Diabetic Peripheral Neuropathy: Assessment and Treatment
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Objectives
1) Describe the clinical features and pathophysiology associated with diabetic peripheral neuropathy
2) Discuss the components for screening and diagnosis of diabetic peripheral neuropathy
3) Discuss pharmacological and non-pharmacological treatments for diabetic peripheral neuropathy.
Diabetic Peripheral Neuropathy (DPN)

- 50% of patients with diabetes will develop DPN
- 50% with DPN will develop painful symptoms
- Frequently underreported and undertreated
  - Leads to increased risk for morbidity, mortality and decreased quality of life
- DPN is one of the leading causes for the development of foot ulcers and amputations
- Health care costs associated with DPN are approximately $10.9 billion per year

DPN: Definition

- Presence of symptoms and/or signs of peripheral nerve dysfunction after the exclusion of other causes in patient with diabetes.
- Results from progressive nerve fiber loss, small fibers are affected in early stages, with large fibers involved in later stages.
- Change in nerve fibers that produce symptoms of paresthesia and pain
Pathogenesis

- Exact cause is unknown
- Results from multiple different biochemical changes - with chronic hyperglycemia being the major contributor
- Caused by a combination of axonal injury caused by nerve ischemia related to:
  - Hyperglycemia
  - Insulin resistance
  - Toxic adiposity
  - Endothelial injury
  - Microvascular dysfunction
- Changes in vascular factors, neuro-structural mechanisms and metabolic interactions contribute development of DPN

Pathogenesis (con’t)

- Metabolic Interactions include:
  - Changes in sodium and calcium channel distribution and expression
  - Varied neuropeptide expression
  - Peripheral sensitization
  - Altered blood flow
  - Axonal atrophy
  - Small fiber damage
  - Glycemic flux
  - Increase in peripheral nerve epineural blood flow
  - Alter foot skin microcirculation
  - Reduced intra-epidermal nerve fiber density
  - Increased thalamic vascularity
  - Autonomic dysfunction
Risk/Contributing Factors

- **POOR GLYCEMIC CONTROL - MAIN RISK FACTOR**
- Length of time individual has had diabetes
- History of:
  - Hypertension
  - Hyperlipidemia
  - Cigarette smoking
- Uncontrolled hypertension main cardiovascular risk factor and can accelerate onset.
- Hyperlipidemia and smoking increase risk for:
  - Development of micro and macro vascular complications

Health Consequences

- Neuropathic pain #1 consequence
- Decreased quality of life
- Decreased functional ability
- Sleep disturbance
- anxiety/depression
- Foot ulcers/amputations - DPN is #1 cause
Clinical Presentation: Acute vs Chronic

- **Acute Sensory (ASN)**
  - Usually develops after episode of DKA or when there has been a sudden change in glycemic levels
  - Rapid onset
  - Present with severe burning pain, aching and nocturnal exacerbations
  - Weight loss is common
  - Allodynia upon sensory testing
  - Normal motor exams
  - Decreased ankle reflexes
  - Complete recovery with 12 months
  - Tight glycemic control is essential.

- **Chronic Sensorimotor**
  - Gradual insidious onset
  - Common in patients with type 2 diabetes
  - Symptoms start in the toes and move proximally
  - Symptoms may move into upper extremities once lower extremities are affected
  - Symptoms include:
    - Burning pain
    - Numbness
    - Possibly weight loss
  - Symptom severity can range from absent to severe
  - Most individuals have moderate symptoms
  - Stocking and glove pattern of sensory loss and absent ankle reflexes may be noted
  - Symptoms can occur intermittently for several years.

Painful Symptoms

*Occurs in 50% of individuals with Chronic DPN*

- **Described as:**
  - Burning sensation
  - Feeling like an electrical shock
  - Stabbing
  - Knifelike
  - Walking on marbles or walking barefoot on hot sand

- **Altered temperature perceptions**
  - Feet feel very warm or cold
  - Nonspecific aching or cramping in feet or legs
  - Increase in pain at night

- **Occurs:**
  - 96% time in feet
  - 69% balls of feet
  - 67% toes
  - 54% dorsum of foot
  - 37% hands
  - 37% calves and heels
  - 39% plantum of foot
SCREENING FOR DPN

- Performed annually
- Single instrument may not be sufficient
- Include history and physical exam
- Include screening for other possible etiologies - i.e. thyroid dysfunction
- Screening methods:
  - Michigan Neuropathy Screening Instrument - Gold Standard
  - Ankle Reflexes
  - 10-g Semmes-Weinstein Monofilament (SWM)
  - 128-Hz tuning fork (vibration perception)
  - Combined tuning fork and SWM
  - Nerve conduction velocities (NCV)

Comparison of screening methods to MNSI as gold standard (@100%)

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankle Reflexes</td>
<td>51.4</td>
<td>97.7</td>
<td>94.9</td>
<td>71</td>
<td>76.8</td>
</tr>
<tr>
<td>10-g SWM</td>
<td>69.7</td>
<td>87.9</td>
<td>82.6</td>
<td>78</td>
<td>79.7</td>
</tr>
<tr>
<td>128-Hz tuning fork</td>
<td>72.5</td>
<td>88.7</td>
<td>84</td>
<td>79.7</td>
<td>81.4</td>
</tr>
<tr>
<td>Combined tuning fork and SWM</td>
<td>89.5</td>
<td>84.9</td>
<td>92.8</td>
<td>89.5</td>
<td>86.5</td>
</tr>
</tbody>
</table>

Monofilament Testing: how to perform 10g test

- Quiet relaxed setting
- Patient should not see where filament is applied
- Apply the monofilament on the inner wrist so patient know what to suspect.
- Use a time one and time two approach, only touch foot at time point - have patient tell you which time they were touched.
- Apply sufficient force to cause the filament to bend or buckle
- Total time includes approach, contact and departure should be about 2 seconds
- Test at least 3 times in an area if not felt
- Do not apply on an ulcer, callus, scar or necrotic tissue - rather apply along perimeter
- 10 sites total should be tested on each foot
- If not felt in area - loss of protective sensation (LOPS) in that area
- 8 or more sites with LOPS than neuropathy needs to be considered.

Vibration Perception Threshold (VPT) & Vibratory sensation testing

VPT:
- Performed with a handheld device that test vibratory sensation
- Probe that is set at 100-Hz, and adjustable amplitude of 0-50 volts.
- Probe is placed at distal hallux
- Amplitude is adjusted until the patient can distinctly sense the stimulus.
- Vibratory threshold of >25 volts considered abnormal a strong predictor of sensory loss
- Equipment is expensive limiting it use in primary care

Vibration Sensation Testing
- Tested with a 128-Hz tuning fork at the interphalangeal joint of the hallux
- Abnormal when the patient cannot perceive sensation while the clinician can
- Allows for possible early detection of sensory neuropathy - not severity of sensory deficit
- Absent sensation at the hallux has been correlated with increase risk for development of foot ulcers.
Michigan Neuropathy Screening Instrument

- Consists of a questionnaire and physical exam
- History (questionnaire) component - 15 yes or no questions
  - Each question is worth 1 point
  - Score ≥ 7 usually indicative of DPN
- Examination component - 5 different assessment areas
  - Appearance
  - Ulceration
  - Ankle reflexes
  - Vibration sensation at the great toe
  - Monofilament exam

<table>
<thead>
<tr>
<th>Question</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are your legs and/or feet numb</td>
<td></td>
</tr>
<tr>
<td>Yes = 1</td>
<td>No = 0</td>
</tr>
<tr>
<td>Do you ever have any burning pain in your legs and/or feet</td>
<td></td>
</tr>
<tr>
<td>Yes = 1</td>
<td>No = 0</td>
</tr>
<tr>
<td>Are your feet too sensitive to touch</td>
<td></td>
</tr>
<tr>
<td>Yes = 1</td>
<td>No = 0</td>
</tr>
<tr>
<td>Do you get muscle cramps in your legs and/or feet</td>
<td></td>
</tr>
<tr>
<td>Yes = 0</td>
<td>No = 1</td>
</tr>
<tr>
<td>Do you ever have any prickling in your legs or feet</td>
<td></td>
</tr>
<tr>
<td>Yes = 1</td>
<td>No = 0</td>
</tr>
<tr>
<td>Does it hurt when the bed covers touch your skin</td>
<td></td>
</tr>
<tr>
<td>Yes = 1</td>
<td>No = 0</td>
</tr>
<tr>
<td>When you get into the tub or shower, are you able to tell the hot from cold water</td>
<td></td>
</tr>
<tr>
<td>Yes = 0</td>
<td>No = 1</td>
</tr>
<tr>
<td>Have you ever had an open sore on your foot</td>
<td></td>
</tr>
<tr>
<td>Yes = 1</td>
<td>No = 0</td>
</tr>
<tr>
<td>Has your doctor ever told you that you have diabetic neuropathy</td>
<td></td>
</tr>
<tr>
<td>Yes = 1</td>
<td>No = 0</td>
</tr>
<tr>
<td>Do you feel week all over most of the time</td>
<td></td>
</tr>
<tr>
<td>Yes = 0</td>
<td>No = 1</td>
</tr>
<tr>
<td>Are your symptoms worse at night</td>
<td></td>
</tr>
<tr>
<td>Yes = 1</td>
<td>No = 0</td>
</tr>
<tr>
<td>Are you able to sense your feet when you walk</td>
<td></td>
</tr>
<tr>
<td>Yes = 0</td>
<td>No = 1</td>
</tr>
<tr>
<td>Do you legs hurt when you walk</td>
<td></td>
</tr>
<tr>
<td>Yes = 1</td>
<td>No = 0</td>
</tr>
<tr>
<td>Is the skin on your feet so dry that it cracks open</td>
<td></td>
</tr>
<tr>
<td>Yes = 1</td>
<td>No = 0</td>
</tr>
<tr>
<td>Have you ever had an amputation</td>
<td></td>
</tr>
<tr>
<td>Yes = 1</td>
<td>No = 0</td>
</tr>
</tbody>
</table>

* Score ≥ 7 considered positive for presence of neuropathy
MNSI - Exam

<table>
<thead>
<tr>
<th>Component</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance: inspect for deformities, dry skin and/or calluses, infection, ulcerations and fissures</td>
<td>Presence of any abnormality = score of 1</td>
</tr>
<tr>
<td>Ankle reflexes</td>
<td>present = 0</td>
</tr>
<tr>
<td></td>
<td>present with reinforcement = .5</td>
</tr>
<tr>
<td></td>
<td>absent = 1</td>
</tr>
<tr>
<td>Vibration (using a 128-Hz tuning fork)</td>
<td>Present = 0</td>
</tr>
<tr>
<td></td>
<td>If examiner senses vibration for ≥ 10 seconds longer = .5</td>
</tr>
<tr>
<td></td>
<td>Absent = 1</td>
</tr>
<tr>
<td>Semmes Weinstein Monofilament exam</td>
<td>8 of 10 correct = 0</td>
</tr>
<tr>
<td></td>
<td>1 - 7 correct = .5 (reduced sensation)</td>
</tr>
<tr>
<td></td>
<td>No correct answers = 1</td>
</tr>
</tbody>
</table>

*Score ≥ 2.5 considered positive for neuropathy

Nerve Conduction Testing

- Requires referral to a neurologist or physiatrist who is trained in electromyography.
- Can be useful in detecting diabetic neuropathy
- Most sensitive and specific for the detection of diabetic neuropathy
- Their use is recommended for quantitative confirmation diabetic neuropathy
- Has potential for earlier diagnosis
Diagnosis of DPN

- DPN is considered a diagnosis of exclusion
- Individuals with painful DPN should have further testing ensure an accurate diagnoses
- Need to rule out other possible causes:
  - Peripheral vascular disease
  - Spinal stenosis
  - Malignancy
  - Arthritis
  - Alcohol abuse
  - Other neurological (MS) or endocrinological causes (Thyroid disorders)

Treatment

- Glycemic control - most important factor
- Need to address and manage associated factors:
  - Hypertension
  - Smoking
  - Body mass index (BMI)
- Goal of treatment mainly aimed at managing pain
- Need also to consider management of other symptoms that impact quality of life and function
  - Fall prevention
    - May need to consider physical/occupational therapy
    - Education related to fall prevention needs to be done
- Pharmacological agents for pain management is commonly used
- Non pharmacological therapies
  - Reiki
  - Electrical stimulation
Pharmacological Treatment

- Tricyclic agents (first line for painful DPN)
- Selective serotonin reuptake inhibitors (SSRI)
- Serotonin-norepinephrine reuptake inhibitors (SNRI)
- Anticonvulsants
- Opioids
- Topical Agents

Tricyclic Agents

- Amitriptyline, Imipramine, Clomipramine
- Amitriptyline has been shown to have the greatest response over placebo
- Use TCA’s with caution in certain populations
  - Narrow-angle glaucoma
  - Benign prostatic hypertrophy, orthostasis
  - Urinary retention
  - Impaired liver function
  - Thyroid disease
  - Adults 60 years of age or older
- Do not use in patients with:
  - Heart failure
  - Arrhythmias
  - Recent myocardial infarction
SSRI’s and SNRI’s

- Usually tolerated better
- Fluoxetine, Venlafaxine and Duloxetine
  - Have shown promise in treatment of DPN
- Duloxetine is 1 of few medications approved by FDA for treatment of painful DPN
- Venlafaxine added to gabapentin has shown to improve the response

Anticonvulsants

- Gabapentin and Sodium Valproate should be considered
  - Good alternatives to TCA’s
  - Better tolerated and have lower risk profile
  - Gabapentin should be used as first line in individuals who do not respond to or have a contraindication to a TCA
- Pregabalin can be effective -
  - Schedule 5
  - High abuse profile
  - Should be administered with caution
- Should not use:
  - Topiramate
  - Oxcarbazepine
  - Lamotrigine
  - Lacosamide should
Opioids

- Agents effective in reducing pain associated with DPN
  - Morphine Sulfate
  - Tramadol
  - Oxycodone
- There is not evidence to support the use of 1 over the other
- Should be used with caution
- Chronic use can be associated with development of
  - Rebound headaches
  - Other novel pain syndromes
  - Development of tolerance - requiring frequent dose increases
- Should not be used in individuals with low abuse threshold

Topical agents

- Capsaicin and Lidoderm patches should be considered
- Capsaicin can reduce pain associated with DPN by additional 40%
- Lidoderm reduced pain by additional 30%
- Should be added to existing systemic treatments to achieve pain reduction and resolution.
### Medication: Recommended Dosing

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic’s</td>
<td>Amitriptyline</td>
<td>10 - 100 mg HS</td>
</tr>
<tr>
<td></td>
<td>Nortriptyline</td>
<td>25 - 150 mg at HS</td>
</tr>
<tr>
<td></td>
<td>Desipramine</td>
<td>25 - 150mg at HS</td>
</tr>
<tr>
<td>SSRI’s or SNRI’s</td>
<td>Venlafaxine XR</td>
<td>150 - 215 mg per day</td>
</tr>
<tr>
<td></td>
<td>Duloxetine</td>
<td>60 - 120 mg per day</td>
</tr>
<tr>
<td></td>
<td>Paroxetine or Citalopram</td>
<td>Up to 40 mg per day</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Pregabalin</td>
<td>160 - 600 mg daily divided into 2 - 3 doses</td>
</tr>
<tr>
<td></td>
<td>Gabapentin</td>
<td>300 - 600 mg TID</td>
</tr>
<tr>
<td>Opioid</td>
<td>Morphine</td>
<td>15 - 120 mg total per day</td>
</tr>
<tr>
<td></td>
<td>Tramadol</td>
<td>50 to 400 mg total per day</td>
</tr>
<tr>
<td></td>
<td>Oxycodone controlle release</td>
<td>10 - 60 mg total per day</td>
</tr>
<tr>
<td>Topical Agents</td>
<td>Capsaicin cream</td>
<td>0.075% qid</td>
</tr>
<tr>
<td></td>
<td>Lidocaine 5% patch</td>
<td>Up to 3 patches per day, patches can be worn for 12 hours per 24 hour period. May wear more than 1 patch at the same time</td>
</tr>
</tbody>
</table>

### Non Pharmacologic Therapies

- Can improve quality of life
- Electrical Stimulation and Magnetic Field Treatment can be effective
  - Some studies have reported a large effect on decreasing pain levels
- Exercise
  - Improve quality of life and improve symptoms
  - Moderate aerobic and resistance exercises, balance training all associated with decrease in symptoms
  - Initially individuals should be evaluated by a physical therapist
**DPN Screening and Treatment Algorithm**

- **Patient with DM**
  - Annual Screening for DPN
    * Include both history and physical exam
  - Positive for DM
    - Develop treatment goals
    - Optimize and stabilize glycemic control
    - Rule out other possible causes
  - Negative for DM
    - Continue Annual Screening
  - Reports Neuropathic pain
    - Start on TCA if appropriate
    - Start Anticonvulsant
    - Start SSRI/SNRI
    - Opiate Therapy
    - Add topical agent at anytime
  - Non-Pharmacological interventions
    * Recommend as appropriate

**Summary**

- DPN is often underreported and underdiagnosed
- DPN can increase risk for poor quality of life, falls, development of foot ulcers and infections
- DPN increases risk for amputation
- Patients with diabetes should be screened annually
  - Screening should be comprehensive
- Other possible etiologies need to be ruled out
- Multiple therapies may need to be used to achieve desired outcome