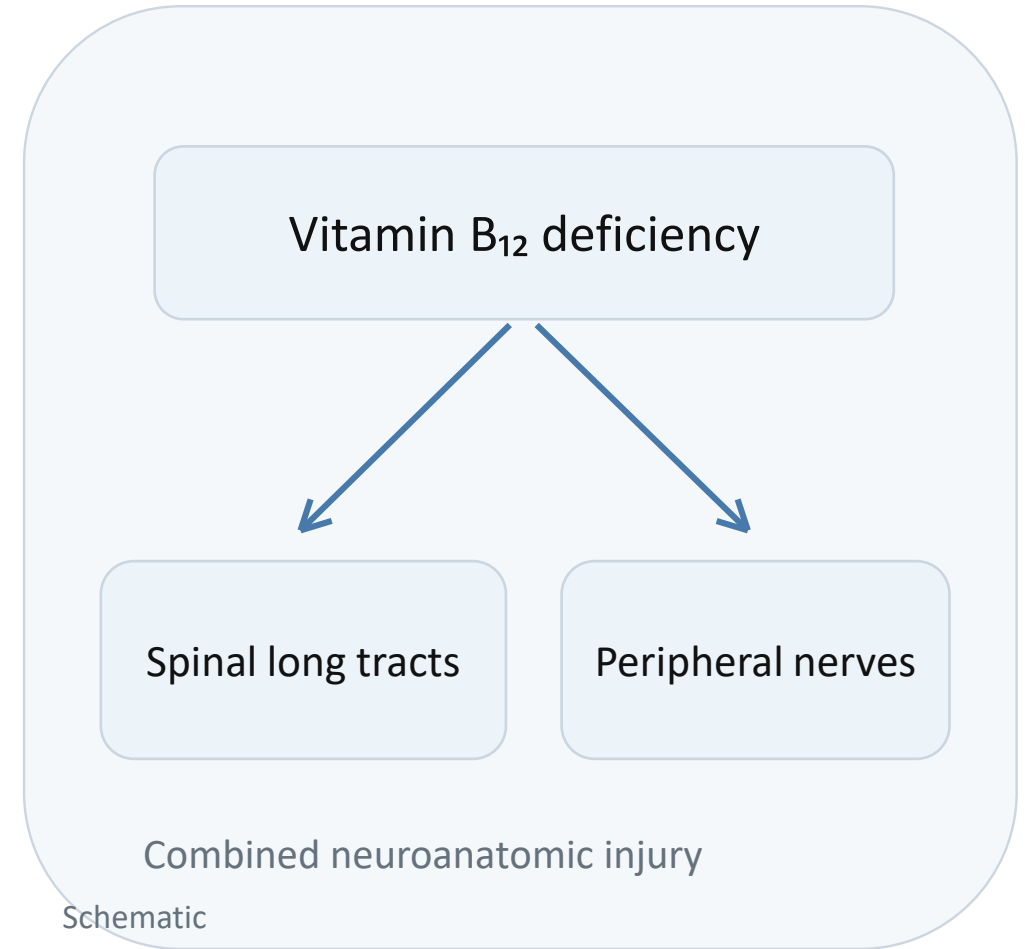


Vitamin B₁₂ deficiency involves two sites

Peripheral nerves can be damaged in vitamin B₁₂ deficiency.

The classic lesion is subacute combined degeneration involving spinal long tracts.

The source frames this disorder as combined central and peripheral involvement.

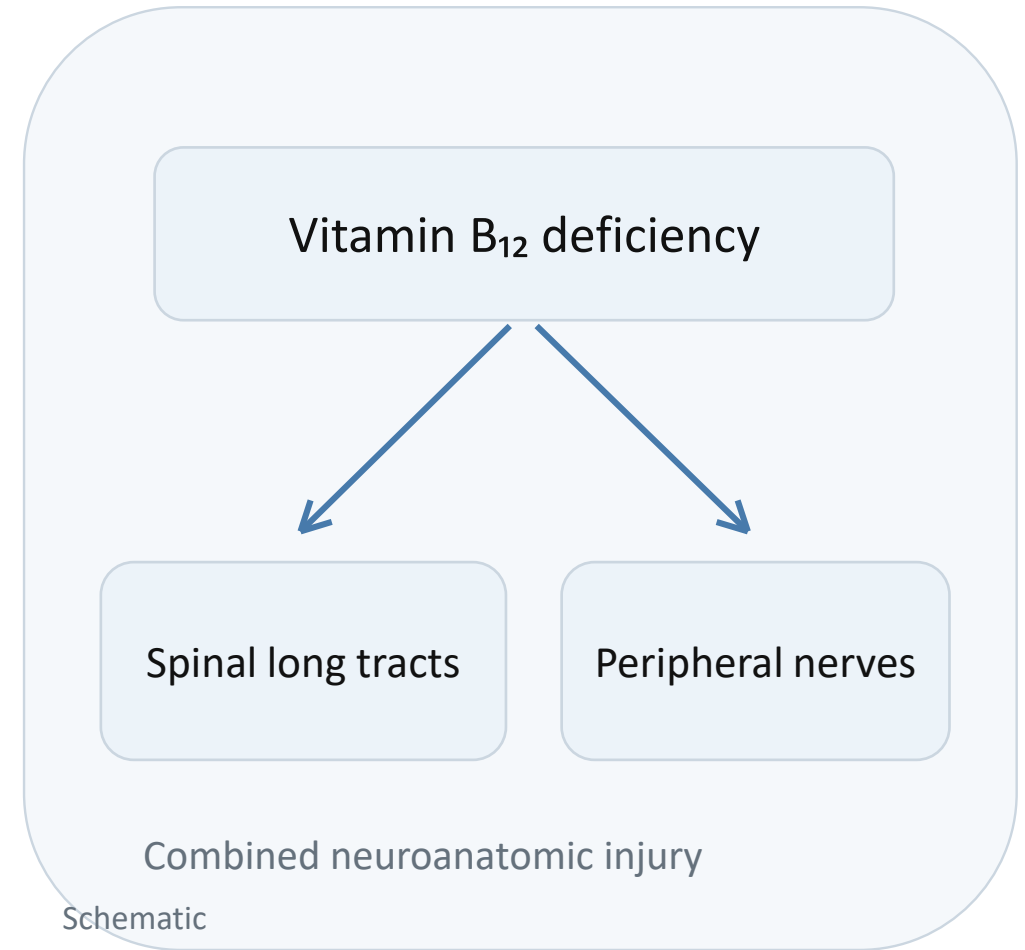


B₁₂ deficiency is not merely distal axonopathy

Spinal cord long-tract pathology is central to the classic phenotype.

Peripheral nerve damage can occur alongside spinal cord injury.

This broader neuroanatomic scope separates it from an isolated distal neuropathy.



Other deficiencies: Thiamine and pyridoxine

Vitamin B₁ (thiamine) deficiency is associated with peripheral neuropathy.

Vitamin B₆ (pyridoxine) deficiency is also listed among nutritional causes.

The supplied section does not specify separate morphology or diagnostic thresholds.

Thiamine (B₁)

Pyridoxine (B₆)

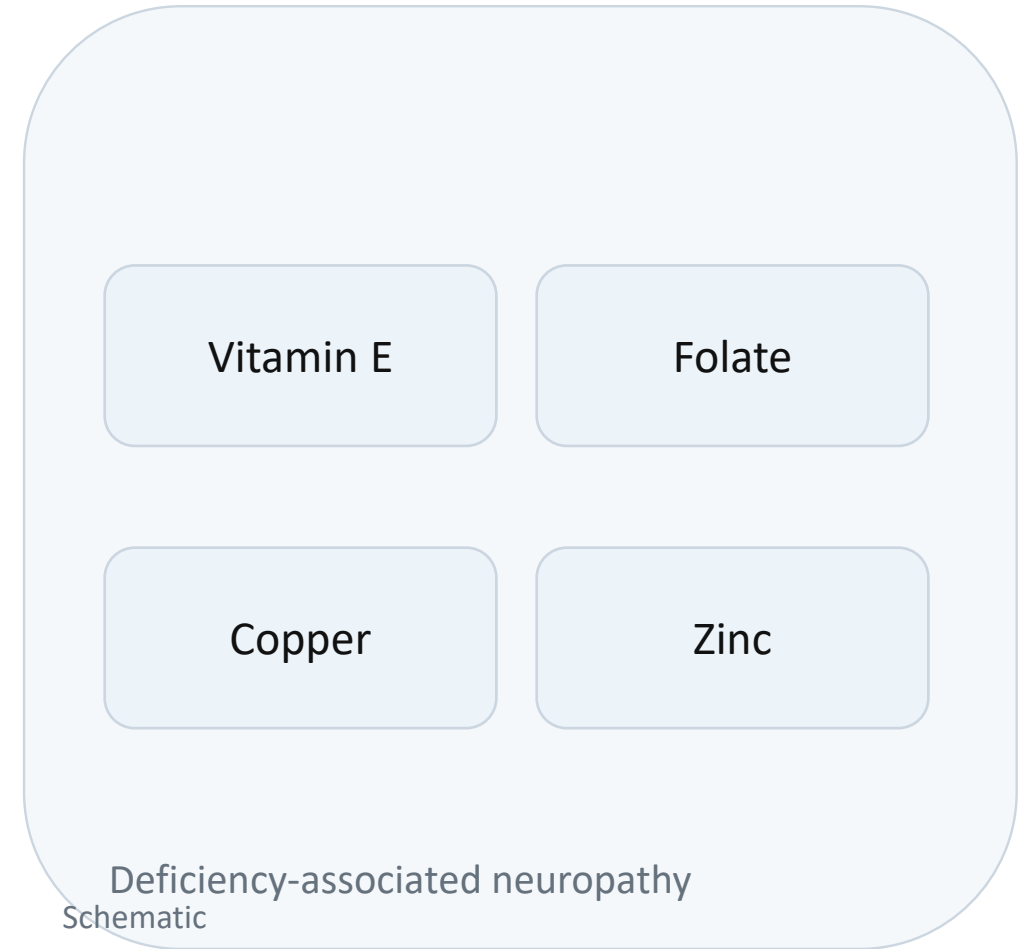
Deficiency-associated neuropathy
Schematic

Other deficiencies: E, folate, copper, zinc

Vitamin E (tocopherol) deficiency is associated with neuropathy.

Folate, copper, and zinc deficiency are also named in the source.

The excerpt does not provide a unique clinical phenotype for each deficiency.



Other etiologies at a glance

Condition	Pattern emphasized by Robbins	Characteristic association
Uremia	Distal symmetric; mainly axonal	Cramps; dysesthesia; reduced reflexes
Hypothyroidism	Focal compression or distal sensory axonal	Carpal tunnel possible
Hyperthyroidism	Rare GBS-like neuropathy	Myopathy more common
Vitamin B ₁₂ deficiency	Peripheral + spinal long-tract	Subacute combined degeneration
Other deficiencies	Peripheral neuropathy association	B ₁ , B ₆ , E, folate, Cu, Zn

Predominant lesions across etiologies

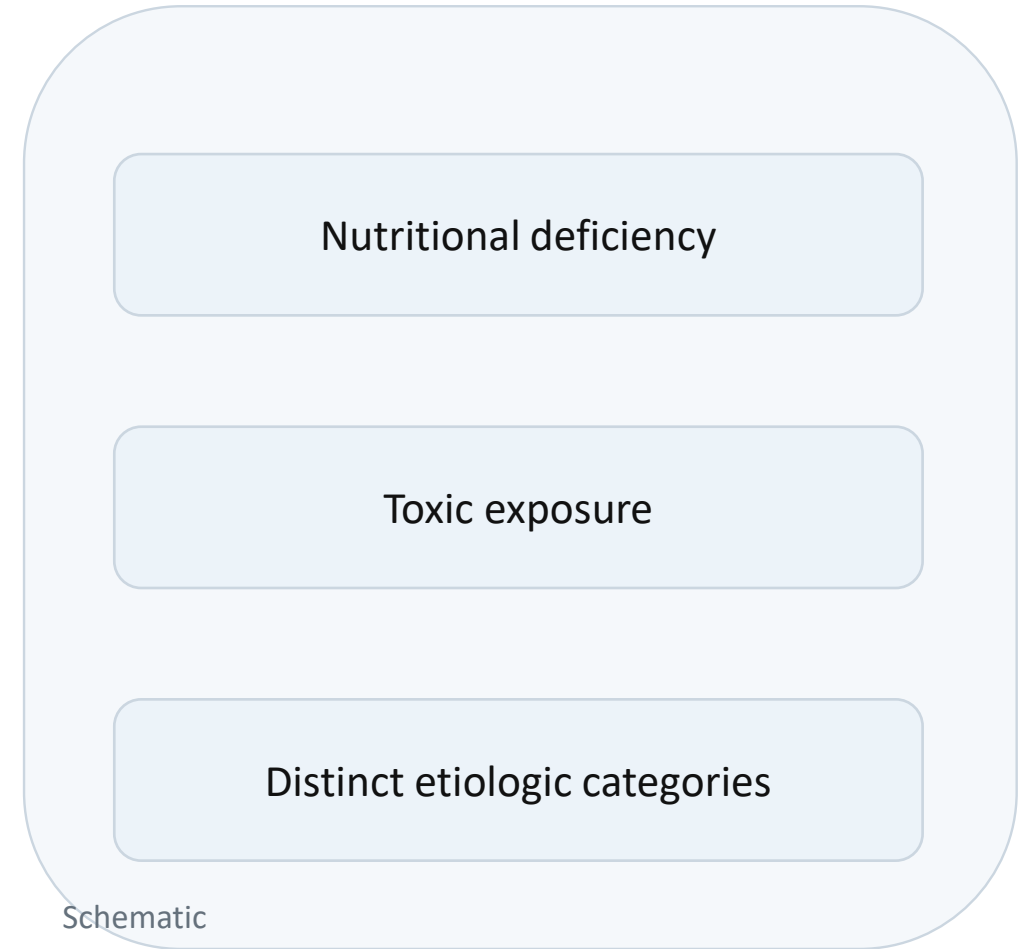
Etiology	Primary pattern in Robbins table 27.1
Diabetes	Axonal degeneration / regeneration
Uremia	Axonal degeneration / regeneration
Hypothyroidism	Axonal degeneration / regeneration
Nutritional deficiency (selected)	Axonal degeneration / regeneration
Vitamin B ₁₂ deficiency	Mixed axonal degeneration and demyelination

Do not conflate toxicity and deficiency

Alcohol can damage peripheral nerves independently of nutritional deficiency.

Heavy metals and organic solvents are recognized toxic causes.

Toxic neuropathy is a neighboring etiologic category, not a subtype of nutrient deficiency.



A pathology-centered reasoning sequence

Locate the distribution: Distal symmetric, focal, or plexus-like.

Identify predominant sensory, autonomic, or motor involvement.

Relate axonal or mixed pathology to the clinical setting without overclaiming cause.

Distribution and fiber type

Lesion pattern

Underlying systemic disease

Schematic

Teaching case: Distal diabetic sensory loss

ILLUSTRATIVE PRESENTATION

A person with long-standing diabetes has gradually ascending, symmetric foot numbness and reduced pain sensation.

Which lesion pattern best links distribution to pathology?

Interpretation

Length-dependent distal axonal degeneration; Sensory fibers are affected most prominently.

The prolonged “dying-back” process accounts for distal onset and proximal progression.

Teaching case: Autonomic involvement

ILLUSTRATIVE PRESENTATION

A patient with diabetic distal neuropathy also reports lightheadedness on standing and incomplete bladder emptying.

How should these additional manifestations be classified?

Interpretation

Diabetic autonomic neuropathy accompanying sensorimotor polyneuropathy.

Autonomic axons mediate postural adjustment and bladder function; Coexistence is common.

Teaching case: Neuropathy with renal failure

ILLUSTRATIVE PRESENTATION

A patient with renal failure experiences distal dysesthesias, muscle cramps, and reduced tendon reflexes.

What morphologic pattern is expected?

Interpretation

Predominantly axonal degeneration, occasionally with secondary demyelination.

This combination matches the textbook description of uremic neuropathy.

Teaching case: Focal thyroid-associated deficit

ILLUSTRATIVE PRESENTATION

A patient with hypothyroidism has sensory symptoms restricted to the territory of one compressed nerve.

Which pattern is more appropriate than diffuse polyneuropathy?

Interpretation

Compression mononeuropathy; Carpal tunnel syndrome is an example.

A named nerve territory localizes the lesion to a focal peripheral nerve.

Teaching case: Spinal and peripheral signs

ILLUSTRATIVE PRESENTATION

A patient with nutritional deficiency develops findings referable to long spinal tracts as well as peripheral nerve dysfunction.

Which source-described deficiency has this classic combined pattern?

Interpretation

Vitamin B₁₂ deficiency.

Subacute combined degeneration involves spinal long tracts and peripheral nerves.

Synthesis: Five diagnostic distinctions

Diabetes: A largely sensory, length-dependent axonopathy with vascular changes.

Diabetic autonomic and asymmetric forms broaden the clinical spectrum.

Uremia and hypothyroidism may also cause distal axonal neuropathies.

Vitamin B₁₂ deficiency can combine spinal and peripheral pathology.

Deficiency and toxic exposure must remain distinct etiologic categories.

Diabetes: Axonal + vascular

Uremic / thyroid neuropathy

Nutritional mechanisms

Schematic

Primary reference

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition (2026).

Chapter 27: Peripheral Nerves and Skeletal Muscles.

Core topic: Metabolic, Hormonal, and Nutritional Neuropathies.

Foundational context: anatomy, axonal neuropathies, and anatomic patterns.