New Developments in Peripheral Neuropathy

Outline & Overview
- Basic Statistics and Demographics
- Review Pathophysiology
- Discuss DPN Assessment
- Demonstrate a Novel Screening Device
- Management & Benefits of Treatment

The World of Non-Healing Wounds

Diabetes: the fastest growing disease in the US
Diagnosed Diabetes Among Adults: Age-Adjusted Percentage

Chronic Disease Trends – a growing problem

Major Complications of Diabetes Mellitus
- Neuropathy
- Microvascular disease
- Retinopathy, Nephropathy
- Protein glycosylation
- Macrovascular disease – CAD, CVD, PVD
- Immunopathy – susceptibility to infection
Diabetes Related Major Lower Extremity Complications

- Ulceration
- Infection
- Lower extremity amputation
- Charcot foot (Osteoarthropathy)

Lower Extremity Amputation

- 25% lifetime occurrence of lower extremity ulceration
- 0.5-3.0% annual cumulative incidence of ulcer
- Ulceration leads to longer hospitalizations
- Foot ulcers are the precursor to amputation in 85% of lower extremity amputation in diabetic patients
  - 7-20% of ulcers subsequently require an amputation
- Diabetes is the leading cause of non-traumatic amputation and over 60% of all are diabetic and averaging 82,000 per year

Diabetes Related Amputation

- Toe amputations are most common amputation (2.6/1000)
- Below the knee (1.6/1000), AKA (0.8/1000)
- 15-20 times higher in DM than non-DM
- Direct and indirect costs for diabetic foot disease can easily exceed $6 billion/year
- $20,000-60,000 per event, greater cost the higher the amputation

Etiology: Lower Extremity Ulcers

- Peripheral Arterial Disease (PAD)
- Peripheral Neuropathy (DPN)
- Foot Pathology/Deformities

These factors will commonly contribute to the development of Diabetic Foot Ulcers that can take several paths depending on the underlying factors

Pathways to Amputation

Pathology: U S W E R

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Diabetic Neuropathy

Diabetic Neuropathy Definition

“The presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after other causes have been excluded”

Diabetic Neuropathy

- Etiology
  - Multifactor
  - Exact mechanism not completely understood
- Manifestations
  - Subclinical
  - Clinical
- Significant impact on quality of life
- Significant financial cost
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Causes of Diabetic Neuropathy
- Metabolic
  - High blood glucose, long duration of diabetes, abnormal lipids, and possibly low levels of insulin
- Neurovascular
  - Damage to the blood vessels that carry oxygen and nutrients to nerves
- Autoimmune
  - Inflammation in nerves, oxidative stress
- Mechanical
  - Direct trauma/injury to nerves
- Lifestyle
  - Smoking or alcohol use

Etiology & Pathophysiology

- Alterations in nerve blood flow

- Schwann cell (SC) dysfunction: Primary demyelination, secondary segmental demyelination due to impairment of axonal control of myelination, re-myelination, SC proliferation, atrophy of denervated bands of SC, basal lamina hypertrophy.

- Neuronal degeneration & progressive impairment of regeneration (esp. thin myelinated fibres)

- Neuronal damage caused by hyperglycemia (activation of the polyol pathway, synthesis of AGE products, excess activation of PKC-driven pathways, microangiopathy of the vasa nervorum)

- Oxidative stress

Diabetic Neuropathy

- Reduced nerve function results in the Insensate Foot

- DM Neuropathy is the MOST IMPORTANT RISK FACTOR leading to ulceration

- DM Neuropathy is present in more than 80% of DM patients with foot ulcerations

- Increases amputation risk 1.7 fold
  - 12 fold increase in amputation if deformity is present
  - 36 fold increased amputation risk if history of prior ulcer
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Diabetic Tri-Neuropathy

- **Sensory Neuropathy**
  - LOPS “Loss of Protective Sensation”
  - Begins in feet can follow to hands

- **Motor Neuropathy**
  - Presents with Contracted digits
  - Intrinsic Muscular wasting, weakness, foot drop

- **Autonomic Neuropathy**
  - Decrease natural body oil production & sweat
  - Anhidrosis: decrease perspiration and excess drying

Manifestations

- Pain and/or paresthesias
- Numbness
- Autonomic neuropathy
  - dry/scaling skin
- Motor changes
- Edema formation

DFU Evaluation Essentials

- **Wound Assessment**
  - Classification, culture, radiologic, R/O osteomyelitis

- **Vascular Assessment**
  - pulses, toe and ankle pressures, TCOM’s, venous or arterial symptoms

- **Dermatologic Assessment**
  - Interdigital area, skin quality, integrity, atrophy callus, ulcerative or pre ulcerative changes and toenails

- **Musculoskeletal Assessment**
  - deformities such as hammer toes, bunions, evaluate pressure areas, muscle strength, weakness, contractures, joint ROM and gait

- **Neurological Assessment**
  - evaluate sensory perception, DTR’s, loss of protective sensation

Detection of Neuropathy

**Brush Test**

**Objective:**
- The brush test can be used to identify mechanical allodynia.

**Pinprick Test**

**Objective:**
- The pinprick test is used to identify hyperalgesia and hypoesthesia.
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**Hot/Cold Test**

Objective:
- Hot/Cold test is used to identify thermal alldynia (the abnormal sensation of pain from the stimulus of hot or cold).

**Vibration Test**

Objective:
- The vibration test can evaluate the integrity of large nerve fibres.
- This test is a rapid, reliable assessment, requiring less than 60 seconds to administer.

**Monofilament Test**

Objective:
- The two-site Semmes-Weinstein (SW) monofilament test is used to identify loss of sensitivity for people with diabetes.
- SW monofilaments come in several strengths, including: 4.17, 5.07, and 6.1 (1, 10 and 75gm force respectively).
- Less than 7 of 10 pressure sites patient has an absent protective threshold.

**Semmes Weinstein Monofilament Examination**

- Four studies were identified which directly compared SWME with NCS and encompassed 1065 patients with, and 52 patients without diabetes mellitus.
- Sensitivity ranging from 57-93% (57% (95% CI, 44% to 68%) to 93% (95% CI, 77% to 99%)
- Specificity ranging from 75-100% (75% (95% CI, 64% to 84%) to 100% (95% CI, 63% to 100%)
- Positive predictive value (PPV) ranging from 84-100% (84% (95% CI, 74% to 90%) to 100% (95% CI, 87% to 100%)
- Negative predictive value (NPV) ranging from 36-94% (36% (95% CI, 29% to 43%) to 94% (95% CI, 91% to 96%)

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Semmes Weinstein Monofilament Examination

- Conclusion of the meta analysis:
  - Current literature suggests that nerve conduction study is the gold standard for diagnosing DPN

Sudoscan

- A non-invasive device which quickly assesses sudomotor (sweat gland) function via Reverse Iontophoresis and Chronoamperometry
- Sudomotor function is used as a marker for small fiber peripheral neuropathy
- Abnormal sweat response is often associated with populations at risk for diabetes

Sudoscan

- Iontophoresis
  - using an electric charge to open up skin pores for a drug to enter through the skin
- Reverse Iontophoresis
  - using a small electric charge to draw OUT ions (in our case chloride) from the sweat glands
- Chronoamperometry
  - incremental step up of the electric charge used to measure the current produced

Confounders

- Conditions may cause abnormal Sudoscan results from temporary or permanent nerve damage

<table>
<thead>
<tr>
<th>Possible causes of SUDOSCAN disruption</th>
<th>Suggested evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connective tissue disease, autoimmune disease, hereditary conditions (Fibromyalgia, Tangier’s, Von Willebrand’s)</td>
<td>See details for specific diagnostic testing in references</td>
</tr>
<tr>
<td>Hypothalamic</td>
<td>Testing fluid panel</td>
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<tr>
<td>Medication abuse, history of alcoholism</td>
<td>Medical history, clinical examination, liver function tests</td>
</tr>
<tr>
<td>Psychological (stress, anxiety, antidepressants)</td>
<td>Medical history, review current and past medications</td>
</tr>
<tr>
<td>Viral infection (HSV, Hepatitis C, Lyme disease)</td>
<td>Two-week history, specialized neurological and infection disease studies</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Medical history, clinical examination, TSH and free T4 levels</td>
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</tbody>
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Sudorimetry

- Measuring sweat gland function as a biomarker for Autonomic Nervous System function
- Sympathetic innervation
  - Thin, Unmyelinated C-fibers: no protective coating – easily damaged
  - Long: from spine to soles of feet: sensitive to length-dependent damage (dying back disorders)
- Therefore sweat dysfunction will be the first detectable damage to the small fibers of the peripheral nervous system
- BEFORE ANY CLINICAL SIGNS OR SYMPTOMS

Small Fiber Neuropathy

- Superficial pain (C-fiber type)
- Electric shock, burning, allodynia
- Autonomic dysfunction
- Thermal imperceptions
- Decreased Sweating
- Normal strength and reflexes
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Large v Small Fiber

<table>
<thead>
<tr>
<th>Large Nerve Fibers</th>
<th>Small Nerve Fibers</th>
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<tbody>
<tr>
<td>Soft Touch</td>
<td>Pain Sensation</td>
</tr>
<tr>
<td>Motor (Movement), Function, Reflexes</td>
<td>Cold and Warm Sensations</td>
</tr>
<tr>
<td>Vibration</td>
<td>Autonomic Functions: Blushing, Sweating, GI/ODI, Insult Rate, Blood Pressure</td>
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<tr>
<td>Foot Sensation, Balance</td>
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Pay-off: Sensation - 2-Point Discrimination

- Large fiber neuropathy may signal advanced disease
- Detect neuropathy as early as possible in order to correct the underlying disease and possibly reverse the neuropathy
- Prevent progression of the neuropathy to ulcers, amputations
- Decrease mortality from autonomic neuropathy

Small Fiber Assessment

It is critical to measure small fibers:

- All patients should be assessed for diabetic peripheral neuropathy starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter

ADA Recommendations

- Exclude non-diabetic etiologies
- Stabilize DM/ Metabolic control
- Diet & Exercise
- Pain management

Management Strategy

- Pain management ladder

Pharmaceutical Management

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<th>Parameters</th>
<th>Significance</th>
</tr>
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<tr>
<td>Tight glucose control</td>
<td>Can reverse the changes but only if the neuropathy and diabetes is recent in onset</td>
</tr>
<tr>
<td>Tricyclic antidepressants (TCA’s)</td>
<td>Amitriptyline, Nortriptyline Effective but suffer from multiple side effects that are dosage dependent</td>
</tr>
<tr>
<td>Serotonin reuptake inhibitor (SSRI’s)</td>
<td>Fluoxetine, Paroxetine, Sertraline and Citalopram FDA not approved, no more efficacious than placebo in several controlled trials</td>
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<tr>
<td>Antiepileptic drugs (AED’s)</td>
<td>Gabapentin &amp; Pregabalin Emerging as first line treatment for painful neuropathy</td>
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<tr>
<td>Methylcobalamin</td>
<td>Exerts neuroprotective effects, regenerates myelin sheath</td>
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Pain Management Ladder

- Monotherapy
- Combinations
- Additional Measures

First-line TCA Low-dose TCA + AE Paracetamol
- Antiepileptic (AE) Acupuncture
- Opioid with TCA or AE Physiotherapy
- Opioid
- Capsaicin
- Intrathecal drug delivery
- Neuromodulation

Managing Neuropathic Pain: New Approaches for Today’s Clinical Practice

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Detection & Treatment Matters

- Intensive glycemic control was associated with a reduction of 40% - 60% in the development or progression of neuropathy.
- The reduction in complications (Risk of DPN and CAN (64% and 45%, respectively, P<0.01) persisted despite the return of the hemoglobin A1c to pretreatment levels.
  - Legacy Effect: Aggressive early intervention to produce later rewards.

Summary

- Understanding, Detecting and Treating Diabetic Peripheral Neuropathy is CRITICAL to successful attainment of the goal of amputation prevention.
- Small Fiber screening can significant contribute to care of the patient with DFU.
- Sudoscan is available for clinical use to screen for small fiber neuropathy.

Thank You