DIABETES & NEUROPATHY

Objectives:

*Pathogenesis / Classification of diabetic neuropathy

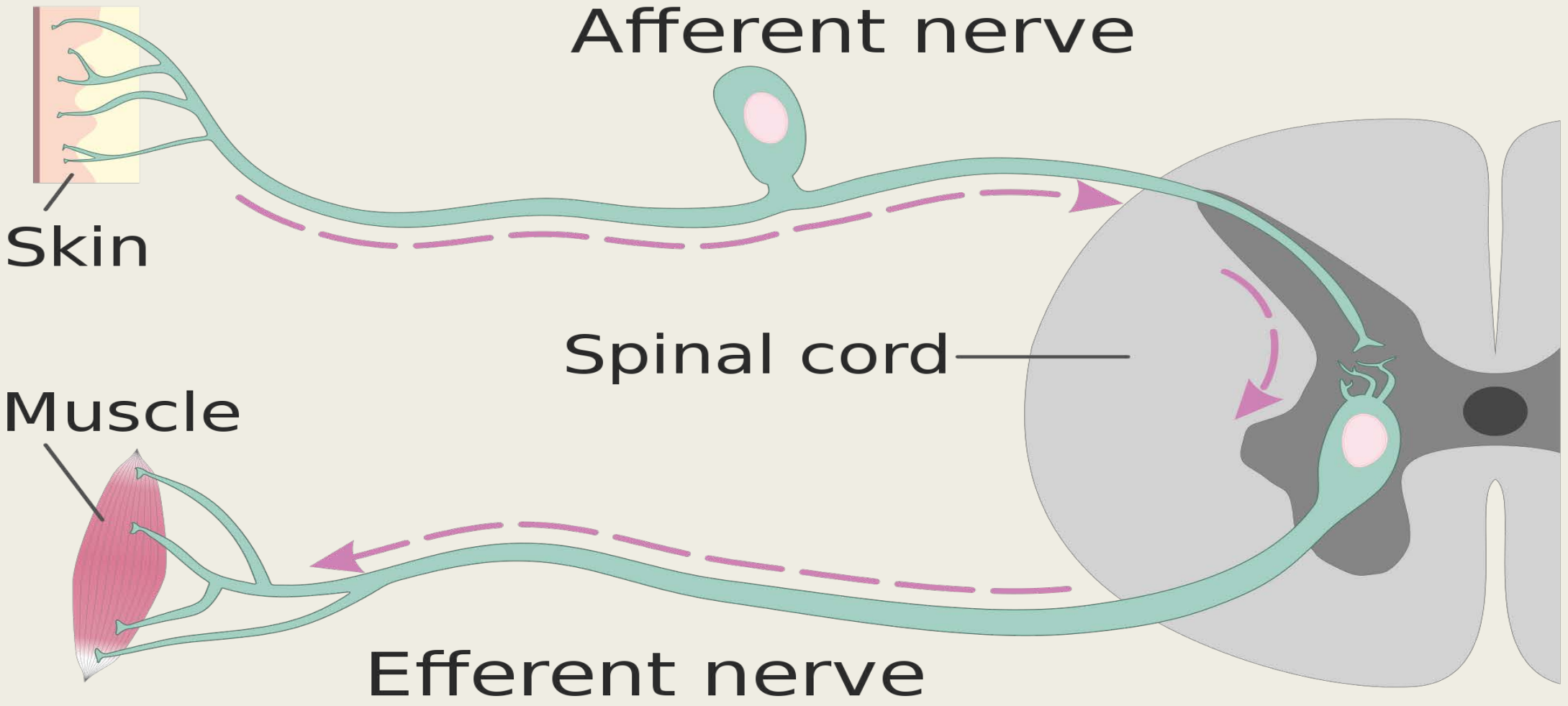
*The spectrum of diabetic neuropathies

*Treatment of diabetic neuropathies

The Diabetic Neuropathies

- One of the most common & disabling complications of diabetes.
- Diabetes itself is the most common cause of neuropathy worldwide
- Approximately 66% of Type 1 and 59% of Type 2 diabetics will develop symptomatic neuropathy during their lifetime *(or.. about 50% of all diabetics will eventually develop neuropathy)*
- Subclinical neuropathy, and neuropathy associated with the pre-diabetic state of impaired glucose tolerance affects even more individuals.
- Multiple large clinical cohorts have extended the known risk factors to include the metabolic syndrome, glycemic variability, dyslipidemia, and smoking

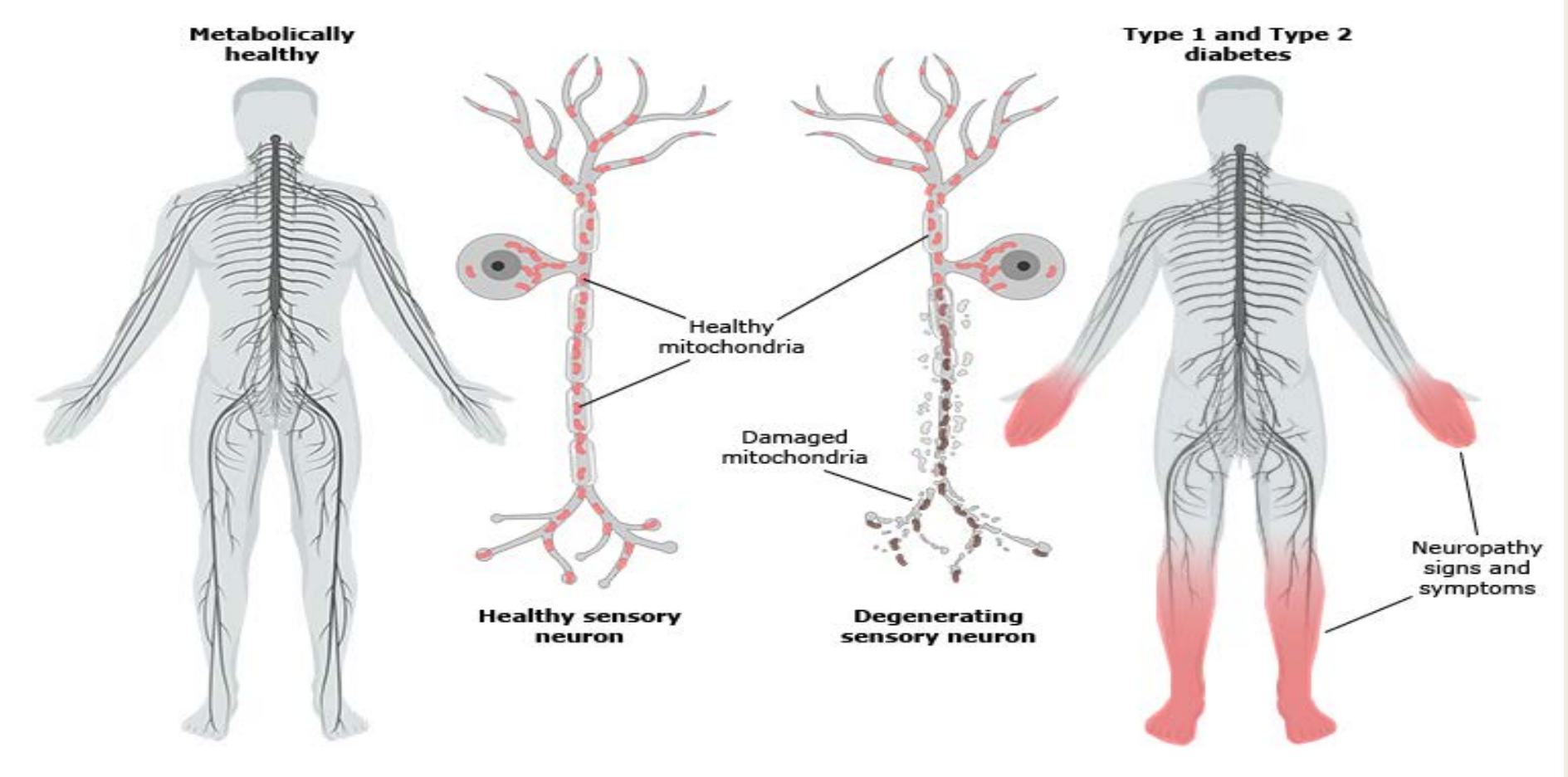
Axons from (CNS) motor neurons relay signals to muscles, while axons from CNS sensory neurons receive signals from skin and joints. Axons are frequently 20,000 times longer than their corresponding cell bodies. Schwann cells provide supporting myelin for a fraction of sensory axons, but many sensory axons are unmyelinated, making them more susceptible to damage. In addition, CNS sensory neurons are not protected by the blood-nerve barrier, unlike motor neurons, adding to their vulnerability.



Pathogenesis of Distal Symmetric Polyneuropathy (the most common form of diabetic neuropathy)

*Length dependent “dying back” axonopathy.

*Fiber selective pattern - preferentially affects the more vulnerable distal sensory and autonomic fibers, leading to the progressive loss of sensation that underlies the clinical manifestations of diabetic polyneuropathy (relative sparing of motor axons).



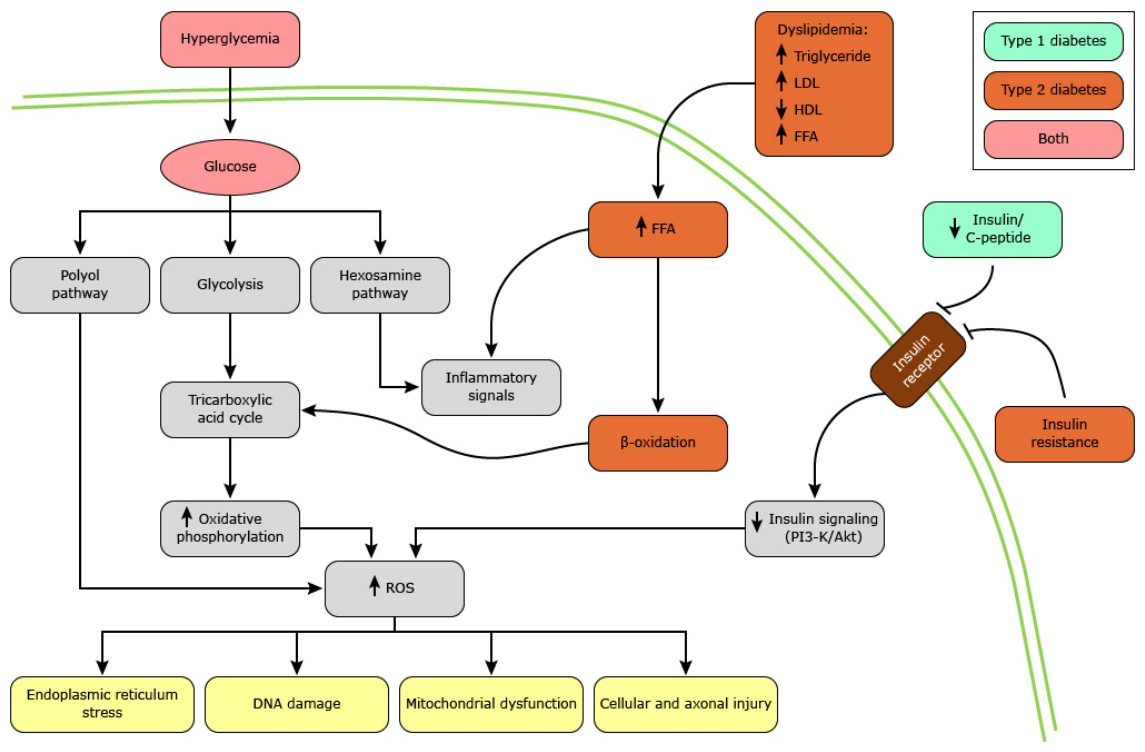
PATHOGENESIS

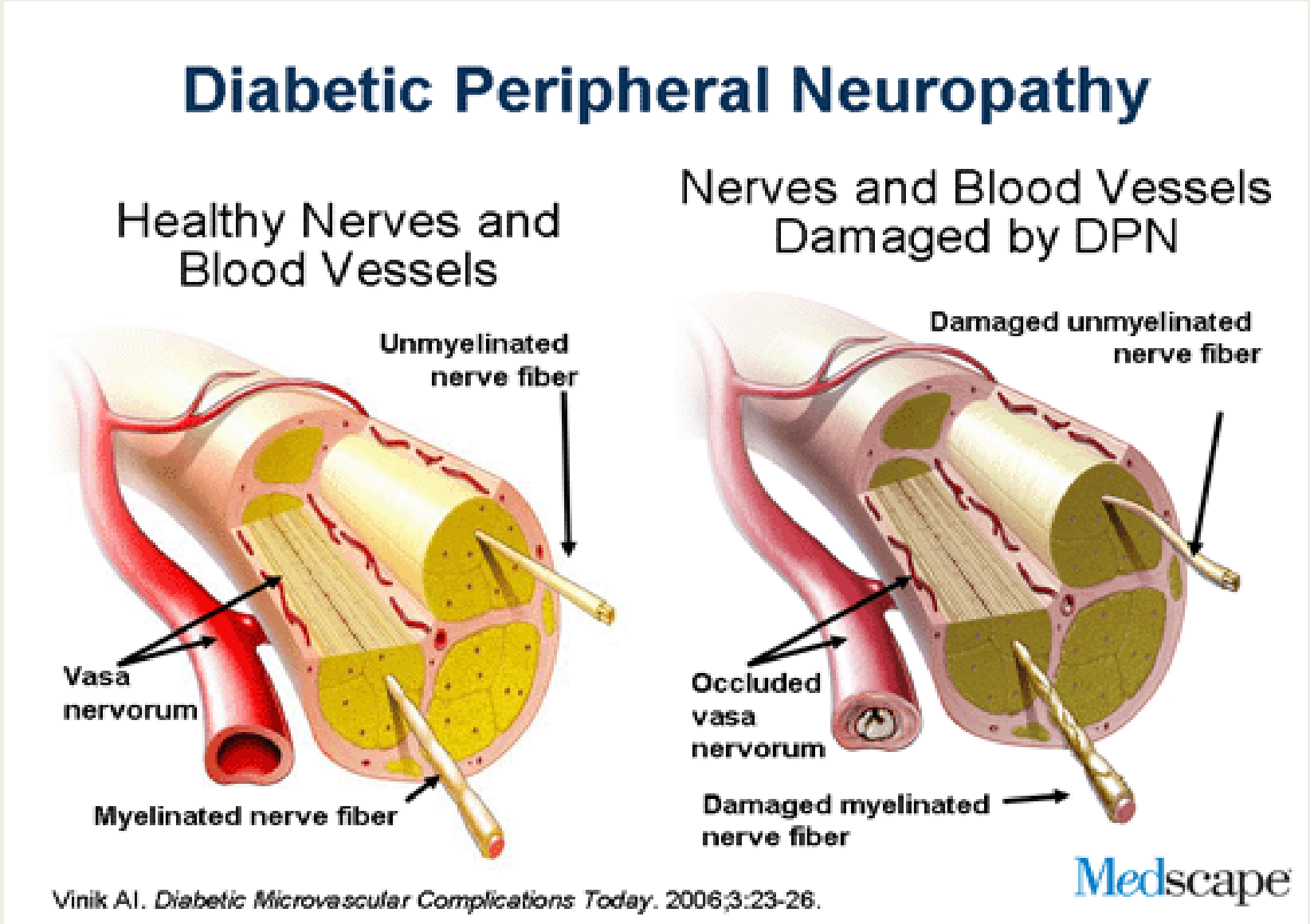
*No longer considered “one single disrupted pathway”

* multiple differentially regular pathways that converge to promote mitochondrial dysfunction with bioenergetic failure and oxidative damage of axons.

*Ischemic and metabolic factors may operate together. Ischemia itself has metabolic consequences that may be exacerbated by insulin deficiency and hyperglycemia. Inflammation, specifically acute phase reactants and interleukins, may also play a role.

Nerve Fiber Repair: Peripheral nerve repair is impaired in diabetes. This complication may be due to disease-induced loss of neurotrophic peptides that normally mediate nerve repair, regeneration, and tonic maintenance





- Distal symmetric neuropathy caused by diabetes - functionally and morphologically indistinguishable from many other metabolic neuropathies (ie uremic, alcoholic) **EXCEPT** –in diabetic neuropathy, morphologic abnormalities of the vasa nervorum are present early in the course of the disease and may parallel the severity of the nerve fiber loss.

- Thus, morphologic characteristics of diabetic neuropathy support a vascular **component,** although most damage is likely secondary to metabolic impairment and loss of required energy in the distal sensory axons.

Classification of the Diabetic Neuropathies

1. Symmetric Polyneuropathy

2. Autonomic Polyneuropathy (it is a separate classification, but this very frequently co-occurs with #1)

3. Polyradiculopathies (DLRPN, truncal / thoracic polyradiculopathy)

4. Mononeuropathies (ulnar, median, peroneal; mononeuritis multiplex)

5. Other (less common):

Treatment induced neuropathy

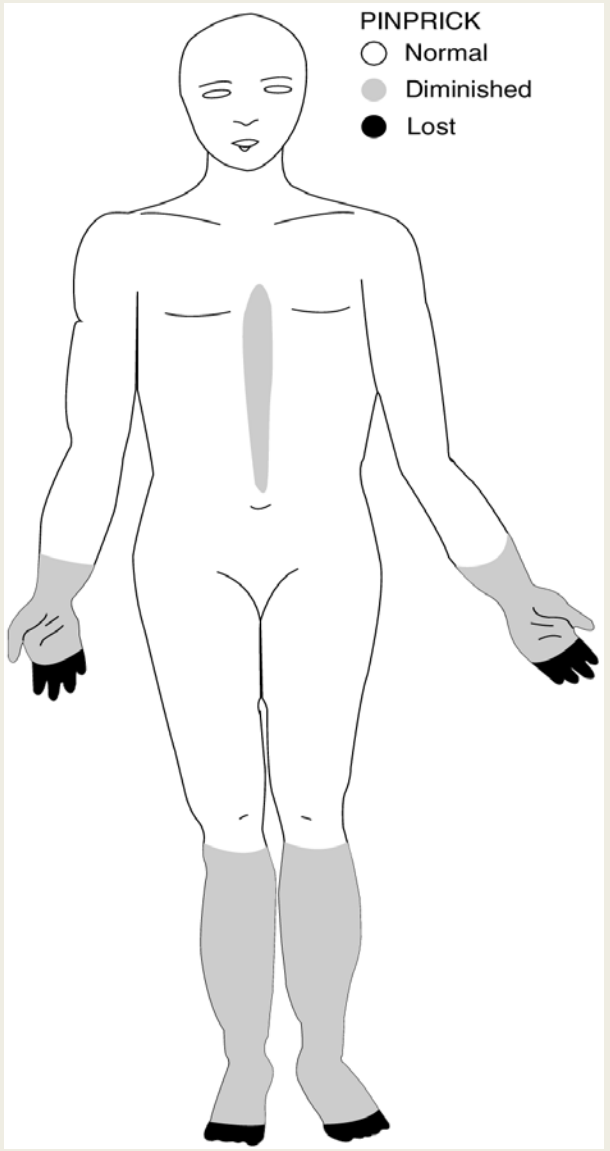
Diabetic neuropathic cachexia; diabetic anorexia

Distal Symmetric Neuropathy

- Length dependent (stocking/glove)
- Most common diabetic neuropathy; more than 80% of patients with diabetic neuropathy have DSP/A.
- In both type 1 & Type 2 DM, risk factors for neuropathy include poor glycemic control, HTN, smoking and cardiovascular disease
- Persons with mildly impaired glucose tolerance without frank DM are also at risk (check with a 2 hour oral glucose tolerance test)
- Can affect large fibers or small fibers. Usually these co-exist. In small fiber neuropathy, it is mainly small, unmyelinated nerve fibers that are affected, and in these cases, standard EMG/NCV testing is **NORMAL.**

Distal Axonal Degeneration

Cuirass Distribution



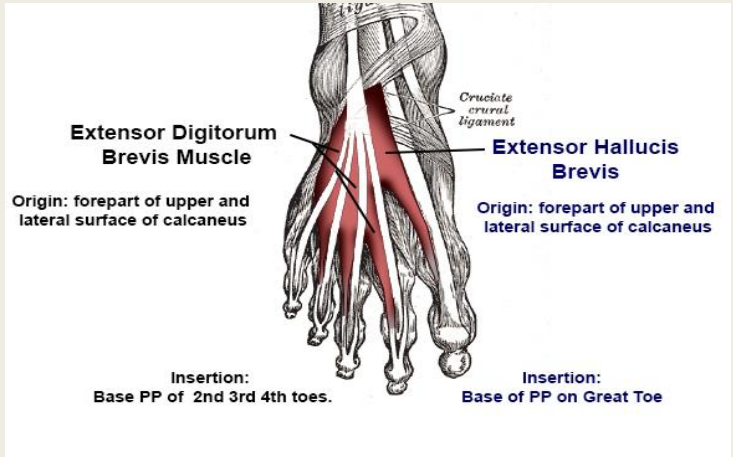
Distal symmetric sensorimotor/autonomic polyneuropathy, cont'd

Clinical Features:

*sensory predominant
*advances proximally
*numbness, tingling, discomfort in toes are frequent initial complaints – followed by UNSTEADY GAIT
*pain very common
*cramping sensations are common
*Nocturnal allodynia (feet against bedclothes)
*True WEAKNESS very rare (if present – wasting of EDB is occasionally present)
*autonomic symptoms

Physical Signs:

Symmetrically impaired vibration, position, touch, thermal and pain senses in the distal lower limbs that slowly advance proximally over time.
*Vibratory sense is often heralding sign.
*As time goes on, may also include the middle chest/abdomen (cuirass sign)
*Lost ankle jerks (large fiber)



Differential Diagnosis:

Not difficult if long standing hyper-glycemia; retinopathy; nephropathy.

Remember – diabetes is a common disorder, and diabetics who develop distal symmetric sensory neuropathies unaccompanied by renal or retinal changes should not be assumed to have DSP/A. They should be evaluated for coincident metabolic/toxic, hereditary or dysimmune conditions associated with polyneuropathy, along with disorders of lumbar spine and spinal cord.

Course and Prognosis

- One population based study showed 10% worsened over 2 years; 81% unchanged and 9% improved.
- Highly variable, but many never progress beyond a stage of numb feet, mildly unsteady gait, and occasional discomfort.
- Neuropathy, once established, is not significantly improved by strict glycemic control. It may help halt progression.
- In this kind of “typical” diabetic neuropathy presentation, additional testing offering highest yield is to check SPEP/IFE and B12 (with homocysteine, MMA).
- Full set of work-up for DSP: Tier 1: CBC, CMP, FBS/A1C/OGTT, b12 (mma and homocysteine); ESR, SPEP/IFE; toxic exposure history. Consider also: tft’s, lipid, ana, rf, anti ro/la, lyma elisa/wb, HCV, ACE

Autonomic Neuropathy

- Almost always accompanied by symptomatic or asymptomatic somatic neuropathy (clinical / subclinical). Many experts consider that DAN is really just part of the larger category of distal peripheral neuropathy.

- Low et al. (2004) reviewed the autonomic symptoms and standardized autonomic testing of patients with diabetes mellitus (Type 1 and 2) and of control patients, and found that 54% of patients with Type 1 diabetes, and 73% of patients with Type 2 diabetes had objective autonomic impairment, but this was generally in the mild range. Only 14% of the diabetic patients in that study had moderate to severe generalized autonomic failure.

- Symptomatic autonomic neuropathy difficult to assess, since many symptoms are vague.

- Most studies strongly suggest that once established, autonomic dysfunction steadily progresses; enhanced in the aged patient.

Clinical Effects of Autonomic Neuropathy

Cardiovascular

GI

Peripheral Sudomotor

Genitourinary

Other

Cardiovascular Autonomic Neuropathy

- **Resting tachycardia** *(earliest manifestation may be resting tachycardia)*
- **Orthostatic Hypotension** (*very common*)
- **Postural Tachycardia** *(increase in HR without a drop in BP, can cause dizziness, lightheadedness, etc)*- note a diagnosis of POTS should not be made in individuals **with diabetes**; a more appropriate diagnosis would be diabetic autonomic neuropathy.
- **Increased Mortality** (two meta-analysis) Several potential mechanisms:

  ** diminished perception of cardiac ischemia*
  ** Reduced cardiovascular response to physiologic stressors such as surgery or infection*
  **Association between DAN and cardiac arrhythmias due to alterations in QT interval*
  **Alterations in the balance between sympathetic and parasympathetic systems have been considered to be pro-arrhythmogenic*
  **Denervated myocardial tissue that has focal areas of reinnervation may be at increased risk for arrhythmia*

  Despite the evidence that DAN is associated with increased cardiac morbidity and mortality, sudden cardiac death in patients with DAN may have a stronger relationship with atherosclerotic heart disease than with DAN itself.

- **Sleep apnea** — There is evidence that sleep apnea and respiratory arrest may contribute to the increased mortality complicating diabetic autonomic neuropathy.

Testing Autonomic Function-Cardiovascular

Parasympathetic function:

*Heart rate variability to deep breathing

*Heart rate response to standing (30:15 ratio….ratio of R-R interval measured at beats 30 and 15 after standing)

*Heart rate response to Valsalva maneuver (Valsalva ratio…. ratio of longest to shortest R-R interval measured while performing the Valsalva maneuver)

Sympathetic adrenergic function:

*Beat to beat BP response to a Valsalva

*Systolic / diastolic BP change in response to tilt table testing

Sympathetic cholinergic function:

*QSART

*Thermoregulatory sweat test

*Sympathetic skin response

Treatment Autonomic Neuropathy-Cardiovascular

1. Try to prevent disease progression (modifiable risk factors such as smoking, HTN, hyperlipidemia, hyperglycemia)

2. Med review to try and remove meds that may worsen orthostatic hypotension

3. Pharmacologic options: fludrocortisone, midodrine, octeotride for patients who are refractory

4. Non-pharmacologic changes

- Rise Slowly
- Head of bed raised 10-20 degrees
- Tensing the legs by crossing them while actively standing on both legs. In one report of patients with autonomic neuropathy, this procedure raised the cardiac output by 16 percent and the systemic blood pressure by 13 percent [92]. It can therefore minimize postural symptoms.
- Performing dorsiflexion of the feet or handgrip exercise before standing.

Diabetic Autonomic Neuropathy – Other Clinical Manifestations:

Peripheral sudomotor/vasomotor neuropathy–

*loss of sweat function in stocking/glove (so can have proximal hyperhidrosis to compensate)

*Changes in texture of skin, itching, edema, callus, loss of nails

*Pain (“small fiber neuropathy”)

GI:

Common – gastroparesis and diarrhea are characteristic.

Other:

Pupillary abnormalities- can result in failure in dark adaptation and difficulty driving at night.

Urogenital:

Erectile dysfunction: *(increases with age; once commences, impotence almost always permanent)*

Bladder dysfunction: incomplete emptying, reduced urinary flow, recurrent infections

Testing Autonomic Function, other

GI Autonomic Testing

*Gastric emptying scintigraphy

*Isotope Based breath test

Urologic autonomic testing

*Post void residual

*urodynamic studies

Pupillary autonomic testing:

*Pupillometry

Sudomotor

*Skin biopsy (for small fiber neuropathy)

The Proximal Multifocal Neuropathies

1)Diabetic Amyotrophy / Diabetic Lumbosacral Radiculoplexus neuropathy (DLRPN)

2) Thoracolumbar Truncal Neuropathy

Previously – these two entities felt to be DISTINCT, pathogenetic entities.

Recent studies – not only considerable co-occurrence and overlap, but also strikingly vasculopathic histologic changes in the lumbosacral condition.

The 2 conditions are considered to exemplify the same disorder, occurring at slightly different levels of the neuro-axis.

DLRPN *(diabetic, lumbosacral radiculoplexus neuropathy)*

AKA - diabetic amyotrophy, diabetic femoral neuropathy

CLINICAL:

**Cardinal feature – PAINFUL, asymmetric onset of weakness in the proximal limbs

Most common:

*middle aged and elderly type 2 DM males with GOOD GLYCEMIC CONTROL.

*often associated with weight loss, often PROFOUND

Often occurs early after a diagnosis of DM – is RARELY accompanied by nephropathy/retinopathy (as in DSP)

Aching pain – often severe – initial symptom. Usually one side of the hip/thigh PROXIMALLY. RARELY – can affect distal leg.

Frequently – this SPREADS to the other leg

Then – asymmetric, progressive weakness of one or both proximal L/E (usually anterior thigh)

EVENTUALLY HOWEVER – weakness is also present in the distal limbs (eventually)

DLRPN (cont'd)

Variable – sensory/autonomic involvement

Some cases – may begin with distal limb weakness, pain in lower back

Patellar jerks – absent on one/both sides; AJ's depressed or absent if co-existent neuropathy

Evolution –can occur over weeks /months

DISABLING – can cause very severe weakness

Monophasic – recovery is variable. Most improve slowly.

Better if unilateral; worse if bilateral

Pain – usually subsides over weeks/months

No established treatment – Some controlled trials show using corticosteroids, IVIG, plasma exchange, or a combination can help with PAIN but not overall outcome.

EMG/NCV:

*Will show a poly-radiculopathy/plexopathy, or a pure radiculopathy; perhaps an associated distal polyneuropathy. EMG'er will need good clinical history to properly diagnose.

DIFF DX:

Retroperitoneal hemorrhage
Necrotizing Vasculitis
Lumbar/hip disease
Diabetic muscle infarction

MRI lumbar spine/plexus

Vasculitis lab screen

CSF – could be helpful (increased protein)

Nerve biopsy rarely useful

DLRPN (cont'd)

- Again – this is a **different entity** than typical diabetic symmetric polyneuropathy
  - *seen in good glycemic control history, soon after diagnosis, absence of retinopathy/nephropathy*
- This is secondary to a non-necrotizing, multi-focal, inflammatory micro-vasculitis with evidence of ischemic injury.
- Some suggest that the inflammatory infiltrate reflects an IMMUNE MEDIATED disorder; others maintain that the inflammatory cells are SECONDARY
- Would note, that this disorder can also occur in NON-DIABETIC patients *(idiopathic radiculoplexus neuropathy).*
- The demonstration of abundance microvasculopathy in DLRPN (and in the corresponding syndrome of those patients who are NOT diabetic) is strong evidence in favor of an ischemic, as opposed to a purely hyperglycemic/metabolic, etiology for this condition.

Diabetic Thoraco-lumbar truncal Radiculoneuropathy

- Painful, intercostal/lumbar radiculoneuropathy.
- May appear alone, or WITH DLRPN
- More common with older type 2 diabetics; frequently associated with weight loss
- THORACIC SYNDROME PREDOMINATES – lumbar dysfunction often undetected.
- Onset – can be sudden or subacute
- Local thoracic or abdominal pain is HALLMARK – occasionally bilateral
- Can look like a zoster (without rash), lyme radiculoneuropathy
- Knife-like, burning, band-like, hard to wear clothes because of INTOLERABLE allodynia
- Can sometimes see an abdominal protruberance due to denervation
- Usually lasts 2-5 months
- Diagnosis – straightforward. If atypical – consider spinal MRI.
- EMG, if done, can show denervation in paraspinal and /or abdominal wall intercostals (but most emg'ers wouldn't do this)

Focal Limb Neuropathies (entrapment)

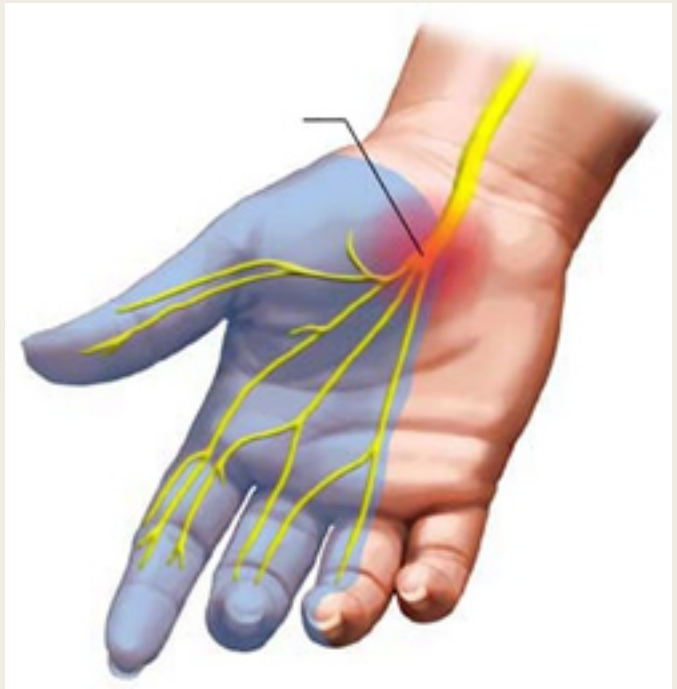
Carpal Tunnel Syndrome:

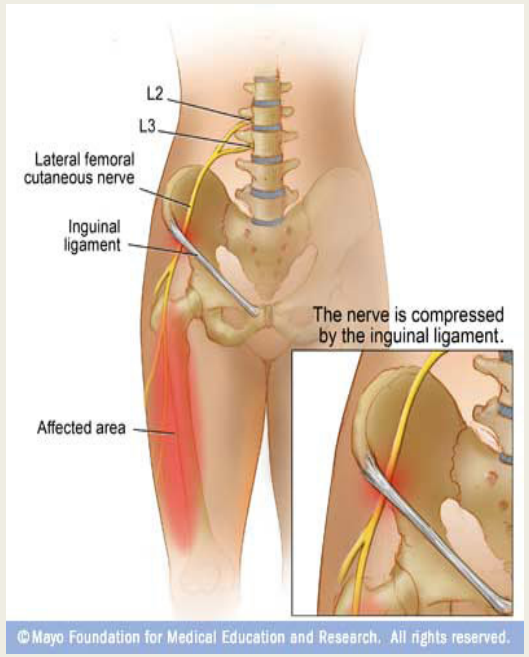
*present in about 14% of diabetics WITHOUT DSP and in 30% if DSP is present!!

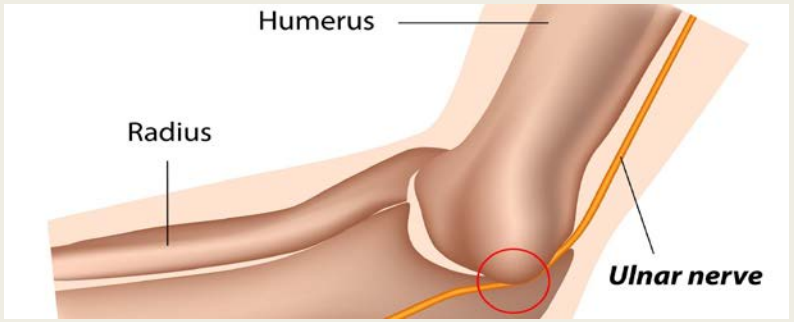
By comparison – there is about a 2% prevalence in a reference population

There is also an increased incidence of peroneal, ulnar and lateral femoral cutaneous nerve entrapments.

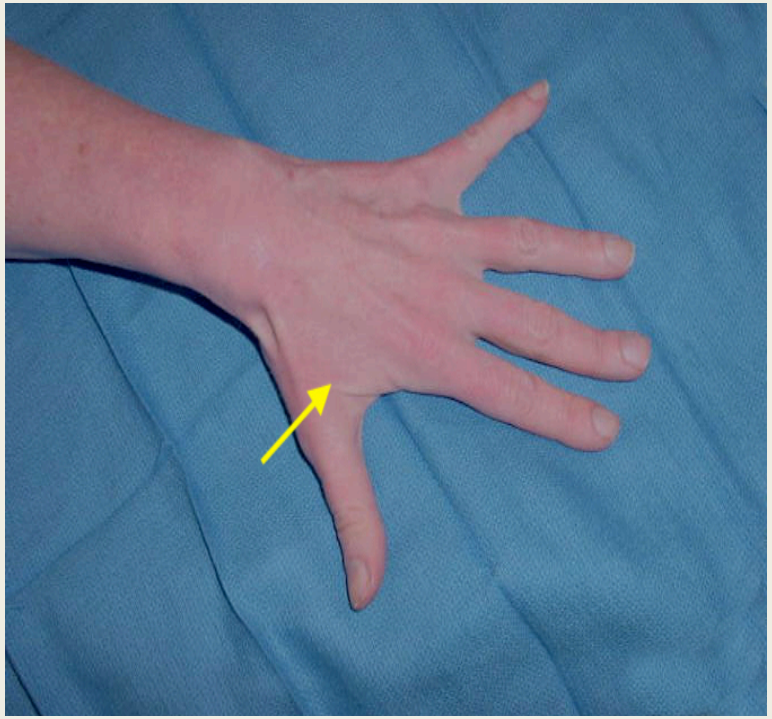
Multiple entrapments in one patient can be seen (mononeuritis multiplex), but consideration should be given to underlying vasculitis as a potential etiology.



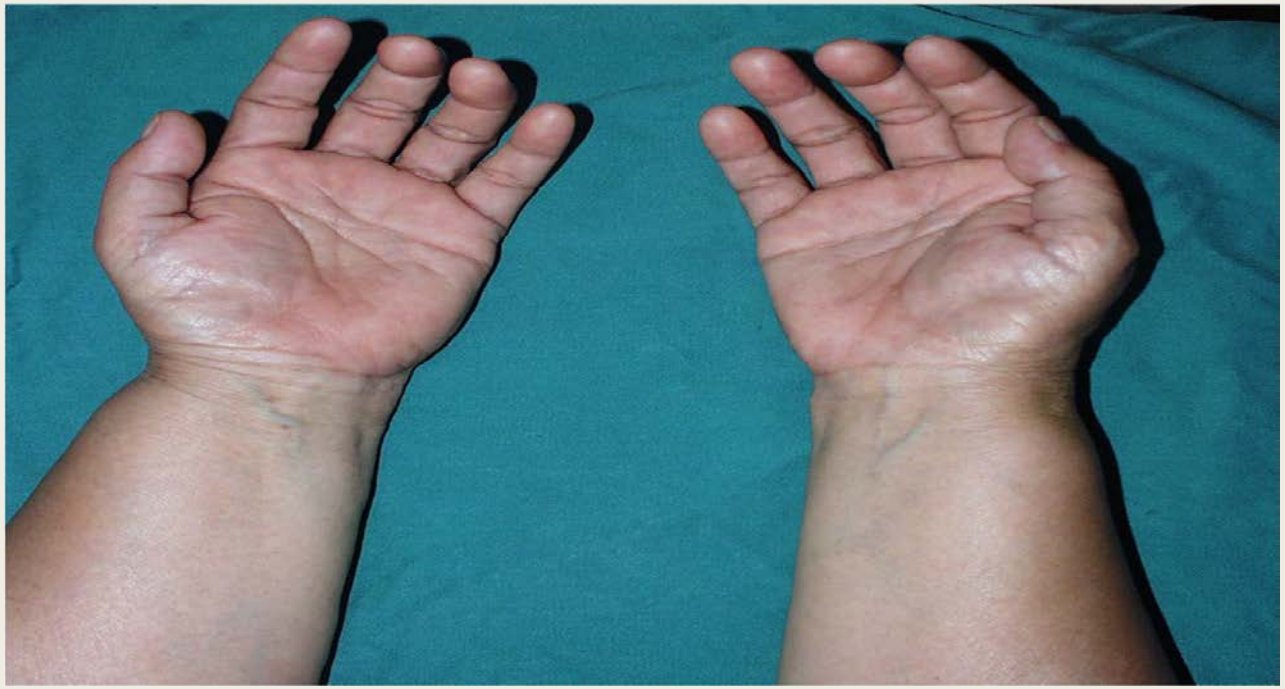




FDI atrophy



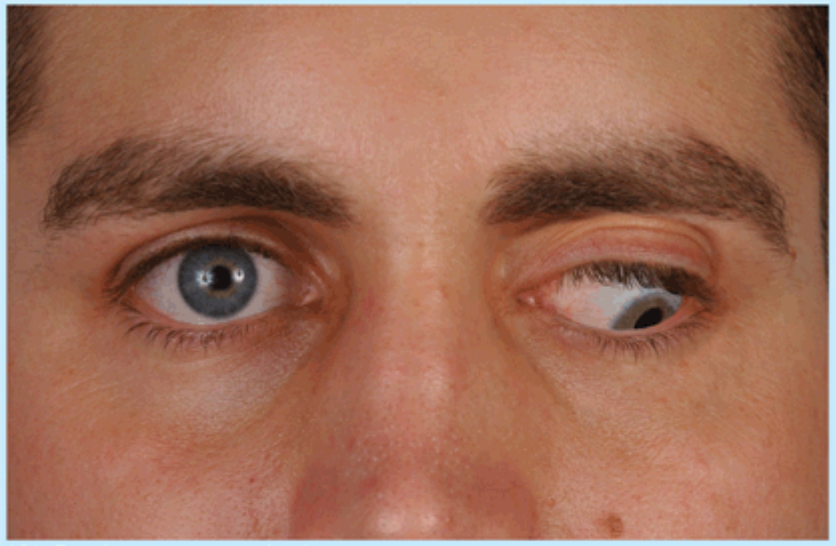
APB atrophy



Isolated Cranial Neuropathies

Typically age over 50
Trochlear (4th nerve) may accompany oculomotor

*Onset – **ABRUPT***



(A) Oculomotor paralysis

(B) Abducent paralysis

ABDUCENS (6TH nerve)

May be PAINLESS

OCULOMOTOR (3rd nerve)

PAINFUL

May have orbital discomfort for days prior to onset

Paralysis of the extraocular muscles is near total

Pupils should be spared

MRA is needed if younger age or pupillary change

Ischemic lesions may be present in either the extra-axial oculomotor nerve or in the fasicular fibers in the midbrain

Acute Painful Neuropathy (Diabetic Neuropathic Cachexia)

- Starts right after severe, precipitous unintentional weight loss and POOR glycemic control.
- RARELY – unaccompanied by weight loss
- Gradual onset of intolerable burning pain over the soles of feet/legs with allodynia are hallmarks
- Pain may be diffuse, limbs, trunk
- NO WEAKNESS
- Monophasic – restoration of glycemic control and weight gain are associated with diminished pain
- Note – a similar condition may occur in anorexic females (intentional weight loss)-"diabetic anorexia"
- Some experts have argued that this entity is part of the spectrum of DPN with the same underlying mechanism and pain fibers being predominantly involved. This monophasic course, the lack of correlation between diabetes mellitus duration, and the neuropathy with associated weight loss, makes it unlikely to be part of DPN

Treatment-Induced Neuropathy (insulin neuritis)

- Uncommon, small fiber involvement
- Acute, acral painful syndrome coincident within weeks of insulin therapy
- Pathogenesis - uncertain, but proposed mechanisms include endoneurial edema and ischemia , apoptosis from glucose deprivation , and microvascular neuronal injury due to recurrent hypoglycemia.

Hyperglycemic Neuropathy

- Newly diagnosed, poorly controlled diabetics may experience an episode of TRANSIENT acral pain / paresthesias
- Most improve following establishment of consistent glycemic control

Nod to Bells Palsy

- Herpes simplex virus activation has become widely accepted as the likely cause of Bell's palsy in most cases.
- Herpes zoster is probably the second most common viral infection associated with facial palsy.
- In a recent article published in European Neurology, a clinical analysis of 372 cases and review of related literature did show that diabetes mellitus was the most common co-morbid condition accompanying Bells palsy.
- Alternate postulated mechanisms of Bell's palsy include a genetic predisposition in some cases and ischemia of the facial nerve . Diabetes is a risk factor for microangiopathy, which may lead to Bell's palsy via microcirculatory failure of the vasa nervosum.

Nod to Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

- Occurs in both TYPE 1 AND TYPE 2
- May be more frequent than idiopathic CIDP
- Classic CIDP – progressive weakness and predominantly DISTAL sensory symptoms over 2 months. Weakness is characteristically symmetric and generalized (proximal and distal).
- The presence of PROXIMAL weakness clinically, differentiates CIDP from the more common length-dependent axonal polyneuropathies.

Diagnosis

- EMG/NCV – for all neuropathy presentations that are felt clinically to be within the peripheral nervous system (using emg/ncv as an extension of the clinical exam). Multiple consensus panels recommend the inclusion of electrophysiologic testing in the evaluation of diabetic neuropathy.
- Autonomic Testing – typically in a lab that does specifically, autonomic testing (ie academic centers)
- Skin Biopsy – small fiber neuropathy

Diagnostic Pitfalls in Diabetic neuropathy

Superimposed neuropathies

- *Severe weakness or demyelination: CIDP
- *Severe proprioceptive loss: sensory neuronopathy

Superimposed entrapments (cts, ulnar neuropathy, peroneal)

Thoracic/abdominal/spinal disorders mimicking truncal neuropathy

Structural / neoplastic spinal or plexus disease mimicking diabetic lumbosacral radiculoplexus neuropathy

Diabetic muscle infarction mimicking diabetic lumbosacral plexus neuropathy

Aneurysm versus diabetic third nerve palsy

AMERICAN ACADEMY OF NEUROLOGY

Guideline Update: "Oral and Topical Treatment of Painful Diabetic Polyneuropathy" Practice Guideline Update, December 27, 2021.

Practice Guidelines (*updated in 12/21 from 2011 guidelines*). .An update was needed to review a large number of new randomized controlled trials of the treatment of pain in people with painful diabetic neuropathy and to highlight the alternatives to opioid use in this population. AAN does NOT recommend using opioids.

This guideline also evaluates the effects of **different medication classes** on painful diabetic neuropathy, whereas most previous guidelines and systematic reviews have focused solely on individual medications. Understanding whether medications of the same class have similar or different effects on pain reduction has implications for optimal treatment of this common condition, such as considering other factors such as cost when choosing between pain medications of the same class and which medications to switch to after a treatment failure.

Gabapentinoids

- Gabapentin is **probably** more likely than placebo to improve pain (SMD 0.53; 95% confidence interval [CI], 0.22–0.84; medium effect, moderate confidence; 1 Class I study).
- Pregabalin is **possibly** more likely than placebo to improve pain (SMD 0.29; 95% CI, 0.13– 0.45; small effect, low confidence; 8 Class I and 7 Class II studies).
- Mirogabalin is **possibly** more likely than placebo to improve pain (SMD 0.21; 95% CI, 0.02–0.40; small effect, low confidence; 2 Class II studies). •

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

- Duloxetine is **probably** more likely than placebo to improve pain (SMD 0.50; 95% CI, 0.26– 0.74; moderate effect, moderate confidence; 2 Class I and 5 Class II studies).

- Desvenlafaxine is **possibly** more likely than placebo to improve pain (SMD 0.25; 95% CI, 0.07–0.43; small effect, low confidence; 1 Class II study). • Three Class I and 6 Class II studies were included for medications of this class, including 1 for venlafaxine, 1 for desvenlafaxine, and 7 for duloxetine.

- SNRIs are **probably** more likely than placebo to improve pain (SMD 0.47; 95% CI, 0.34–0.60; small effect, moderate confidence; 3 Class I and 6 Class II studies).

Tricyclic Antidepressants (TCAs)

- In addition to 1 new study, 2 Class I or Class II studies were identified for amitriptyline from the systematic review of the 2011 guideline.11 Amitriptyline is **possibly** more likely than placebo to improve pain (SMD 0.95; 95% CI, 0.15–1.8; large effect, low confidence; 1 Class I study and 2 Class II studies).

- No Class I or Class II studies were found for other TCAs; therefore, the best estimate for the class effect is based solely on amitriptyline studies. …. TCAs are **possibly** more likely than placebo to improve pain (SMD 0.95; 95% CI, 0.15–1.8; large effect, low confidence; 1 Class I study and 2 Class II studies). The I2 value for heterogeneity was 80%.

Sodium Channel Blockers

- Valproic acid: Three Class II studies were identified, including 1 new Class II study. VPA is **possibly** more likely than placebo to improve pain (SMD 0.86; 95% CI, 0.38–1.33; large effect, low confidence; 3 Class II studies).

- Sodium Channel Blockers Class Effect: Five Class II studies were included for medications of this class: (1) lamotrigine, (2) lacosamide, (1) oxcarbazepine and (1) valproic acid. Sodium channel blockers are **probably** more likely than placebo to improve pain (SMD 0.56; 95% CI, 0.25–0.87; medium effect, moderate confidence; 5 Class II studies).

Other Oral Medications:

- Nabilone, a synthetic cannabinoid, is ***probably more likely than placebo*** to improve pain (SMD 1.32; 95% CI, 0.52–2.13; large effect, moderate confidence; 1 Class I study).
- Ginkgo biloba is ***possibly more likely than placebo*** to improve pain (SMD 0.83; 95% CI, 0.48–1.18; large effect, low confidence; 1 Class II study). • Ginkgo biloba is possibly more likely than placebo to improve pain (SMD 0.83; 95% CI, 0.48– 1.18; large effect, low confidence; 1 Class II study).
- • Tocotrienols, which belong to the vitamin E family, are ***possibly no more likely than placebo*** to improve pain (SMD 0.09; 95% CI, −0.14 to 0.32; low confidence; 1 Class II study).
- Nutmeg extract is ***possibly no more likely than placebo*** to improve pain (SMD –0.01; 95% CI, −0.46 to 0.44; low confidence; 1 Class II study).

Topical Medications

- Capsaicin is ***possibly more likely than placebo*** to improve pain (SMD 0.30; 95% CI, 0.14– 0.47; small effect, low confidence; 1 Class I study of 8% and 1 Class II study of 0.075%). •
- Nitrosense patch is ***possibly more likely than placebo*** to improve pain (SMD 0.59; 95% CI, 0.03–1.15; medium effect, low confidence; 1 Class II study).
- • Citrullus colocynthis is ***possibly more likely than placebo*** to improve pain (SMD 0.91; 95% CI, 0.36–1.45; large effect, low confidence; 1 Class II study).
- • Glyceryl trinitrate spray is ***possibly more likely than placebo*** to improve pain (SMD 1.19; 95% CI, 0.55–1.83; large effect, low confidence; 1 Class II study).
- • Topical clonidine is ***possibly no more likely than placebo*** to improve pain (SMD 0.29; 95% CI, −0.01 to 0.58); low confidence; 1 Class II study).
- • Buprenorphine transdermal patches are ***possibly no more likely than placebo*** to improve pain (SMD 0.23; 95% CI, −0.09 to 0.55; low confidence; 1 Class II study)

Muscle & Nerve, 2019 article (AANEM monograph)

INTEGRATIVE NEUROMUSCULAR MEDICINE: NEUROPATHY AND NEUROPATHIC PAIN: CONSIDER THE ALTERNATIVES

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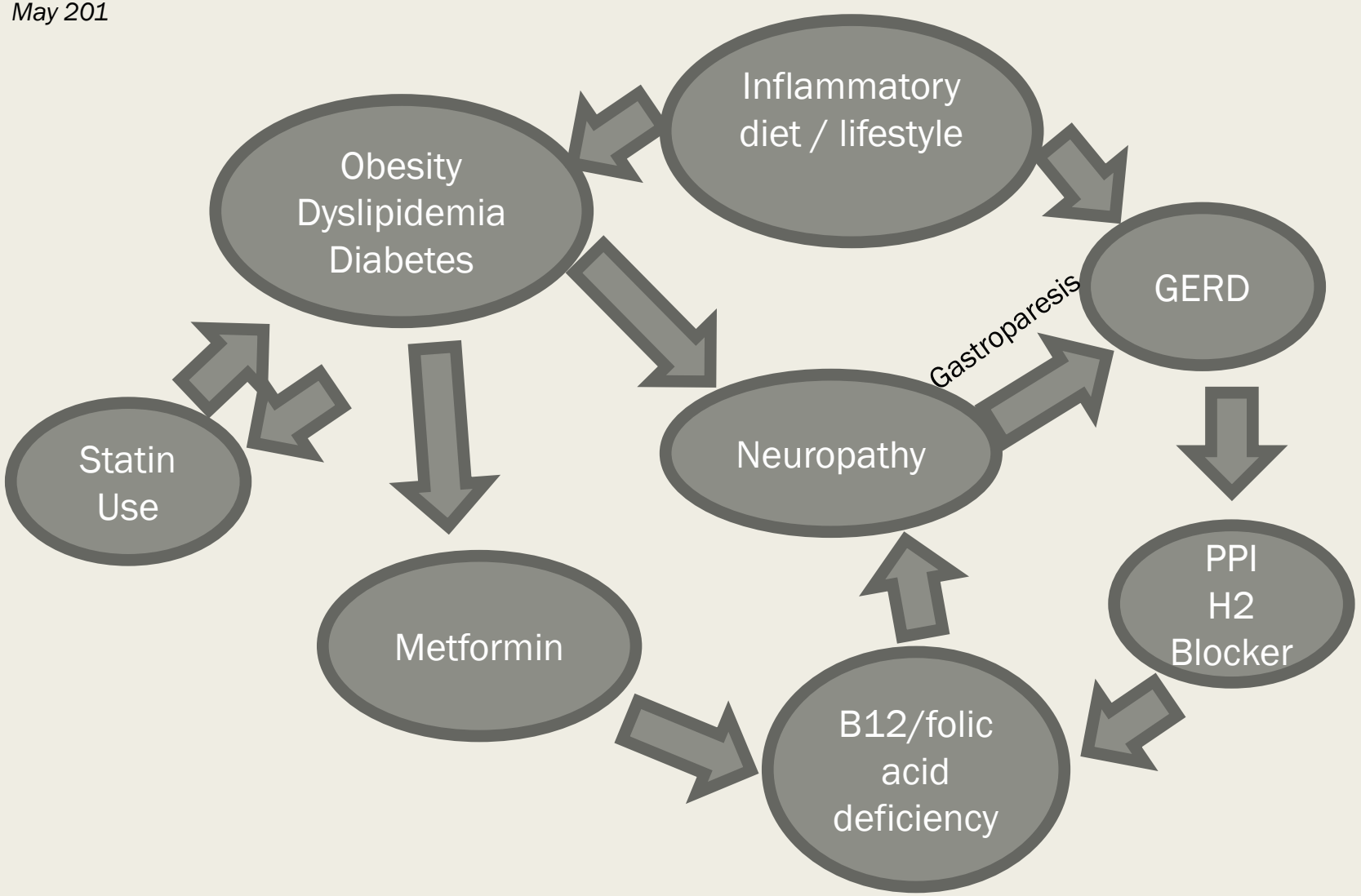
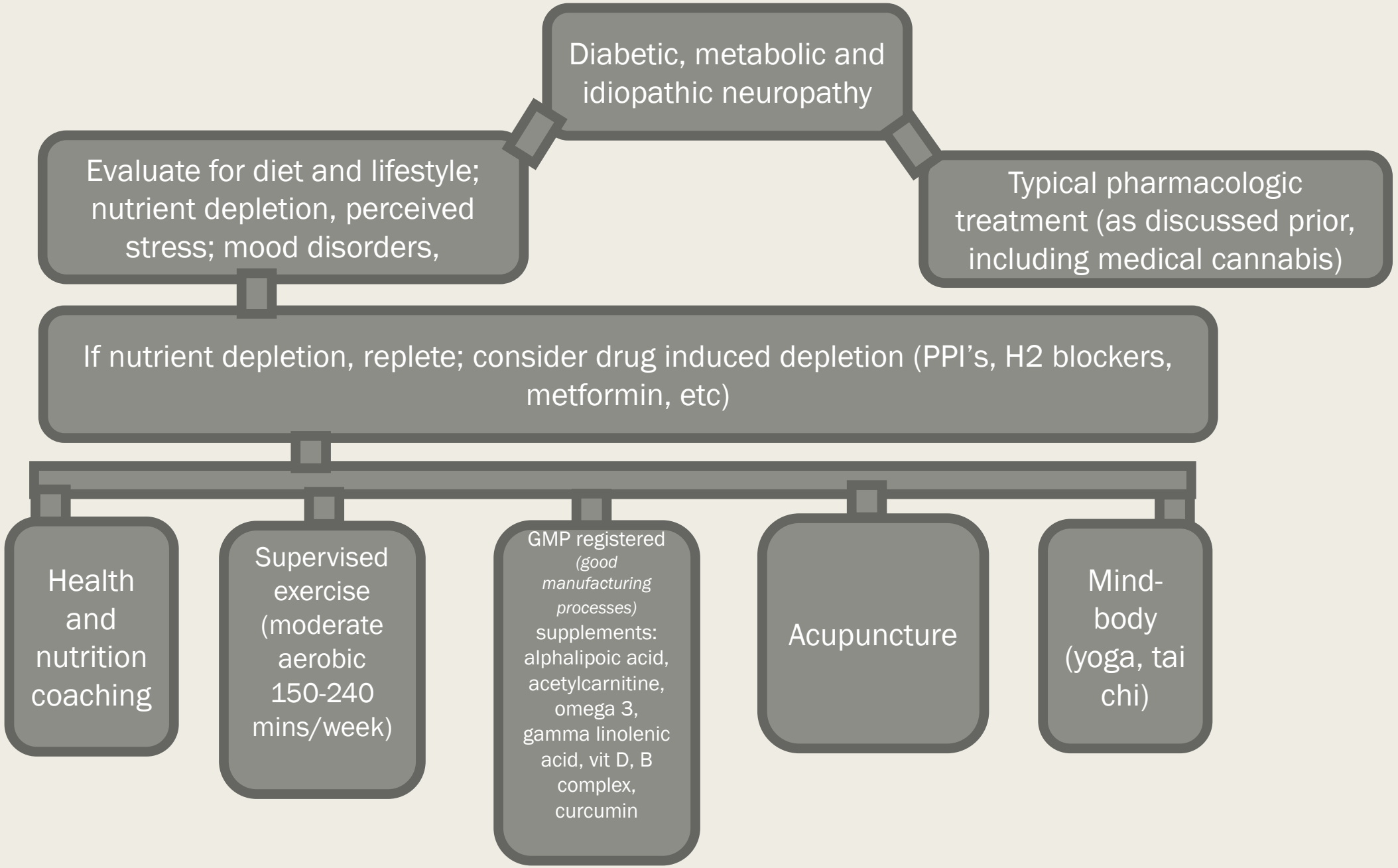


Outline of the literature in support of safe use of lifestyle and CAM approaches to the tx of neuropathic pain and peripheral neuropathy focusing on diet/exercise and nutraceuticals.

*Potential Neuropathy Cascade


Diabetic, metabolic and idiopathic neuropathy
Evaluate for diet and lifestyle; nutrient depletion, perceived stress; mood disorders,
Typical pharmacologic treatment (as discussed prior, including medical cannabis)
If nutrient depletion, replete; consider drug induced depletion (PPI's, H2 blockers, metformin, etc)
Health and nutrition coaching
Supervised exercise (moderate aerobic 150-240 mins/week)
GMP registered (good manufacturing processes) supplements: alphalipoic acid, acetylcarnitine, omega 3, gamma linolenic acid, vit D, B complex, curcumin
Acupuncture
Mind-body (yoga, tai chi)

Ultimate Goal of Therapy for Diabetic Neuropathy

**REDUCTION OF PAIN-not necessarily “eliminating” pain

Thank you