Microvascular Complications in Diabetes

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Microvascular Complications

- Hyperglycemia
  - Eye
    - Retinopathy
    - Cataract
    - Glaucoma
    - Blindness
  - Kidney
    - Nephropathy
      - Microalbuminuria
      - Gross albuminuria
    - Kidney failure
    - Death and/or disability
  - Nerves
    - Neuropathy
      - Peripheral
      - Autonomic
    - Amputation

Death and/or disability
Diabetic Kidney disease / Nephropathy

- Type 1 DM
  - 20-30% of those with disease > 15 yr.
- Type 2 DM
  - incidence of renal disease 5-10% in Caucasian, 15-20% in African American, 50% in Pima Indians
Diabetes:
The Most Common Cause of ESRD

Primary Diagnosis for Patients Who Start Dialysis

![Graph showing primary diagnoses for dialysis patients over time]

- Diabetes: 50.1%
- Hypertension: 27%
- Glomerulonephritis: 13%
- Other: 10%

No. of Patients (thousands)

- 1984: 243,524
- 1988: 281,355
- 1992: 520,240

Projections:
- 2000: 450,000
- 2004: 550,000
- 2008: 600,000

r² = 99.8%


Definition of abnormal albumin excretion

<table>
<thead>
<tr>
<th></th>
<th>Urinary AER (mg/24h)</th>
<th>Urinary AER (mg/min)</th>
<th>Urine albumin to creatinine Ratio (mg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 30</td>
<td>&lt; 20</td>
<td>&lt; 30</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>30 – 300</td>
<td>20- 200</td>
<td>30 – 300</td>
</tr>
<tr>
<td>Macralbuminuria (overt nephropathy)</td>
<td>&gt; 300</td>
<td>&gt;200</td>
<td>&gt; 300</td>
</tr>
</tbody>
</table>
Recommendations: Nephropathy

- To be consistent with newer nomenclature intended to emphasize the continuous nature of albuminuria as a risk factor, the terms “microalbuminuria” (30–299 mg/24 h) and “macroalbuminuria” (>300 mg/24 h) will no longer be used, but rather referred to as persistent albuminuria at levels 30–299 mg/24 h and severely increased albuminuria levels >300 mg/24 h.

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Risk Factors for Diabetic Nephropathy

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>Cigarette smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycemic control</td>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td></td>
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<tr>
<td>Duration of diabetes/ Age</td>
<td></td>
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<tr>
<td>Family history</td>
<td></td>
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<tr>
<td>Ethnicity</td>
<td></td>
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<tr>
<td>Male gender</td>
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</tbody>
</table>
**Natural History of Nephropathy in Type 1 Diabetes**

<table>
<thead>
<tr>
<th>Stage of Hyperfiltration</th>
<th>Microalbuminuria</th>
<th>Macroalbuminuria</th>
<th>Azotemia (Renal Failure)</th>
<th>End Stage Renal Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normoalbuminuria</strong></td>
<td></td>
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<tr>
<td><strong>Stage of Hyperfiltration</strong></td>
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<tr>
<td><strong>Microalbuminuria</strong></td>
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<tr>
<td><strong>Macroalbuminuria</strong></td>
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<tr>
<td><strong>Azotemia (Renal Failure)</strong></td>
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</tr>
<tr>
<td><strong>End Stage Renal Disease</strong></td>
<td></td>
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</tr>
</tbody>
</table>

- **Normoalbuminuria**
- **Stage of Hyperfiltration**
- **Microalbuminuria**
- **Macroalbuminuria**
- **Azotemia (Renal Failure)**
- **End Stage Renal Disease**

**Natural Hx DM Renal Disease**

- Progression of diabetic nephropathy
  - Microalbuminuria (urinary albumin excretion \( \geq 30 \text{ mg/mg creatinine or } \geq 30 \text{ mg/24 h} \))
  - Blood pressure rises
  - Overt nephropathy or clinical macroalbuminuria (urinary albumin excretion \( \geq 300 \text{ mg/mg creatinine or } \geq 300 \text{ mg/24 h} \))
  - Hypertension develops/worsens
  - Glomerular filtration rate (GFR) begins to fall
Screening for albuminuria

- Urine Albumin Concentration
  - 24 hour urine collection
  - Timed urine collection
  - Urine albumin conc early morning specimen
- Urine Albumin –to –Creatinine Ratio
  - Untimed urine sample
  - Preferred screening strategy
- Limitations -fever, exercise, heart failure, poor glycemic control

Consider Other Causes of Chronic Kidney Diseases

- Rapidly decreasing GFR
- Rapidly increasing protein excretion or acute onset of nephrotic syndrome
- Refractory Hypertension – ( need more than 3 drugs – look for secondary causes of HTN )
- Active Urine sediment
- More than a 30% reduction in GFR after initiation of therapy with ACE or ARB
- TYPE 1 DM: If DM duration <10yrs or no diabetic retinopathy suggestive of other cause
Pathology

Light micrograph of a normal glomerulus. There are only 1 or 2 cells per capillary tuft, the capillary lumens are open, the thickness of the glomerular capillary wall (long arrow) is similar to that of the tubular basement membranes (short arrow), and the mesangial cells and mesangial matrix are located in the central or stalk regions of the tuft (arrows).

Courtesy of Helmut G Rennke, MD.
Diabetic nephropathy

Light micrograph showing diffuse and nodular (N) glomerulosclerosis in diabetic nephropathy. Note the dense appearance of the deposits and the rim of cells around the nodules, which distinguish this disorder on light microscopy from fibrillary glomerulonephritis or amyloidosis.

Courtesy of Helmut Rennke, MD.

Advanced diabetic glomerulosclerosis

Light micrograph in advanced diabetic nephropathy shows diffuse and nodular mesangial expansion and characteristic hyaline thickening of the arteriole at the glomerular hilum (arrow). Although not shown, diabetes typically affects both afferent and efferent arterioles; in comparison, only the afferent arteriole is usually involved with hypertensive injury.

Courtesy of Helmut Rennke, MD.
Electron micrograph of a normal glomerulus

Electron micrograph of a normal glomerular capillary loop showing the fenestrated endothelial cell (Endo), the glomerular basement membrane (GBM), and the epithelial cells with its interdigitating foot processes (arrow). The GBM is thin, and no electron-dense deposits are present. Two normal platelets are seen in the capillary lumen.

Courtesy of Helmut Rennke, MD.

Basement membrane thickening in diabetic nephropathy

Electron micrograph in diabetic nephropathy shows a 2 to 3 fold increase in the thickness of the glomerular basement membrane (GBM). Although not seen, the mesangium is also expanded by basement membrane-like material, a process that contributes to nodule formation and glomerulosclerosis. Mes: mesangium; Ep: epithelial cell.

Courtesy of Helmut Rennke, MD.
The Dual Significance of Proteinuria

- Relation between Diabetic Nephropathy and Retinopathy

- In diabetes and hypertension, proteinuria (albuminuria) is also an indicator of injury in the systemic circulation
  - Proteinuria (albuminuria) is associated with increased cardiovascular risk

Proteinuria as a Risk Factor for Mortality in Type 2 Diabetes

Preservation of Renal function

• Type 1 DM
  – ACE Inhibitors
  – Remission or regression

ACE-I Is More Renoprotective Than Conventional Therapy in Type 1 Diabetes

[Graph showing comparison between Baseline creatinine ≥1.5 mg/dL over years of follow-up for Conventional (n=202) and Captopril (n=207) treatment groups.]

Summary & Recommendations

• Type 1 DM
  – Screening -5yrs after the diagnosis

  – **ARB data lacking**

  – Persistant Microalbuminurea/ BP >130/80mmHg
    start ACE

  – Microalb/ Normotensive –Limited data- suggest
    treatment ACE

  – No Microalb and Normotensive – No Evidence

Type 2 Diabetes and Nephropathy

• Good blood pressure control has proven critical
to slow the progression of nephropathy in type
2 diabetes

• New guidelines for good blood pressure control
  are:
  • <130/80 mmHg (American Diabetes Association)
  • <125/75 mmHg for patients with renal insufficiency with
greater than 1 g/d of proteinuria (JNC VI)

• Multiple antihypertensive agents will be needed
to achieve good blood pressure control

• ARBs or ACE-Inhibitors are indicated for the
treatment of type 2 diabetes with nephropathy

www.hypertensiononline.org
IRMA II Incidence of Progression to Diabetic Nephropathy

Incidence of Diabetic Nephropathy (%)

Placebo 150 mg of irbesartan

Placebo 300 mg of irbesartan

0 3 6 12 18 22 24 Months of Follow-up

Placebo (n) 201
Irbesartan 195
150 mg (n) 164
167
Irbesartan 300 mg 194
180

P<0.001 for difference between 300 mg irbesartan group and placebo


IRMA II Change in Urinary Albumin Excretion*

% change in urinary albumin excretion

Placebo

150 mg of irbesartan

300 mg of irbesartan

0 3 6 12 18 22 24 Months of Follow-up

*P<0.001 for difference between both irbesartan groups and placebo

Preservation of Renal function

• Protein Restriction
• ACE inhibitor or ARB
• ACE inhibitor plus ARB –X
• ARB plus aliskiren –X (Tekturna Alltitude)
• Aldosterone antagonism
• Other antihypertensive drugs and combinations
• Salt intake and proteinuria

Summary & Recommendations

• Factors associated with remission Microalbuminurea
  – Short duration of microalbuminurea
  – Better HbA1C, BP control, Lipid Mx
• Type 2 DM
  – Yearly evaluation starting at diagnosis
  – Persisten Microalbuminurea/ BP >130/80mmHg
    start ACE or ARB
  – Microalb/ Normotensive –Limited data- suggest treatment
  – No Microalbumin and Normotensive – No Evidence for treatment
Recommendations: Nephropathy Treatment (1)

• Nonpregnant patient with >/= 30 mg albumen per 24 hours
  – Use either ACE inhibitors or ARBs (A)
  – Do not use the combination
  – If one class is not tolerated, the other should be substituted (E)

For people with diabetes and diabetic kidney disease (albuminuria >30 mg/24 h), reducing the amount of dietary protein below usual intake is not recommended because it does not alter glycemic measures, cardiovascular risk measures, or the course of GFR decline. A Diabetes Care 2014; 37: suppl 1 pp S 43.

• An ACE inhibitor or ARB for the primary prevention of diabetic kidney disease is not recommended in diabetic patients with normal blood pressure and albumin excretion < 30 mg/24 h. B
  – Diabetes Care 2014; 37: suppl 1 pp S 42
Screening for Proteinuria

- Yearly for both Type 1 and 2
- Type 1: deferred for 5 yrs after the onset
- Type 2: At the time of diagnosis
- Use of Albumin/creatinine ratio preferred.
ADA 2014 BP Goals

• People with diabetes and hypertension should be treated to a systolic blood pressure (SBP) goal of <140 mmHg. B
  – Lower systolic targets, such as <130 mmHg, may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden. C

• Patients with diabetes should be treated to a diastolic blood pressure (DBP) <80 mmHg. B

Diabetes Care 2014, 37: suppl1 pp S 36

Prevention/Treatment of Nephropathy

• Achieve glycemic control, HbA1c below 7% while avoiding hypoglycemia.
• Maintain BP in mid normal range: 130/80 (125/75 once proteinuria), preferably with ACE or ARB
• Stop smoking
• Correct dyslipidemia
• Restricting dietary protein intake (.8 gm/kg/day once there is proteinuria) ?? – NEW GUIDELINES DON’T SUPPORT THIS
Recommendations: Nephropathy

• To reduce risk or slow the progression of nephropathy
  – Optimize glucose control (A)
  – Optimize blood pressure control (A)

• To be consistent with newer nomenclature intended to emphasize the continuous nature of albuminuria as a risk factor, the terms “microalbuminuria” (30–299 mg/24 h) and “macroalbuminuria” (>300 mg/24 h) will no longer be used, but rather referred to as persistent albuminuria at levels 30–299 mg/24 h and levels >300 mg/24 h.

Recommendations: Nephropathy

• An ACE inhibitor or ARB for the primary prevention of diabetic kidney disease is not recommended in diabetic patients with normal blood pressure and albumin excretion < 30 mg/24 h. B
  – Diabetes Care 2014; 37: suppl 1 pp S 42
Diabetic Neuropathy

Fig. 1. A simplified view of the peripheral nervous system and description of the underlying causes of small- and large-fiber neuropathies (8). A alpha fibers are large myelinated fibers, in charge of motor functions and muscle control. A alpha/beta fibers are large myelinated fibers too, with sensory functions such as perception to touch, vibration, and position. A delta fibers are small myelinated fibers, in charge of pain stimuli and cold perception. C fibers can be myelinated or unmyelinated and have both sensory (warm perception and pain) and autonomic functions (blood pressure, heart rate regulation, sweating, etc.). GIT indicates gastrointestinal tract; GUT indicates genitourinary tract.
Classification

- Distal Symmetric polyneuropathy
- Autonomic neuropathy
- Thoracic and lumbar nerve root disease
- Individual cranial and peripheral involvement causing focal mononeuropathies esp occulomoter (CN III) and median nerve
- Asymmetric involvement of multiple peripheral nerves
Clinical Presentation

Symptoms
- Asymptomatic
- Numbness or loss of feeling (asleep or “bunched up sock under toes” sensation)
- Prickling/Tingling
- Pain: Aching, Burning, Lancinating Pain
- Unusual sensitivity or tenderness when feet are touched (allodynia)

Signs
- Diminished vibratory perception
- Absent or reduced knee and ankle reflexes
- Reduced protective sensation such as pressure, hot and cold, pain
- Diminished ability to sense position of toes and feet
- Small muscle weakness and wasting & overcompensation of large muscles (hammer toe, loss of handgrip)

Symptoms and signs progress from distal to proximal over time.

DPN affects the limbs symmetrically and progresses from distal to proximal over time.

- DPN is characterized by a stocking and glove distribution
  - Bilateral symmetrical distribution of signs and symptoms
  - Affects lower limbs first
  - Progresses from distal (toes) to proximal (knee) over time.

Diabetic Neuropathy (Boulton), 2001
Focal Syndromes

- Onset acute and usually self limiting
- Due to vascular insult
- Peripheral: ulnar, median, radial, peroneal, femoral, lateral cutaneous of the thigh

(Needs to be distinguished from entrapment syndromes- median, ulnar where Treatment is splinting or surgery)

Focal Neuropathies

- Cranial neuropathies: V. Rare; Involve the III, IV, VI, VII cranial Ns; Symptoms typically resolve in 2-3 months.
- Truncal neuropathy: Subacute; Painful paresthesias in the trunk, either unilateral or bilateral.
- Diabetic Amyotrophy: long standing diabetics with poor control; Severe neuropathic pain and uni- or bilateral muscle weakness and atrophy in proximal thigh muscles
- Spinal stenosis is common in people with diabetes and should be differentiated from proximal neuropathies and amyotrophy
Clinical Manifestations of Autonomic Neuropathy

• **Cardiovascular:**
  – Postural Hypotension, Postprandial hypotension, Fixed tachycardia, Sudden cardiac death

• **GI**
  – Esophageal motility disorders, Gastroparesis, Constipation, diarrhea

• **Genitourinary**
  – Sexual Dysfunction, Bladder dysfunction

### Clinical features to Distinguish Neuropathy and Vascular Disease

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Neuropathy</th>
<th>Vascular Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of pain</td>
<td>Feet &gt; calves</td>
<td>Calves, thigh, buttocks &gt;feet</td>
</tr>
<tr>
<td>Quality of pain</td>
<td>Sharp/ Superficial / burning /tingling</td>
<td>Deep ache</td>
</tr>
<tr>
<td>Present at rest</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Effect of walking</td>
<td>Pain improves</td>
<td>Pain worse</td>
</tr>
<tr>
<td>Pain worse in bed</td>
<td>Yes</td>
<td>NO</td>
</tr>
<tr>
<td>Preceded by recent BS change</td>
<td>Sometimes</td>
<td>NO</td>
</tr>
</tbody>
</table>
Key components of the diabetic foot exam

<table>
<thead>
<tr>
<th>Inspection</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologic</td>
<td></td>
</tr>
<tr>
<td>Skin status: color, thickness, dryness, cracking</td>
<td></td>
</tr>
<tr>
<td>Sweating</td>
<td></td>
</tr>
<tr>
<td>Infection: check between toes for fungal infection</td>
<td></td>
</tr>
<tr>
<td>Ulceration</td>
<td></td>
</tr>
<tr>
<td>Calluses/blistering: hemorrhage into callus?</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
</tr>
<tr>
<td>Deformity, eg, claw toes, prominent metatarsal heads, Charcot joint</td>
<td></td>
</tr>
<tr>
<td>Muscle wasting (guttering between metatarsals)</td>
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</tr>
</tbody>
</table>

Neurological assessment

10-g monofilament + 1 of the following 4

- Vibration using 128-Hz tuning fork
- Pinprick sensation
- Ankle reflexes
- VPT

Vascular assessment

- Foot pulses
- ABI, if indicated

Check Between Toes
Tuning Fork test

- 128Hz Tuning Fork
- Ball of Rt or Lt big toe
- bony prominence bilaterally situated at the dorsum of the first toe just proximal to the nail bed.
Diagnostic Tests for Diabetic Peripheral Neuropathy

- Routine screening
  - Foot exam
  - Ankle reflexes
  - Tuning fork vibration detection screening
  - Monofilament screening test

- Diagnostic tests
  - Electrophysiology
  - Neurological examination
  - Quantitative sensory testing
  - Nerve conduction velocity measurements

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Diabetic Peripheral Neuropathy
Can Result in Tissue Damage

1. Early tissue damage
2. Clawing toes; left: callus and superficial ulceration on 4th digit dorsum; right: Charcot, dorsal ulcer on 2nd digit
3. Typical neuropathic plantar ulcer on the right foot, callus on both feet
4. Callus scraped away, revealing ulcers

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Photograph: Diabetic Neuropathy (Skelton), 2001.

Images: 1-4; Rayat A, Malik MBBS, PhD, MRCP
Treatment of DPN

1. Treat specific underlying pathogenic mechanism
2. Treat symptoms and improve quality of life
3. Prevention of progression and treatment of complications
**Anti-depressants**

- Inhibit re-uptake of NE, serotonin or both
- NRI: Desipramine, Amitriptyline, nortriptyline
- SSRI: Paroxetine, Fluoxetine, Sertraline
- Dual selective inhibitor: Duloxetine, venlafaxine
- Anti-cholinergic effects, orthostatic hypotension and sexual side effects limit use.
Anticonvulsants

- Carbamazepine 200mg BID: shooting or electric shock like pain
- Gabapentin: Reduced pain, improved sleep. (Weight gain)
- Pregabalin: Significantly improved pain scores (Somnolence, ataxia, confusion)
- Topiramate: Reduced pain score, pain intensity and sleep disruption
### Treatment options for painful diabetic neuropathy

<table>
<thead>
<tr>
<th>Antidepressants</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Tricyclics</strong></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline 25 to 100 mg at night</td>
<td></td>
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<tr>
<td>Nortriptyline 25 to 100 mg at night</td>
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</tr>
<tr>
<td>Doxepin 25 to 100 mg at night</td>
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<tr>
<td><strong>Others</strong></td>
<td></td>
</tr>
<tr>
<td>Duloxetine 60 to 120 mg daily</td>
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<tr>
<td>Venlafaxine 75 to 225 mg daily</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Anticonvulsants</th>
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</thead>
<tbody>
<tr>
<td>Pregabalin 300 to 600 mg daily</td>
<td></td>
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<tr>
<td>Sodium valproate 300 to 1200 mg daily</td>
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<tr>
<td><strong>Others</strong></td>
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<tr>
<td>Capsaicin topical cream 0.075 percent</td>
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<tr>
<td>Lidocaine patch</td>
<td></td>
</tr>
<tr>
<td>Alpha-lipoic acid 600 mg once daily</td>
<td></td>
</tr>
<tr>
<td>Isosorbide dintrate spray</td>
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<tr>
<td>Transcutaneous electrical nerve stimulation (TENS)</td>
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</tr>
</tbody>
</table>

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### Algorithm for Treatment of Symptomatic DPN

**Diabetic Neuropathies, Endocr Pract. 2007;13(No. 5) 561**

**Symptomatic neuropathy**

**Exclude nondiabetic etiologies**

**Stabilize glycemic control**

<table>
<thead>
<tr>
<th>Tricyclic antidepressants</th>
<th>(eg, nortriptyline hydrochloride, 50 to 100 mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticonvulsants</strong> (eg, gabapentin, 600 to 1200 mg/d; pregabalin, 150 to 300 mg/d; topiramate, 25 to 100 mg/d)</td>
<td></td>
</tr>
<tr>
<td><strong>Selective serotonin-norepinephrine reuptake inhibitors</strong> (eg, duloxetine hydrochloride, 40 to 60 mg/d)</td>
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</tr>
<tr>
<td><strong>Opioid or opioid-like drugs</strong> (eg, tramadol, oxycodone)</td>
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<tr>
<td><strong>Combination treatments</strong></td>
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</tbody>
</table>

*Fig. 7. Algorithm for managing symptomatic diabetic neuropathy, modified from Boulton et al (15). Nonpharmacologic, topical, or physical therapies can be useful at any time (eg, capsaicin, acupuncture). The only 2 drugs approved in the United States for the treatment of painful diabetic neuropathy are pregabalin and duloxetine. However, based on the number needed to treat, tricyclic antidepressants are the most cost-effective drugs.*
ADA Guidelines: Neuropathy Screening and Treatment

- Screen all patients for distal symmetric polyneuropathy using simple clinical tests
  - Type 2 diabetes: at diagnosis
  - Type 1 diabetes: 5 yrs after diagnosis and at least annually thereafter
- Electrophysiological testing rarely needed except in cases where atypical clinical features are present
- Institute screening for cardiovascular autonomic neuropathy
  - Type 2 diabetes: at diagnosis
  - Type 1 diabetes: 5 yrs after diagnosis
- Medications for relief of symptoms related to distal symmetric polyneuropathy and autonomic neuropathy

ADA Guidelines: Foot Care

- All patients with diabetes
  - Annual foot exam to identify high-risk conditions and risk factors predictive of ulcers and amputations
- Provide foot self-care education
- Multidisciplinary approach for patients with foot ulcers, high-risk feet (previous ulcer or amputation)
- Refer to foot care specialist:
  - LOPS and structural abnormalities
  - History of prior lower-extremity complications
- Include in initial PAD screenings:
  - History for claudication and assessment of pedal pulses
  - Consider obtaining ABI
- Refer positive ABI, significant claudication for further vascular assessment and consider exercise, medications, surgical options

ABI=ankle-brachial index; LOPS=loss of protective sensation; PAD=peripheral arterial disease
Diabetic Retinopathy

- Diabetes is the leading cause of new cases of blindness in adults aged 20 to 74 years

- Incidence of blindness 25 times higher than the non-diabetic population

- Diabetic retinopathy is responsible for 12,000 to 24,000 new cases of blindness each year

- After 20 years of diabetes, >60% of patients with type 1 or 2 diabetes have some degree of retinopathy
Classification of Diabetic Retinopathy

- Mild nonproliferative
- Moderate and severe nonproliferative diabetic retinopathy
- Proliferative

Pathogenesis of Vascular Damage

Capillary walls weakened by loss of pericytes are more susceptible to the formation of microaneurysms.

- Damage to pericytes leads to:
  - Hyperpermeability
  - Vascular damage
  - The formation of hemorrhagic spots

Vascular damage within the temporal vascular arcade and near the macula would be sight-threatening, but this is rare.

Retinal blot hemorrhages

Diabetic retinopathy, showing several blot hemorrhages (arrows). These lesions are due to vascular occlusion and rupture.

*Courtesy of David McCulloch, MD.*
Color fundus photograph of proliferative diabetic retinopathy displaying severe neovascularization along the superior arcade (NVE).

Advanced traction retinal detachment due to severe neovascularization.

Color fundus photograph showing advanced traction retinal detachment due to extremely severe neovascularization on the disc and arcades, which has drawn the retina toward the vitreous cavity.
Visual loss from Diabetic Retinopathy

- Macular edema
- Hemorrhage from new vessels
- Retinal detachment
- Neovascular Glaucoma

Natural History of DR
Prevalence of Retinopathy vs Duration of Type 2 Diabetes

Patients with retinopathy (%)

Time of diagnosis


Strict glycemic control slows progression of retinopathy

Cumulative incidence of progressive retinopathy in patients with type 1 diabetes and very mild to moderate nonproliferative retinopathy who were treated with either conventional (dashed line) or intensive (solid line) insulin therapy for nine years. There was an increasing benefit of intensive therapy over time, although intensive therapy was associated with transient worsening in the first year (p <0.001).

Data from The Diabetes Control and Complications Trial Research Group, N Engl J Med 1993; 329:977.
Natural History of DR

- Transient worsening with intensive insulin therapy
- Worsening during pregnancy

DCCT:EDIC in Type 1DM

Conventional group encouraged to switch to intensive treatment

Diabetic Retinopathy

Benefits of Tight Glycemic Control (DCCT)

Patients with Type 1 Diabetes Receiving Either Intensive or Conventional Treatment

Primary-Prevention Cohort (n=726) vs. Secondary-Prevention Cohort (n=715)

Percentage of Patients Developing Retinopathy

- Conventional Therapy vs. Intensive Therapy:
  - Year of Study:
    - 0
    - 10
    - 20
    - 30
    - 40
    - 50
    - 60
- p < 0.001

DCCT: Diabetes Control of Complications Trial

Intensive therapy: external insulin pump or three or more daily insulin injections and frequent blood glucose monitoring.

Conventional therapy: 1 or 2 daily insulin injections.


ADA Guidelines: Retinopathy Screening and Treatment (1 of 2)

- Optimize glycemic and BP control to reduce risk or slow progression of diabetic retinopathy
- Initial dilated and comprehensive eye exam by an ophthalmologist or optometrist
  - Adults and children ≥10 yrs with type 1 diabetes: within 5 yrs after diabetes onset
  - Patients with type 2 diabetes: shortly after diagnosis
  - Repeat eye exam annually for all patients, less frequently (every 2-3 yrs) following ≥1 normal exam
  - More frequent exams with progressing retinopathy
- Fundus photographs may be used to screen for retinopathy
  - Not a substitute for comprehensive eye exam

Continued on next slide
ADA Guidelines: Retinopathy Screening and Treatment (2 of 2)

- Pregnant women with preexisting diabetes
  - Eye exam and retinopathy counseling in first trimester
  - Close follow-up throughout pregnancy and 1 yr postpartum
- Macular edema, severe NPDR, any PDR
  - Refer to ophthalmologist specializing in retinopathy
- Laser photocoagulation therapy
  - Indicated to reduce risk of vision loss for high-risk PDR, clinically significant macular edema, some cases of severe NPDR
- Anti-vascular endothelial growth factor (VEGF) therapy
  - Indicated for diabetic macular edema
- Presence of retinopathy not a contraindication to aspirin therapy for cardioprotection

NPDR=nonproliferative diabetic retinopathy; PDR=proliferative diabetic retinopathy

### Ophthalmologic examination schedule

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Recommended first examination</th>
<th>Minimum routine follow-up*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 diabetes</td>
<td>Within 5 years after diagnosis of diabetes once patient is age 10 years or older*</td>
<td>Yearly</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>At time of diagnosis of diabetes</td>
<td>Yearly</td>
</tr>
<tr>
<td>Pregnancy in preexisting diabetes</td>
<td>Prior to conception and during first trimester. Counsel on the risk of development and/or progression of retinopathy.</td>
<td>Close follow-up throughout pregnancy and for one year postpartum.</td>
</tr>
</tbody>
</table>

* Abnormal findings necessitate more frequent follow-up.

- Some evidence suggests that the prepubertal duration of diabetes may be important in the development of microvascular complications; therefore, clinical judgment should be used when applying these recommendations to individual patients.
Summary of Epidemiologic Studies

- Microvascular complications are predicted by
  - Duration of diabetes
  - A1C
  - Blood pressure