Diabetic Nephropathy

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What is diabetes?

- **Insulin** lowers blood glucose levels by stimulating the uptake of glucose into skeletal muscle, adipose tissue, and other tissues.

- **Definition:** Diabetes mellitus is a syndrome of inappropriate hyperglycemia due to either insulin deficiency or insulin resistance.
What is diabetes?

Type 1: is absolute deficiency in insulin, due to destruction of pancreatic beta cells

- Autoimmune process
- Onset in youth
What is diabetes?

Type 2: variable degrees of insulin deficiency and resistance

- Associated with obesity
- Onset adult or young adult
Trivia: How large is US population?

A. 26 million
B. 224 million
C. 318 million
D. 512 million
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Trivia: How many people have DM in the US?

A. 1 in 4  
B. 1 in 8  
C. 1 in 16  
D. 1 in 32
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(29 million)
Trivia: How many seniors (>65) have DM in the US?

A. 1 in 2
B. 1 in 4
C. 1 in 8
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Major complications of DM:

- **Macrovacular** (accelerated atherosclerosis):
  - coronary artery disease (heart attacks)
  - cerebrovascular disease (strokes)
  - peripheral vascular disease (gangrenous limbs)

- **Microvascular**:
  - retinopathy (blindness)
  - neuropathy (also from direct glucose neurotoxicity)
  - dermopathy
Major complications of DM:

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- **Microvascular**:
  - retinopathy (blindness)
  - neuropathy (also from direct glucose neurotoxicity)
  - dermopathy
  - nephropathy
Major complications of DM:

- **Diabetic nephropathy (DN)** is a microvascular complication of DM that is characterized by progressive development of:
  - microalbuminuria (not picked up by urine dipstick)
  - macroalbuminuria (picked up by dipstick)
  - renal failure
Risk factors for DN

- African American, Hispanic, or American Indian origin
Risk factors for DN

- Genetic predisposition in families
  - DM ≠ DN
    - Only ~ 20-30% diabetics develop DN
    - Only ~ 50% diabetics with poor control develop DN
    - Patients with good control can develop DN
  - Familial clustering of DN cases
Risk factors for DN

• Poor control of blood pressure
• Poor control of blood sugars
• Type 1 diabetes before age 20
• Smoking
• Oral contraceptives
Risk factors for DN

- Low birth weight
Epidemiology of DN

• Diabetic nephropathy is relatively rare before 10 years, peaks at 15-20 years and, if the patient has not been affected by 20 years, is unlikely to get the disease
Instant recall: How many diabetics would develop Diabetic Nephropathy?

A. 90-100%
B. 40-50%
C. 20-30%
D. 10-15%
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Epidemiology of DN

There are ~ 29,000,000 diabetics in the US. There are ~ 200,000 diabetics on dialysis (0.7%)
DN is a leading cause ESRD

US, CDC 2011
What's Your Bread and Butter?
A 70 year old Caucasian female has developed ESRD secondary to diabetic nephropathy. She is asking you how long she can expect to live on dialysis. Which statement sounds correct to you:

A. Survival of diabetics on dialysis is 90% after 3 yrs
B. Survival of diabetics on dialysis is 70% after 3 yrs
C. Survival of diabetics on dialysis is 50% after 3 yrs
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C. Survival of diabetics on dialysis is 50% after 3 yrs
TYPE 2 DIABETES: Taking control

Pat Sweitzer was diagnosed with Type 2 diabetes in her late 40s. Now at 81, she has lost both legs, uses a pacemaker, receives dialysis 3 times a week, and is legally blind due to diabetes. "I wasn't as careful as I could have been, no. So I have to blame myself for that," says Sweitzer. "I never thought of what was going to happen. I don't think anyone does when they're first diagnosed."

Learn more about Type 2 diabetes at ydr.com/diabetes
Clinical Stages of DN

- **nl GFR (100 ml/min)**
- **Urine Alb (30 mg/d)**
- **Urine Alb (300 mg/d)**
- **ESRD**

GBM Thickening Mesangial Expansion → Nodular Sclerosis (Kimelstiel-Wilson)
Clinical Stages of DN

1. Clinical Latency (0-10 years)
2. Microalbuminuria (incipient DN, 10-15 years)
3. Overt proteinururia (overt DN, 15-20 years)
4. Renal failure (>20 years)

Stage of Nephropathy

<table>
<thead>
<tr>
<th>Urine dipstick</th>
<th>Microalbumin</th>
<th>Overt Nephropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Negative</td>
<td>Positive</td>
</tr>
</tbody>
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Urine Albumin Level

- 0: Normal
- 24 Hour ACR: 30 mg/day, 2.0 mg/mmol
- 300 mg/day, 20.0 mg/mmol
- 1000 mg/day, 66.7 mg/mmol
Clinical Stages of DN and histopathology

Clinical latency stage
- Renal hypertrophy
- Enlarged kidney size
- Increased GFR
- No proteinuria
- Normal BP
Clinical Stages of DN and histopathology

Microalbumururia stage

• Normal GFR
• Urinary albumin excretion of 30-300 mg/day
• Hypertension
Clinical Stages of DN and histopathology

Microalbumuria stage

- Glomerular & tubular basement membrane thickening
Clinical Stages of DN and histopathology

Microalbumuria stage

Mesangial matrix expansion with thickening of capillary basement membranes
Clinical Stages of DN and histopathology

Overt Proteinuria stage

• Decreasing GFR
• UAE >300 mg/day
Clinical Stages of DN and histopathology

Overt proteinuria stage

• Nodular glomerulosclerosis (Kimmelstiel-Wilson nodules)
Clinical Stages of DN and histopathology

Overt proteinuria stage

• Nodular glomerulosclerosis (Kimmelstiel-Wilson nodules)
Clinical Stages of DN and histopathology

Overt proteinuria stage

- Arterioles often show thickening of their walls by deposition of glycosylated protein and arteriosclerosis.
Clinical Stages of DN and histopathology

Renal Failure stage
• Rapid progression to ESRD left untreated
• Nephrotic syndrome
• Hypertension
Clinical Stages of DN and pathology

Renal Failure stage

- Grossly small, contracted kidneys with granular surface
Histopathology in DN recap

Glomerular structural lesions
• Glomerular hypertrophy
• Glomerular basement membrane thickening
• Arteriosclerosis and hyalinosis
• Mesangial matrix expansion
• Diffuse glomerulosclerosis
• Nodular glomerulosclerosis (Kimmelstiel-Wilson)
Histopathology in DN recap

Non-glomerular structural lesions
• Tubuloepithelial cell hypertrophy
• Tubular basement membrane thickening
• Interstitial fibrosis and tubular atrophy
Differential Diagnosis

• Idiopathic nodular glomerulosclerosis
  – Same histopathology but no diabetes
Differential Diagnosis

• Amyloidosis
  – Systemic deposition of proteins in a beta-pleated sheet conformation
    • AL (monoclonal light chains)
    • AA (inflammatory conditions like chronic infections or rheumatoid arthritis)
    • Miscellaneous (familial etc)
Amyloidosis

Functional protein (soluble form)

Proposed cross-beta unit of amyloid fibril (R. Tycko, 2002)

Obtaining amyloid structure is very difficult

Amyloid aggregation (very stable, insoluble)
Amyloidosis
Amyloidosis
Amyloidosis

Congo red stain with apple green birefringence
Pathogenesis of DN

Hyperglycemia

**Functional changes**
- Hyperperfusion
- Afferent vasodilation
- Efferent vasoconstriction
- Intraglomerular HTN
- Hyperfiltration

**Metabolic changes**
- Advanced glycation end-products (AGEs)
- Cytokines (TGF-β)
- Pro-renin
- Endothelial dysfunction
- Glucose toxicity
- ROS

**Structural changes**
- Renal hypertrophy
- Mesangial expansion
- GBM thickening
- Glomerulosclerosis
Hyperglycemia

• Single most important factor in development of DN
• Hyperglycemia induces mesangial cell expansion
• Chronic hyperglycemia results in advanced glycosylation end products (AGEs)
• Decrease in GBM surface heparan sulfate
  – Increased permeability to albumin across GBM
From metabolic to structural changes
From metabolic to structural changes
Hyperglycemia

• Hyperglycemia is pertinent to sustain established lesions

• Removal of hyperglycemia allows reparative mechanisms to occur
  – Glomerular pathology can recover with prolonged maintenance of euglycemia
Photomicrographs of Renal-Biopsy Specimens Obtained before and after Pancreas Transplantation from a 33-Year-Old Woman with Type 1 Diabetes of 17 Years' Duration at the Time of Transplantation (Periodic Acid–Schiff, x120). NEJM
Functional changes

- GFR can initially rise up to 20% within 4 years of diagnosis
- Intra-glomerular hypertension
  - Dilation of the afferent arteriole
- Glomerular hypertrophy
Renal hemodynamics - normal

Glomerulus

Afferent Arteriole

Glomerular Capillary Pressure normal

Efferent Arteriole
With diabetic nephropathy

Afferent Arteriole

Increased Intraglomerular Pressure

Efferent Arteriole
From metabolic to functional changes

Activation of intra-renal hormones/cytokines
• Renin-angiotensin
• Pro-renin
• Transforming growth factor β (TGF β)
• Endothelins
• Insulin-like growth factor I
• Platelet-derived growth factor
• Protein kinase C (PKC)
Prevention of DN

- Strict glycemic control
- Antihypertensive therapy
- Identify and remove barriers to compliance
Importance of glycemic control

Intensive insulin:
- Partially reverses hyperfiltration and glomerular hypertrophy
- Delays development of significant albuminuria
- May stabilize or attenuate proteinuria in pts with albuminuria

Strict glycemic control prevents microalbuminuria in patients with type 1 Diabetes mellitus
Anti-hypertensive therapy in prevention

• Goal BP is <130/80 in patients with DM
• Goals of therapy:
  – Reduce incidence of diabetic nephropathy
  – Improve cardiovascular morbidity and mortality
Nonpharmacologic interventions

- Exercise
- Reduction in BMI
- Smoking cessation
- Low salt/low saturated fat diet

- All decrease cardiovascular mortality and morbidity
Screening

• Onset and progression can be delayed
  – Screening very important
• Ideal marker would be one that predicts DN before it develops
• Microalbuminuria remains best marker
Screening: microalbumin test

• Relatively late marker of DN
• Measured by radioimmunoassay
• Diagnosis:
  – 2/3 urine samples show >30mg/g albumin excretion
  – Measured by spot urine for albumin and creatinine (>30mg/g)
• Screen at least 5 years after diagnosis and yearly thereafter
Screening

- Test for microalbuminuria
  - No
  - Positive for albumin
    - Yes
      - Condition present that may invalidate urine albumin excretion
        - Yes
          - Treat and/or wait until resolved.
          - Result still positive after test repeated.
        - No
          - Repeat microalbuminuria test over a 3- to 6-month period.
    - No
      - Screen again in 1 year.
  - No
    - 2 of 3 tests positive
      - Yes
        - Microalbuminuria present. Treatment required.
Treatment of DN

- Renoprotection with RAS blockade
  - ACE I or ARB
- Blood pressure control
- Glycemic control
- Dietary protein restriction
- Lipid control
Anti-hypertensives in treatment

- Goal BP <125/75 with any significant UAE
- BP control single most important factor in delaying progression to CKD and cardiovascular end-points
- Treatment with ACE or ARB’s provides additional benefit beyond BP control
Angiotensin converting enzymes inhibitors (ACE)

• Anti-hypertensive effects
• Lowers intra-glomerular pressure by selectively dilating efferent arterioles
• Anti-proteinuric effects
• Anti-hypertrophic effects
  – Via attenuation of angiotensin II and TGF-β
Diabetic nephropathy

Efferent arteriole constricts to increase intraglomerular pressure.
ACE I/ARB on glomeruli

Reduced Intraglomerular Pressure

ACEI/ARBs preferentially vasodilate efferent arteriole to reduce IGP
ACE I/ARB on glomeruli

- Reduced Intraglomerular Pressure
- ACEI/ARBs preferentially vasodilate efferent arteriole to reduce IGP
Effect of proteinuria reduction

• Reduction in proteinuria is directly related to intraglomerular pressure
• In non-diabetics, reduction in proteinuria is predictive of improved renal outcomes
• Same appears to be true for diabetics
KEEP CALM AND USE ACE INHIBITORS
Glycemic control

• Proven in prevention, but less clear in treatment, especially when GFR is declining
• May stabilize micro and macro-albuminuria with tight glucose control for years
• Caution needed with:
  – Metformin: contraindicated with renal failure
  – Insulin often requires dose reduction
Chris is a 45yo male with type 2 DM and HTN for 17 years. His sugars and BPs are poorly controlled, even when he (rarely) presents for physician care. He presents to the ED with HTN and SOB. Physical exam reveals BP 180/110. He has 3+anasarca/edema. What would you expect his urine to reveal?

A. Proteinuria of 3.9 grams/24 hrs
B. Proteinuria of 390 mg
C. Proteinuria of 100 mg
D. No proteinuria
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What is NOT expected to be seen on the urine studies?

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John is a 40 yo male with type 2 diabetes for the past 5-6 years. He presents to you for routine evaluation. He is concerned about the development of kidney problems. **What will be the first sign of diabetic nephropathy?**

A. Elevated serum creatinine  
B. Hypertension  
C. Microalbuminuria  
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B. Hypertension
C. **Microalbuminuria**
D. Glucosuria
Tom is a 50 yo male with type 2 DM, HTN, dyslipidemia who presents to clinic for routine follow up. Glucose has been running 90 fasting (normal). He feels fine.

**Physical exam**
- BP 155/80. P80
- Heart/Lungs normal
- +edema

**Labs:**
- HGBA1C 6%
- Creatinine 2.0 mg/dL
- Urinalysis with 2-3+ proteinuria, quantification 2.5grams

**Meds**
- Glyburide 5 mg bid
- Lipitor 10 mg daily
- Amlodipine 5 mg daily
What would you recommend to treat diabetic nephropathy?

A. Changing to insulin
B. Increasing glyburide
C. Increase amlodipine
D. Start enalapril
E. Recommend protein restriction
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Now you can

• Recognize patients at risk for Diabetic Nephropathy
• Recognize DN in clinical setting
• Recognize DN under microscope
• Describe how hyperglycemia leads to nephropathy
• Recommend a screening program to a patient with diabetes
• Recommend a prevention plan to a patient with diabetes
• Recommend a treatment plan to a patient with diabetes