Diabetic Retinopathy and Neuropathy: 2018 Clinical Practice Guidelines

Richard Arakaki, M.D.
Phoenix Area Diabetes Consultant
August 9th 2018

Disclose no conflict of interest
Complications and Co-morbidities of Diabetes

• Macrovascular Complications
  • Heart disease, peripheral arterial, CHF, and stroke

• Microvascular Complications
  • Retinopathy: Blindness, eye problems
  • Nephropathy: CKD and ESRD
  • Neuropathy

• Foot Disease
  • Ulcers and Amputations

• Co-morbid conditions
  • Hypertension; hyperlipidemia; obesity

Trends in age-standardized rates of diabetes-related complications among U.S. adults with diabetes, 1990-2010

A Decade of Dramatic Reduction in Rates of ESRD

- End Stage Renal Disease (ESRD) in AI/AN persons with diabetes has been reduced by over 40%.
- This reduction is greater than that achieved in any other racial group.
- The average medical costs of one year of care of a patient on dialysis in 2011 dollars was $88,000.
- Savings to Medicare, IHS and other payers are thus measured in $millions, freeing up resources for other pressing health needs.
Reduction of Diabetes ESRD in AI/AN: Addressing Multiple Factors

- Blood Pressure Control
  - Average BP: 132/76 mmHg in 2016

- Blood Sugar Control
  - Mean A1c level decreased by 10% between 1996-2016

- Use of Renin Angiotensin System Inhibitors
  - 76% of patients prescribed medications in 2014
  - 36% higher than in NHANES cohort (2009-2014)

- Increase Screening for diabetes nephropathy
  - 62% of patients over the age of 65 yrs had UACR test in 2015
  - Compared with 40% among Medicare patients with diabetes in 2013

IHS, Division of Diabetes Treatment and Prevention
Improvement in DM Retinopathy among AI/AN: JVN Program Data

• IHS Joslin Vision Network Teleophthalmology Program (JVN)
  • Established in 2000
  • Exemplary telemedicine program
• Retrospective data analysis of 54,000 AI/AN people with diabetes who participated in the JVN program 2011-2016
• Compare with studies done in the 1980s and 1990s, the prevalence of diabetic retinopathy decreased by over 50%
Table 2. Numbers (n) and percentages (%) of IHS-JVN patients by level of DR and DME.

<table>
<thead>
<tr>
<th>Severity level</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Apparent DR</td>
<td>36381</td>
<td>80.0</td>
</tr>
<tr>
<td>Mild NPDR</td>
<td>4284</td>
<td>9.4</td>
</tr>
<tr>
<td>Moderate NPDR</td>
<td>3698</td>
<td>8.1</td>
</tr>
<tr>
<td>Severe NPDR</td>
<td>67</td>
<td>0.1</td>
</tr>
<tr>
<td>PDR</td>
<td>1052</td>
<td>2.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>45482</td>
<td>100.0</td>
</tr>
<tr>
<td><strong>DME</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>44806</td>
<td>97.7</td>
</tr>
<tr>
<td>Not Clinically Significant</td>
<td>653</td>
<td>1.4</td>
</tr>
<tr>
<td>CSDME</td>
<td>394</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>45853</td>
<td>100.0</td>
</tr>
<tr>
<td><strong>STR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>43055</td>
<td>95.8</td>
</tr>
<tr>
<td>Present</td>
<td>1904</td>
<td>4.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>44959</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Conclusions

Prevalence of DR in this cohort was approximately half that in previous reports for AI/AN, and prevalence of DME was less than that reported in non-AI/AN populations. A similar reduction in diabetes related end-stage renal disease in the same population and time period has been reported by other researchers. Since these two diabetic complications share a common microvasculopathic mechanism, this coincident change in prevalence may also share a common basis, possibly related to improved diabetes management.
Vascular complications of diabetes: mechanisms of injury and protective factors

Fig. 1. Selected mechanisms of injury and protective factors determining development of diabetic vascular complications
This diagram illustrates that in the normal state, factors with protective functions in the vasculature can render blood vessels less susceptible to vascular disease and can counteract mechanisms which promote vascular injury. In diabetes, however, glucose and lipid metabolites promote mechanisms of injury and, at the same time, inhibit factors with protective functions in the vasculature. Abbreviations: AGE, advanced glycation end-products; APC, activated protein C; FFA, free fatty acids; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NFκB, nuclear factor κB; PDGF, platelet-derived growth factor; PKC, protein kinase C; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor. Artwork by Leah A. Klein.

Complications of Diabetes: Retinopathy

• About 40% prevalence of retinopathy among all patients
• Approximately 20% of patients have retinopathy at DM diagnosis
• Diabetes is leading cause of new cases of blindness among adults ages 20–74 years; 12 – 24 K new case/yr
• 655,000 (4.4% of those with diabetes) had advanced diabetic retinopathy that could lead to severe vision loss
• 1.5%/year of patients with DM need Laser treatment

# Diabetic Retinopathy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Background retinopathy</strong></td>
<td>Microaneurysms (saccular pouches due to capillary distension)</td>
</tr>
<tr>
<td></td>
<td>Dot/blot haemorrhages</td>
</tr>
<tr>
<td></td>
<td>Hard exudates (lipid deposits related to extravascular leaks)</td>
</tr>
<tr>
<td><strong>Pre-proliferative</strong></td>
<td>Cottonwool spots (areas of retinal ischaemia)</td>
</tr>
<tr>
<td></td>
<td>Venous beading</td>
</tr>
<tr>
<td></td>
<td>Intraretinal microvascular abnormalities</td>
</tr>
<tr>
<td><strong>Proliferative retinopathy</strong></td>
<td>Neovascularisation:</td>
</tr>
<tr>
<td></td>
<td>- new vessel disc</td>
</tr>
<tr>
<td></td>
<td>- new vessel elsewhere</td>
</tr>
<tr>
<td><strong>Advanced eye disease</strong></td>
<td>Vitreous haemorrhage</td>
</tr>
<tr>
<td></td>
<td>Traction retinal detachment</td>
</tr>
<tr>
<td></td>
<td>Rubeosis iridis</td>
</tr>
<tr>
<td></td>
<td>Rubeotic glaucoma</td>
</tr>
<tr>
<td><strong>Maculopathy</strong></td>
<td>Macular oedema</td>
</tr>
<tr>
<td></td>
<td>Hard exudates in macular region</td>
</tr>
</tbody>
</table>
Diabetic Retinopathy: Clinical Consequence

Non proliferative DR
- Asymptomatic

Proliferative DR
- Asymptomatic
- Treatment needed

Severe Vision Loss

Diabetic Macular Edema (DME)
- Asymptomatic

Clinically Significant DME
- ± Asymptomatic
- Treatment needed

Moderate Vision Loss

Scheme and Photos courtesy of Dr. Dawn Clary, Director JVN Tele-ophthalmology Program
10. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes—2018

DIABETIC RETINOPATHY

**Recommendations**
- Optimize glycemic control to reduce the risk or slow the progression of diabetic retinopathy. A
- Optimize blood pressure and serum lipid control to reduce the risk or slow the progression of diabetic retinopathy. A

**Screening**
- Adults with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes. B
- Patients with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist at the time of the diabetes diagnosis. B

**Screening**
- If there is no evidence of retinopathy for one or more annual eye exam and glycemia is well controlled, then exams every 1–2 years may be considered. If any level of diabetic retinopathy is present, subsequent dilated retinal examinations should be repeated at least annually by an ophthalmologist or optometrist. If retinopathy is progressing or sight-threatening, then examinations will be required more frequently. B
- While retinal photography may serve as a screening tool for retinopathy, it is not a substitute for a comprehensive eye exam. E
10. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes—2018

Diabetes Care 2018;41(Suppl. 1):S105–S118 | https://doi.org/10.2337/dc18-5010

DIABETIC RETINOPATHY

Treatment

- Promptly refer patients with any level of macular edema, severe nonproliferative diabetic retinopathy (a precursor of proliferative diabetic retinopathy), or any proliferative diabetic retinopathy to an ophthalmologist who is knowledgeable and experienced in the management of diabetic retinopathy.

- The traditional standard treatment, panretinal laser photocoagulation therapy, is indicated to reduce the risk of vision loss in patients with high-risk proliferative diabetic retinopathy and, in some cases, severe nonproliferative diabetic retinopathy.

- Intravitreous injections of anti-vascular endothelial growth factor ranibizumab are not inferior to traditional panretinal laser photocoagulation and are also indicated to reduce the risk of vision loss in patients with proliferative diabetic retinopathy.

- Intravitreous injections of anti-vascular endothelial growth factor are indicated for central-involved diabetic macular edema, which occurs beneath the foveal center and may threaten reading vision.

- The presence of retinopathy is not a contraindication to aspirin therapy for cardioprotection, as aspirin does not increase the risk of retinal hemorrhage.
Diabetic Retinopathy is PREVENTABLE by adhering to accepted standards of care and established best practices

- Identify all patients with diabetes
- Control for confounding factors and co-morbidities
- Assess level of retinopathy year
- Provide timely treatment

Complications of Diabetes: Retinopathy

50 yo man with DM type 1 presented with ABRUPT and PAINLESS left eye droop and diplopia. Slight orbital for days prior to onset

Examination showed pupils equal and reactive to light.
## Complications of Diabetes: Neuropathy

<table>
<thead>
<tr>
<th>Type of neuropathy</th>
<th>Clinical phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycaemic neuropathy</td>
<td>Reversible, influenced by glucose levels</td>
</tr>
<tr>
<td>Symmetrical sensorimotor neuropathy</td>
<td>Most common presentation, glove and stocking pattern</td>
</tr>
<tr>
<td>Focal neuropathy</td>
<td>Entrapment syndromes (carpal tunnel/meralgia paraesthetica)</td>
</tr>
<tr>
<td></td>
<td>Cranial nerve palsies</td>
</tr>
<tr>
<td></td>
<td>Diabetic amyotrophy</td>
</tr>
<tr>
<td>Autonomic neuropathy</td>
<td>Postural hypotension</td>
</tr>
<tr>
<td></td>
<td>Erectile dysfunction</td>
</tr>
<tr>
<td></td>
<td>Gastroparesis</td>
</tr>
<tr>
<td></td>
<td>Gustatory sweating</td>
</tr>
</tbody>
</table>
Pathology and pathogenetic mechanisms of diabetic neuropathy: Correlation with clinical signs and symptoms

Hyperglycemia

Polyol Pathway
(AR→Sorbitol)
NO↓ & Glutathione ↓

AGE
Glycation
Protein change
Free radicals ↑

Oxidative stress
NO ↓
PARP ↑

Cytokines
Inflammation ↑
Growth factor ↓

I/R injury
Permeability ↑

Peripheral Neuropathy

Fig. 3. Multifactorial etiology of diabetic neuropathy. Hyperglycemia exerts increased polyol pathway, enhanced AGE formation, increased oxidative stress as well as cytokine release. These factors are complicately interactive or independently operate for the cause and development of diabetic neuropathy directly affecting nerve tissues or through nutrient vascular tissues.

Pathology and pathogenetic mechanisms of diabetic neuropathy: Correlation with clinical signs and symptoms

Fig. 2. Natural history of diabetic neuropathy and clinical signs and symptoms with pathological background. With increasing stage of neuropathy, there is a progressive loss of nerve fibers that convey sensation. When the fibers undergo degeneration or impaired remyelination, they release impulse of positive symptoms. With progression of disease, negative symptoms of sensory loss are increased.

• **Diabetic Peripheral Neuropathy**: Patient with type 1 diabetes, duration > 5 yrs and all type 2 patients should be annually assessed. Primary complaints are discomfort or pain or loss of sensations

• **Diabetic Autonomic Neuropathy**: elicited through H and P

• **Gastrointestinal Neuropathies**: suspected in individuals with erratic glycemic controls or GI symptoms without other causes

• **Genitourinary Disturbances**: symptoms of sexual and bladder dysfunction
• **Improve Glycemic Control**

• **Neuropathic Pain:** Pregabalin (anti-convulsant) and duloxetine (selective norEpi and serotonin reuptake inhibitor) and tapentadol (opioid analgesic) are FDA approved medications. Tricyclic antidepressants, venlafaxine, carbamazepine, tramadol, and topical capsaicin are effective but not approved for DPN pain.

• **Orthostatic Hypotension:** difficult to treat; compressive garments, or midodrine and droxidopa are approved by the FDA

• **Gastroparesis:** dietary changes (small meals, reduce dietary fat and fiber), avoid certain medications, metoclopramide approved by FDA (5 days only)

• **Genitourinary Disturbances:** erectile dysfunction – PDE-5 in
## Pharmacologic Agents for the Management of Neuropathic Pain in Patients with Neuropathy

<table>
<thead>
<tr>
<th>Name</th>
<th>Instructions for Starting</th>
<th>Goal Dose</th>
<th>Maximum Dose</th>
<th>Good for Patients with</th>
<th>Consider Alternatives if</th>
<th>Common Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>100 mg TID or 300 mg at bedtime</td>
<td>300 mg TID</td>
<td>3600 mg/d</td>
<td>Seizure disorder</td>
<td>Renal insufficiency</td>
<td>Dizziness, sedation, gait disturbance, confusion, peripheral edema</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>75 mg BID</td>
<td>150 mg BID</td>
<td>600 mg/d</td>
<td>Seizure disorder</td>
<td>Renal insufficiency</td>
<td>Dizziness, sedation, gait disturbance, confusion, peripheral edema</td>
</tr>
<tr>
<td>Amitriptyline/ Nortriptyline</td>
<td>10-25 mg at bedtime</td>
<td>50-100 mg at bedtime</td>
<td>150 mg/d</td>
<td>Insomnia, Migraine</td>
<td>Cardiac disease, arrhythmia, other serotonergic medications</td>
<td>Dry mouth (more common with amitriptyline), sedation, dizziness, confusion, QT-prolongation, orthostatic hypotension</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>30 mg/d</td>
<td>60 mg/d (daily or split BID)</td>
<td>120 mg/d</td>
<td>Depression, anxiety, fibromyalgia</td>
<td>Hepatic failure, other serotonergic medications, anticoagulants</td>
<td>Nausea, dyspepsia, constipation, sedation, dry mouth, dizziness, hyperhidrosis, sexual dysfunction</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>37.5 mg/d (XR)</td>
<td>150 mg/d (XR)</td>
<td>225 mg/d</td>
<td>Depression, anxiety</td>
<td>Uncontrolled hypertension, other serotonergic medications</td>
<td>Nausea, dyspepsia, sedation, dizziness, nervousness, insomnia, hypertension, sexual dysfunction</td>
</tr>
</tbody>
</table>
Neuropathy: Overview

Early recognition and management is important because:

1. Diabetic neuropathy (DN) is a diagnosis of exclusion.
3. Up to 50% of diabetic peripheral neuropathy (DPN) may be asymptomatic.
4. Recognition & treatment may improve symptoms, reduce sequelae, and improve quality of life.
Neuropathy: Recommendations

Screening:

• All patients should be assessed for DPN starting at diagnosis for T2DM and 5 years after diagnosis of T1DM and at least annually thereafter. B

• Assessment for distal symmetric polyneuropathy should include a careful history and assessment of either temperature or pinprick sensation (small-fiber function) and vibration sensation using a 128-Hz tuning fork (for large-fiber function). All patients should have annual 10-g monofilament testing to identify feet at risk for ulceration and amputation. B

• Symptoms and signs of autonomic neuropathy should be assessed in patients with microvascular complications. E

Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S105-S118
Neuropathy: Recommendations (2)

Treatment:

• Optimize glucose control to prevent or delay the development of neuropathy in patients with T1DM A and to slow the progression in patients with T2DM. B

• Assess and treat patients to reduce pain related to DPN B and symptoms of autonomic neuropathy and to improve quality of life. E

• Either pregabalin or duloxetine are recommended as initial pharmacologic treatments for neuropathic pain in diabetes. A
Diabetic Retinopathy and Neuropathy: Summary

Diabetes is associated with significant microvascular complications: retinopathy, neuropathy and nephropathy.

Diabetic retinopathy remains the most common cause of blindness in working-age adults in the developed world.

Neuropathy may manifest in different ways and can be difficult to manage.

Prevention and reduction in progression of microvascular complications requires intensive management of glucose, blood pressure and lipids.
Thank you for your attention.

Questions or Comments?