Microvascular Complications of Diabetes – Prevention and Treatment of Eye, Kidney and Nerve Disease

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Beverly Dyck Thomassian, RN, MPH, BC-ADM, CDE
President, Diabetes Education Services

Diabetes – Microvascular Complications

- Microvascular Complications
  - Diabetic eye disease, nephropathy, neuropathy, foot complications and dental problems
Diabetes—Microvascular Complications and Goals of Care

Objectives:
- Identify 3 microvascular complications
- Describe modifiable and non-modifiable risk factors for diabetes complications
- List screening guidelines

Mechanisms of Tissue Injury by Hyperglycemia

- Glycation pathway
- Hyperglycemia
- Sorbitol pathway
- Glycated proteins (eg, A1C)
- AGEs
- Sorbitol and fructose
- Altered function or turnover
- Receptor-mediated cytokine effects
- Osmotic effects
- Oxidative effects

Quick Question 1

Which of the following are modifiable risk factors for microvascular disease?

A. Blood pressure, glucose levels, smoking
B. Age, type A personality, blood pressure
C. Ethnicity, blood pressure, diet
D. Blood glucose, genetics, activity level

Eye Disease and Education

Diabetes Retinopathy
Other Diabetes Eye Complications
Prevention and Treatment
Promoting Self-Care
The retina is the only portion of the central nervous system visible from the exterior. Likewise the fundus is the only location where vasculature can be visualized.

**Fundus Geography**

- Optic Cup
- Fovea
- Optic Disc
- Macula
- Artery
- Vein

**Eye Disease Overview**

- Leading cause of adult blindness
  - Retinopathy and Diabetic Macular Edema
  - DM = 25x’s risk of ocular complications
  - Including cataracts
- 20% of type 2 have retinopathy at diagnosis
- Only 60% of pt’s receive appropriate treatment
Retinopathy Risk Factors

- Duration of diabetes, age at diagnosis, race other genetic factors
- Glycemic control, hypertension, smoking, hyperlipidemia, proteinuria and renal disease

Cataracts

- Cataracts – elevated glucose levels glycosylate lens, decreasing permeability
- Treatment = surgery
Macular Edema

- Macular edema
  - Risk 10-15% for pt’s with dm 15yrs +
  - macula responsible for central vision
  - retinal thickening w/in 3mm from the macula
  - can impair central vision – causing blurring to blindness
- Tx: focal laser treatment or
- Lucentis, Avastin or Eylea, injected into eye

Macular swelling caused by leaking microaneurisms with exudates (in yellow). Most common cause of visual loss among type 2 diabetes
http://www.virginiaretina.org/diabetic_retinopathy.html
New Approved Treatment for Macular Edema

- Anti-vascular endothelial growth factor (VEGF) therapy is indicated for diabetic macular edema
- Trials using Ranibizumab (Lucentis) Avastin or Eylea demonstrated improved vision with treatment
- Once a month injection

Quick question 2

- Which of the following describes proliferative retinopathy?
  A. Cotton wool spot and hemorrhages
  B. Increased lens opacity
  C. Stiffening of the lens
  D. New blood vessel growth
What is Retinopathy?

- Retina – layer of nerve tissue in back of eye responsible for processing images and light
- Damage to the microvascular layer that nourishes the retina
- Leads to leakage of blood components through vessel walls and creation of unstable blood vessels secondary to hypoxia
- Disturbance in nerve layer = visual symptoms

Natural History of Diabetic Retinopathy

- Mild nonproliferative diabetic retinopathy (NPDR)
  - Microaneurysms only
  - Reexamined annually
- Moderate NPDR
  - Microaneurysms plus other abnormalities
  - Reexamined w/in 6-12 months
### Severe non-proliferative retinopathy

- Any of the following:
  - 20+ intraretinal hemorrhages in each 4 quadrants
  - Venous beading in 2 or > quadrants
  - Prominent intraretinal microvascular abnormalities in 1 or more quadrant
  - No signs of proliferative disease
  - Reexamination several times a year

### Non Proliferative

Dilated capillaries (microaneurisms) leak red blood cells and plasma into retina. Results in retinal hemorrhages, edema and deposits (exudates).
Non - Proliferative to Proliferative Diabetic Retinopathy

Proliferative retinopathy

new blood vessel formation on surface of retina or the optic nerve. Severe visual loss can occur due to vitreous hemorrhage and retinal detachment. Note fine network of new blood vessels on the surface of the optic nerve.
PDR Signs

Blurred central or side vision (left, blurred side vision) or a blind spot in central vision (right) may indicate diabetic retinopathy.
Proliferative Diabetic Retinopathy (PDR)

- Clinical Findings
  - Ischemia induced neovascularization
    - at the optic disk (NVD)
    - elsewhere in the retina (NVE)
  - Vitreous hemorrhage
  - Retinal traction, tears, and detachment
  - Diabetes Macular Edema must also be evaluated

PDR Management

- Management/Treatment
  - 2-4 month follow-up
  - Color fundus photography
  - Panretinal photocoagulation (3-4 month follow-up)
  - Vitrectomy if bleeding into vitreous
  - If macular edema present: fluorescein angiography and injected meds
Fluorescein Angiogram

Fluorescein Angiogram, 5 Minutes After Dye Injection.
Fuzzy white areas represent dye leaking into retina from microaneurisms.
This illustrates the mechanism which causes macular edema.

Pan Retinal Photocoagulation

Decreases risk of severe vision loss by 50% or more
Destroys 12% of retina and loss of visual field.
Once stabilized, can achieve excellent control of PDR
if B/P and BG well controlled.
Retinopathy Prevention

- To reduce the risk or slow the progression of retinopathy
- Optimize glycemic control
- Optimize blood pressure control

Quick Question 3

- Which of the following is correct regarding eye screening for people with diabetes?
  A. All people with diabetes must get a complete eye exam every year
  B. All people diagnosed with type 1 should receive an immediate eye exam.
  C. All people diagnosed with type 2 should receive an immediate eye exam.
  D. People with diabetes over age of 60 should receive an eye exam every 6 months.
Retinopathy Screening

- Screen with initial dilated and comprehensive eye exam by ophthalmologist or optometrist
  - Type 2 at diagnosis, then every 1 to 2 years
  - Type 1 within 5 yrs of dx, then every 1-2 years
- Can use high quality fundus photography as screening tool - Initial exam should be done in person
- Promptly refer pts with macular edema, and severe non-proliferative disease to trained specialist

High Quality Fundus Photography to Screen for Retinopathy

Can detect most clinically significant diabetic retinopathy
- Interpretation of the images
  - Performed by a trained eye care provider
  - May serve as a screening tool for retinopathy, it is not a substitute for a comprehensive eye exam
  - Perform comprehensive eye exam at least initially and at intervals thereafter
Retinopathy Screening

- Women with preexisting diabetes who are planning pregnancy or are pregnant
  - Comprehensive eye examination in the first trimester
  - Close follow-up throughout pregnancy and for 1 year postpartum

Ongoing Retinopathy Screening

After initial exam, then...

- Annual exam
- Less frequent (every 2-3) yrs can be considered if 1 or more normal eye exam
- More frequent exams if retinopathy progressing
Assess adaptation to low vision

- necessary vision to perform self-care skills?
  - insulin
  - BGM
  - read instructions
  - shopping/home safety/transportation

- refer to rehab education (800-AFBLIND)

- psychosocial issues

Prodigy Voice Meter – A+ Access Award Am Fed Blind

Prodigy Meter only completely accessible meter for sale in U.S. - independent access for visually impaired -

- www.prodigymeter.com
- 800-243-2636
- Independent set up
- Self coding
- Audible Memory
- Audible warning/error
- Cost: $84.95
- 50 Strips $34.95
Nephropathy Objectives

- Epidemiology of diabetes nephropathy / Kidney Disease
- Basic functions of the kidney
- Major stages in progression of nephropathy
- Diagnostic tests to assess and monitor renal function
- Treatment and prevention

Quick Question 4

- John’s dad had diabetes and kidney failure. He wants to learn the risk factors for kidney disease. Which of the following describe those at increased risk for kidney disease?
  - A. Excessive alcohol intake and daily Tylenol
  - B. Family history of kidney disease, smoking
  - C. High protein diet and excessive trans-fat intake
  - D. Diet high in processed foods and sodium
Kidney Physiology

- Size and shape of Idaho potato - retroperitoneal
- Filter entire blood volume every 30 minutes
- Excretory organ:
  - Removes water, urea, waste
  - Maintains blood volume
  - Acid base balance and lytes
  - Regulates B/P
  - Synthesizes erythropoietin – RBC
  - Maintains calcium/phosphorus levels, activates vitamin D – helps absorb calcium

Risk Factors of Kidney Disease

- 2 leading risk factors: Hypertension and hyperglycemia
- Other risk factors:
  - Kidney stones, obesity, smoking and CV disease
  - Family history of kidney disease and age 60 or older
- Kidney disease often has no symptoms, can undetected until very late
Diabetic Nephropathy

- Most new cases of Chronic Kidney Disease (CKD) are attributed to diabetes.
- 220,000 people in US have kidney failure due to diabetes (2013)
- Minorities experience higher than average rates of nephropathy and kidney disease

Diabetes and Chronic Kidney Disease (CKD) Considerations

- CVD leading cause of death in CKD
  - microalbuminuria = increased risk of CVD
- 1/4 to 1/3 of insulin cleared by kidney
- renal retinal syndrome
- 70 - 80% of people with diabetse DON’T get kidney disease
- Early and aggressive intervention crucial
What is Nephropathy?

- Hyperglycemia causes renal hyperfiltration and glomerular capillary hyperperfusion.
- Causes functional and structural damage to glomeruli, increasing permeability, proteinuria, mesangial expansion and sclerosis... destroys nephrons
- Due to insufficient insulin, glycosylation, increased growth hormone, glucagon, and vasoactive hormones.

Nephropathy
Keep Kidneys Healthy

To reduce the risk or slow the progression of nephropathy

- Optimize glucose control (A)
- Optimize blood pressure control (A)

Screening for Kidney Disease

- Screen for:
  - Urine Albumin-Creatinine Ratio (UACR) and
  - Glomerular Filtration Rate (GFR):
  - Type 2 at dx then yearly
  - Type 1 with diabetes for 5 years, then yearly
  - Measure serum creatinine and GFR yearly
  - Treat hypertension and intensify as needed
Definitions of Abnormalities in Albumin Excretion

- Urine albumin – creatinine ratio (spot collection)

<table>
<thead>
<tr>
<th>Category</th>
<th>mg/g creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Increased urinary albumin excretion</td>
<td>30-299</td>
</tr>
</tbody>
</table>

- 2 of 3 tests w/in 3-6 mo abnormal to confirm
- Exercise within 24 h, infection, fever, CHF, marked hyperglycemia, and marked hypertension may elevate urinary excretion over baseline values. **ADA**

Stages of Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Table 9.2—Stages of CKD</th>
<th>GFR (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Kidney damage* with normal or increased GFR</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Kidney damage* with mildly decreased GFR</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Moderately decreased GFR</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Severely decreased GFR</td>
</tr>
<tr>
<td>Stage 5</td>
<td>Kidney failure</td>
</tr>
</tbody>
</table>

*Kidney damage is defined as abnormalities on pathological, urine, blood, or imaging tests. Adapted from Levey et al. (37).
### ADA Management of CKD

#### Table 9.3—Management of CKD in diabetes (7)

<table>
<thead>
<tr>
<th>GFR (mL/min/1.73 m²)</th>
<th>Recommended management</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>Yearly measurement of creatinine, urinary albumin excretion, potassium</td>
</tr>
<tr>
<td>45–60</td>
<td>Referral to a nephrologist if possibility for nondiabetic kidney disease exists (duration of type 1 diabetes &lt;10 years, persistent albuminuria, abnormal findings on renal ultrasound, resistant hypertension, rapid fall in GFR, or active urinary sediment on ultrasound) Consider the need for dose adjustment of medications Monitor eGFR every 6 months Monitor electrolytes, bicarbonate, hemoglobin, calcium, phosphorus, parathyroid hormone at least yearly Assure vitamin D sufficiency Consider bone density testing Referral for dietary counseling</td>
</tr>
<tr>
<td>30–44</td>
<td>Monitor eGFR every 3 months Monitor electrolytes, bicarbonate, calcium, phosphorus, parathyroid hormone, hemoglobin, albumin, weight every 3–6 months Consider the need for dose adjustment of medications</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>Referral to a nephrologist</td>
</tr>
</tbody>
</table>

### Kidney disease treatment - ADA

- ACE or ARB NOT recommended for prevention of kidney disease if BP normal and urinary albumin excretion (UAE) < 30 mg/g
- ACE or ARB if UAE of >30 mg/g
- Monitor creat and K⁺ when on ACE or ARB
- When GFR < 60, evaluate/manage potential complications of CKD
- Consider referral to specialist when management is difficult and kidney disease is advanced
- Protein restriction not recommended
Treatment of Chronic Kidney Disease (CKD)

There are four primary treatment options for individuals who experience ESRD:

1. Hemodialysis
2. Peritoneal Dialysis
3. Kidney Transplantation
   - 120,000 Americans waiting for kidney
   - Only 17,000 receive one each year
   - Every day, 12 people die waiting for a kidney
4. No treatment

Psychosocial Issues associated with Chronic Kidney Failure

- depression
- stress
- anxiety
- support groups, counseling and coping skills
Diabetes Nerve Disease Objectives

- Causes of neuropathy
- Different types of neuropathy
- Detection, prevention and treatment
- Key info to teach about neuropathy

Microvascular Disease and Polyol Theory

- hyperglycemia ↑ glucose level in cells
- sorbitol pathway - glucose reduced to sorbitol by aldose reductase
- polyol pathway - sorbitol oxidized to fructose by sorbitol dehydrogenase
- glucose, sorbitol, fructose toxic to cells
- nerve velocity, oxygenation, increases oxidative stress
Quick question 5

- Mary has had diabetes for 10 years and wants to reduce her risk of neuropathy. What are most important steps she can take to limit risk?
  - A. Lose weight and decrease coffee intake
  - B. Control blood glucose
  - C. Take vitamin B12 daily
  - D. Apply capsaicin cream to extremities twice daily.

What is Neuropathy?

- Diabetic Neuropathy (DN) = demonstrable nerve disorder and destruction, either clinical or subclinical- that occurs w/ diabetes, w/out other causes (10% of neuropathy due to other causes)
  - 2 abnormalities present (symptoms, signs, abnormal quantitative test results)
Neuropathy Risk Factors

- Age
- Hypertension
- Hyperglycemia
- Elevated LDL
- Smoking
- Overweight
- Excess alcohol
- Nutrition (eat lots of omega-3 fatty acids)
- Lack of exercise

Quick Question 6

- What 2 office tests can be used to detect diabetes neuropathy?
  
  A. Pin prick and electrophysiology testing
  
  B. Monofilament and tuning fork
  
  C. Hot/Cold discrimination testing
  
  D. Babinski reflex assessment
Nerve disease Screening

- Screen all patients for nerve disease using simple tests, such as a monofilament
  - Type 2 at diagnosis, then annually
  - Type 1 diabetes at 5 years, then annually
- **Tight glycemic control is the only strategy shown to prevent or delay the development and progression of neuropathy.**
- Assess and treat patients to reduce pain and symptoms to improve quality of life.

Skin Biopsy to Assess Neuropathy
3 Types of Neuropathy

- Generalized Symmetrical Polyneuropathy
  - Acute sensory
  - Chronic sensory (distal)
    - Small fiber
    - Large fiber
- Autonomic Neuropathy
- Focal and Multifocal Neuropathy

Generalized Symmetrical Polyneuropathy - Acute Sensory Neuropathy

- Severe pain, wasting, weight loss, depression and erectile dysfunction
- Foot pain- burning, unremitting, deep, sharp, stabbing, “shock like”.worse at night, hypersensitive to light touch
- Associated w/ hyperglycemia or w/ rapid improvement of glucose
- Goal – improve BG – resolve in year
Generalized Symmetrical Polyneuropathy
Chronic Sensorimotor Neuropathy

*Small Nerve Fiber*

- Sensory deficits in distal portions, spreading medially “stocking-glove”
- **Small Nerve Fiber Neuropathy**
  - C-fiber pain = burning and superficial
  - Allodynia (all stimuli interpreted as painful)
  - Later, loss of pressure and temp sensation
  - Decrease blood flow, sweating
  - Detect w/ Monofilament
  - High risk for ulceration, Charcot, gangrene

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Generalized Symmetrical Polyneuropathy
Chronic Sensorimotor Neuropathy – *Large Nerve Fiber*

- Involve sensory and/or motor nerves
- Fibers are myelinated, rapid conductors
- Can detect destruction w/ nerve testing
- Symptoms may be minimal:
  - Impaired vibration perception/position sense
  - Ataxia “moon-walking”, in-coordination
  - Pain described as deep-seated gnawing
  - Shortening of Achilles tendon and claw foot
  - Increased blood flow “hot foot”
Treating Neuropathy

- Improve glycemic control
- Control pain
- Relief from depression from chronic pain
  - Massage, stretching, pain control clinic, TENS, avoiding alcohol, relaxation exercises...

Pharmacologic Therapy for Neuropathy

Try Alpha lipoic acid: 600 – 1,800mg /day

Prescription Therapy

1st line
- Tricyclic antidepressants (ie amitriptyline, nortriptyline)
- Calcium channel modulators (ie gababentin, pregabalin)
- Serotonin Norepinephrine Reuptake Inhibitors (SNRI)

2nd line
- Topical Capsaicin Cream
- Opioids (tramadol, oxycodone)

Reasons for treatment failure:
- Dose too low, inadequate trial, pt expecting elimination of symptoms, not changing class when no response

Ziegler, D Painful diabetic neuropathy. Diabetes Care, 2009
Quick Question 7

Which of the following patients are at most risk for developing diabetes autonomic neuropathy?

A. Diabetes for 1 year with A1c of 7.6%
B. Person with diabetes for 16 years with A1c never above 6.9%
C. Person with type 1 diabetes for 8 years with retinopathy
D. Person with type 2 for 19 years with A1c less than 7.5%

“DAN” Diabetic Autonomic Neuropathy

50% of pt’s with peripheral neuropathy also have DAN

DAN increases M & M rates

- neurogenic bladder, sexual dysfunction
- GI related disorders / gastroparesis
- orthostatic hypotension
- fixed heart rate, silent MI, sudden death
- hypoglycemia unawareness
- sudomotor, pupillary
Sexual Functions as We Age

- 20-30 years: trice daily
- 30-40 years: tri weekly
- 40-50 years: try weekly
- 50-60 years: try weakly
- 60-70 years: try oysters
- 70-80 years: try anything
- 80-90 years: try to remember

A touch of humor from AADE-New Perspectives on Erectile Dysfunction, 1999

Erectile Dysfunction

- Affects about 50% of men with diabetes
- Loss of erections sufficient for intercourse
- Due to combo of vascular and nerve damage
- Tests: penile tumescence to eval if organic or psychogenic
- Treatment:
  - Sildenafil (Viagra), Vardenafil (Levitra), Tadalafil (Cialis)
    - Use caution if taking nitrate drugs. Check w/ MD first
  - Other meds, vacuum devices, prosthetics
  - HRT- testosterone gel, patches, injections, pills
Men w/ DM, 2x risk of low testosterone levels
- Symptoms include low sex drive, ED, depression, lack of energy and vitality
- Low T easily diagnosed and managed, only 10% of men currently treated
- Initial Screening:
  - Total testosterone: if < 300 ng/dl = hypogonadal
  - am testing preferred, repeat to confirm
- Treatment: determine cause, testosterone replacement therapy
Focal Neuropathies

- Often occurs in middle aged pt’s or those w/ polyneuropathy

- 4 major focal neuro
  - mono - compression or entrapment
    - carpal tunnel most common
  - plexopathy - femoral neuropathy
    - pain from hip to ant and lat aspects of thigh
  - radioculopathy - intercostal neuropathy
  - cranial - abrupt onset, HA, eye pain
Neuropathy Key Considerations

- Very common long-term complication often not recognized and treated
- Management/treatment complex
- Thorough history/assessment critical
- Treatment based on underlying process, presentation, and cost effectiveness
- Treatable condition with new therapies on horizon.

The ABC’s of Diabetes Control

A - A1c less than 7%
B - Blood pressure less than 140/90
C - Cholesterol HDL > 40, Triglycerides < 150
D - Drugs- Keep list for emergencies/ MD
E - Exercise and Eyes
F - Food and Feet
G – Glucose checks and goals
H - Healthy Coping - Hoorah for your hard work!
Hyperglycemic Crisis - See Online Courses

Thank You

- Web
  www.diabetesed.net