Diabetic Neuropathies and Erectile Dysfunction: Clinical Perspectives

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Newly diagnosed diabetes: Peripheral neuropathy in 7.5%
After 25 years ~ 50% have a peripheral neuropathy
Peripheral neuropathy present in 66% of type 1 and 59% of type 2 patients
Associated mortality, morbidity, and impaired quality of life

Diabetic Peripheral Neuropathy Epidemiology


Prevalence of Symptomatic Neuropathy Increases with Disease Duration

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Diabetic Peripheral Neuropathy

Major Consequences

- Amputations
  - More than 60% of nontraumatic lower-limb amputations occur in people with diabetes.
  - In 2004, ~71,000 nontraumatic lower-limb amputations were performed in people with diabetes.
- Autonomic Neuropathy
  - A cause of substantial morbidity and mortality, including sudden death
- Pain
  - Neuropathic pain is present in 12–30% of patients with diabetes

Classification

- Focal and multifocal neuropathies
- Symmetrical neuropathies

Focal and Multifocal Neuropathies

- Cranial neuropathy
- Truncal mononeuropathy
- Limb mononeuropathy
- Asymmetrical lower-limb neuropathy

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Symmetrical Neuropathies

- Distal sensory or sensorimotor polyneuropathy
- Autonomic neuropathy
- Treatment-induced neuropathy
- Hyperglycemic neuropathy
- Acute painful neuropathy
- Superimposed chronic inflammatory demyelinating polyneuropathy

DPNP Is Underdiagnosed Despite Guidelines

2005 ADA Survey: Only 1 in 4 patients with symptoms of diabetic neuropathy is diagnosed with the condition

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Nerve Fiber Types

<table>
<thead>
<tr>
<th>Fiber type</th>
<th>Function</th>
<th>Diameter (μ)</th>
<th>CV (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A α</td>
<td>Proprioception, somasensory</td>
<td>12–20</td>
<td>70–120</td>
</tr>
<tr>
<td>β</td>
<td>Touch, pressure</td>
<td>5–12</td>
<td>20–40</td>
</tr>
<tr>
<td>γ</td>
<td>Motor to muscle spindle</td>
<td>3–6</td>
<td>15–40</td>
</tr>
<tr>
<td>δ</td>
<td>Pain exp. cold, touch</td>
<td>2–5</td>
<td>12–30</td>
</tr>
<tr>
<td>B</td>
<td>Preganglionic autonomic</td>
<td>~3</td>
<td>3–15</td>
</tr>
<tr>
<td>C</td>
<td>Thermal, fast pain, mechanoreceptor</td>
<td>0.6–1.2</td>
<td>0.5–2.0</td>
</tr>
<tr>
<td></td>
<td>Postganglionic autonomic</td>
<td>3.3–1.3</td>
<td>0.7–2.3</td>
</tr>
</tbody>
</table>

Large Fiber Sensory Neuropathy

- Loss of vibration sensation
- Loss of proprioception
- Areflexia
- Abnormal nerve conduction studies
Small Fiber Sensory Neuropathy

- Burning or lancinating pain
- Hyperalgesia
- Paresthesias
- Loss of pain and temperature sensation
- Foot ulceration
- Loss of visceral pain

Features: Relate to Fiber Type Involved

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Large Fiber Neuropathy</th>
<th>Small Fiber Neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Burning, electric shocks, stabbing pain</td>
<td></td>
</tr>
<tr>
<td>Exam</td>
<td>Reflexes, proprioception, vibration</td>
<td></td>
</tr>
<tr>
<td>Function</td>
<td>Pressure, balance</td>
<td></td>
</tr>
<tr>
<td>Objective</td>
<td>NCV testing</td>
<td></td>
</tr>
<tr>
<td>Diagnostic Test</td>
<td>Sural nerve biopsy, QST, sural nerve biopsy, skin biopsy, autonomic testing</td>
<td></td>
</tr>
</tbody>
</table>

Neuropathology of DPN

- Mild
- Moderate
- Severe


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**Polyol pathway activation**

- Protein glycation
- Reactive oxygen species formation
- PKC III activation
- Impaired neurotrophic support

**Hyperglycemia**

- Altered cell physiology – Altered gene expression – Altered protein function

- Nerve dysfunction – Nerve damage – Nerve death

PKC = protein kinase C


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**Not All Neuropathies in Patients with Diabetes Are Diabetic Neuropathies**

- Toxins
  - Environmental, metabolic, iatrogenic
- Paraproteinemic neuropathies
- Vitamin deficiencies
- Infections
  - HIV Neuropathy, hepatitis C
- Inherited neuropathies
- Paraneoplastic neuropathies
- Vasculitis, connective tissue and other immune-mediated disorders


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**Consequences of DPN**

- PAN: Burning, Paresthesia, Hyperesthesia, Alldynia, Nocturnal exacerbation
- INSENSITIVITY: Foot ulceration: at least 50% preventable

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Assessment of Peripheral Neuropathy

- Neuropathic symptoms
- Neuropathic signs
- Nerve conduction studies
- Quantitative sensory tests
- Quantitative autonomic assessment
- Intra-epidermal nerve fiber density
- Corneal confocal microscopy
- Quality of life measures


Treatment

- Symptomatic
  - Autonomic dysfunction
  - Pain
- Disease-modifying

Current Therapies for Painful Peripheral Neuropathy

- Antidepressants
  - Tricyclic antidepressants (TCAs)
  - Selective serotonin reuptake inhibitors (SSRIs)
  - Selective serotonin and norepinephrine reuptake inhibitors (SNRIs)
- Anticonvulsants
  - First-generation anticonvulsants
  - Second-generation anticonvulsants
- Anti-arrhythmics
- Topical agents
- N-methyl-D-aspartate (NMDA) receptor antagonists
- Opiates and atypical-opiate analgesics

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**Current Therapies for Painful Peripheral Neuropathy**

- **First-line therapies**
  - Tricyclic antidepressants
  - Duloxetine
  - Gabapentin
  - Pregabalin

- **Second-line therapies**
  - Topical lidocaine
  - Opioids, e.g., oxycodone, tramadol

Level A evidence exists for first-line therapies. Consider combination therapy for refractory patients.


**Autonomic Neuropathy**

**Cardiovascular Autonomic Neuropathy**

- Heart rate changes
  - Postural tachycardia
  - Resting tachycardia
  - Fixed heart rate
- Orthostatic hypotension
- Silent ischemia
- Loss of circadian patterns
- Exercise intolerance

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Gastrointestinal Autonomic Neuropathy

- Esophageal dysmotility
- Gastroparesis diabeticorum
- Constipation
- Diarrhea
- Fecal incontinence

Gastroparesis

- Bloating
- Anorexia
- Early or prolonged satiety
- Upper abdominal distension
- Epigastric discomfort
- Postprandial nausea and vomiting of undigested food

Prokinetic Agents

- Metoclopramide
- Domperidone
- Erythromycin
The Symptoms of Bladder Dysfunction

- Suprapubic fullness
- Frequency
- Nocturia
- Urgency
- Incontinence

Therapy of Bladder Hypomotility

- Behavioral therapy
- Compressive and reflex maneuvers
- Catheterization and collecting devices
- Pharmacotherapy
- Electrical stimulation
- Surgery

Erectile Dysfunction in Diabetes

- Diabetes most common known cause
- Multifactorial
- Prevalence 35–60%
- 28% of males with diabetes developed erectile failure over 5 years
- No clear relationship to diabetes duration
- May be presenting symptom

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Treatment of Erectile Dysfunction

- Oral medications
- Intracavernosal injections
- Topical and intra-urethral agents
- Mechanical devices
- Surgical interventions
- Psychotherapy

PDE5 Inhibitors: Structural Chemistry

- Sildenafil citrate, tadalafil, and vardenafil HCl are competitive inhibitors of PDE5
- They resemble cyclic guanosine monophosphate (cGMP) — the substrate
- Bind to the active site of PDE5
- Competitively displace cGMP from PDE5 site
- Subtle structural differences lead to an effect on potency, selectivity, and pharmacokinetic parameters including Cmax, Tmax, t1/2, and bioavailability

Corbin JD, Francis H. IJCP. 2002;56:453-459.

Pharmacokinetics of PDE5 Inhibitors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sildenafil citrate (fasted 100 mg)</th>
<th>Tadalafil (fasted 20 mg)</th>
<th>Vardenafil HCl (fasted 20 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax, h</td>
<td>1.0</td>
<td>2.0 (0.5-6.0)</td>
<td>0.7-0.9</td>
</tr>
<tr>
<td>t1/2, h</td>
<td>4.0</td>
<td>17.5</td>
<td>4.0-5.0</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>40%</td>
<td>N/A</td>
<td>15%</td>
</tr>
</tbody>
</table>

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**Efficacy of Tadalafil for ED in Men with Diabetes**
- Spanish trial (N=216), 90% with type 2 and 10% with type 1 diabetes
- 3-month, double-blind, placebo-controlled, randomized clinical trial
- Successful intercourse rates (SEP3)
  - 10 mg: 48%
  - 20 mg: 42%
  - Placebo: 20%


**Efficacy of Vardenafil for ED in Men with Diabetes**
- North American clinical trial (N=439, age 33-81 years), majority with type 2 diabetes
- 80% white, 9% African American, 8% Hispanic, and 3% other
- 3-month, double-blind, placebo-controlled, randomized clinical trial
- Successful intercourse rates (SEP3)
  - 10 mg: 49%
  - 20 mg: 54%
  - Placebo: 23%


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