Author(s): Frank Brosius, M.D, 2011

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Kidney Systemic Disease Diabetes

Frank Brosius, M.D.
Diabetic Nephropathy--Objectives

- Understand pathology and pathogenesis
- Identify early clinical predictors or indicators
- Describe most important therapeutic interventions to prevent progression
Diabetic Nephropathy: “You can't cure it so you have to endure it”


American Diabetes Association
Diabetes is the dominant cause of ESRD in USA

Incident ESRD patients; Medical Evidence form data; rates adjusted for age, gender, & race.
Incidence rates of ESRD (per million population): 1997

Incident ESRD patients, by HSA; rates adjusted for age, gender, & race. Excludes patients residing in Puerto Rico & the Territories.

U.S. Renal Data System, 2009
Incidence rates of ESRD (per million population): 2007

Incident ESRD patients, by HSA; rates adjusted for age, gender, & race. Excludes patients residing in Puerto Rico & the Territories.

USRDS 2009
Obesity, metabolic syndrome and type 2 diabetes mellitus

CalorieLab® based on the Behavioral Risk Factor Surveillance System database maintained by the CDC. Rankings use a three-year average for smoothing.
Adjusted five-year survival, by modality & primary diagnosis: 1993-2002: still lousy

Incident dialysis patients & patients receiving a first transplant in the calendar year. All probabilities are adjusted for age, gender, & race; overall probabilities are also adjusted for primary diagnosis. All ESRD patients, 1996, used as reference cohort. Modality determined on first ESRD service date; excludes patients transplanted or dying during the first 90 days (five-year survival probabilities noted in parentheses).
Adjusted five-year survival, by modality & primary diagnosis: 1998-2002: still lousy

Diabetic nephropathy = Cancer
The stages of diabetic nephropathy

- Onset of diabetes
- Insulin treatment
- Poor control
- Optimal control
- Proteinuria
- Antihypertensive therapy


American Diabetes Association
Risk factors for renal disease in Type II DM

- Genetic factors (familial clustering)
- Hyperglycemia
- Hypertension
- Glomerular hyperfiltration/hypertension
- Smoking
- Male gender
- Advanced age
- Race

UpToDate, 2010
Genetic factors

The stages of diabetic nephropathy

ELMO1, NOS3, etc

Family Investigation of Nephropathy of Diabetes (FIND) Consortium

The stages of diabetic nephropathy

Race: Diabetes is the dominant cause of ESRD in USA...more so in AAs

December 31 point prevalent ESRD patients; rates adjusted for age & gender.
The stages of diabetic nephropathy

Screening for diabetic nephropathy:

1) Microalbuminuria

<table>
<thead>
<tr>
<th>Category</th>
<th>Spot collection (μg/mg creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>30–299</td>
</tr>
<tr>
<td>Macro (clinical)-albuminuria</td>
<td>≥300</td>
</tr>
</tbody>
</table>
Evaluation of microalbuminuria

• Test type 1 patients after 5 years and every year thereafter
• Test type 2 patients every year
• If positive, rule out transient causes of microalbuminuria (e.g., CHF, exercise (within 24 hr), infection, fever, severe HTN)
• Repeat 2 times in 3-6 months

– Microalbuminuria = 2/3 tests positive.
Screening for diabetic nephropathy:
2) Estimate GFR

“Measure serum creatinine at least annually in all adults with diabetes regardless of the degree of urine albumin excretion. The serum creatinine should be used to estimate GFR and stage the level of chronic kidney disease (CKD), if present.”

from Standards of Medical Care in Diabetes-2010
DIABETES CARE, VOLUME 32, SUPPLEMENT 1, JANUARY 2010
The stages of diabetic nephropathy

The normal glomerulus

- Proximal convoluted tubule
- Endothelial cell
- Visceral epithelial cell (Podocyte)
- Bowman's space
- Mesangium
- Efferent arteriole
- Distal convoluted tubule
- Parietal epithelial cell
- Capillary lumen
- Basement membrane
- Mesangial cell
- Extraglomerular mesangium
- Macula densa
- Afferent arteriole
- Juxtaglomerular apparatus
Pathology of DM nephropathy

Normal Glomerulus
- Capillary lumen
- Mesangial cell

Early Diabetic Glomerulus
- Podocyte damage & loss
- Thickened BM
- Expanded mesangium

- Afferent and efferent hyaline arteriolosclerosis
- Interstitial fibrosis and tubular atrophy

Source Undetermined
Pathology of DM nephropathy

- Normal glomerulus
- Diffuse mesangial sclerosis
- Nodular mesangial sclerosis
Pathology of DM nephropathy

Normal Glomerulus
- Capillary lumen
- Mesangial cell
- Mesangium

Early Diabetic Glomerulus
- Podocyte damage & loss
- Thickened BM
- Expanded mesangium

- Afferent and efferent hyaline arteriolosclerosis
- Interstitial fibrosis and tubular atrophy

Source Undetermined
Podocyte loss predicts progression of nephropathy

The stages of diabetic nephropathy

The pathogenesis of diabetic nephropathy: A proposed schema

Diabetic milieu

- Glomerular basement thickening
- Renal hypertrophy
- Glycosylation of plasma proteins
- Altered chemical composition of glomerular components

- Permeability detects
- Increased leakage of plasma proteins into glomerulus
- Proteinuria

- Cellular proliferation increased matrix production
- Mesangial expansion and glomerular capillary basement membrane thickening

- Glomerulosclerosis
- Cellular injury
- Decreased glomerular filtration rate

Source Undetermined
Simpleminded model of pathogenesis of DM nephropathy

Renal preglomerular vasodilation

Systemic hypertension

Glomerular hypertension

Hyperglycemia
Genetic factors
Δ metabolism of glom. cells

Glomerular sclerosis

from T. Hostetter
The normal glomerulus

- Proximal convoluted tubule
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Glomerular sclerosis

Simpleminded model of pathogenesis of DM nephropathy

from T. Hostetter
Potential mechanisms for increased matrix production in hyperglycemia

- TGF-β
- AII
- Stretch
- GLUT1
- AGES
- ROS
- NADH/NAD
- PKCβ
- ERKs
- DAG
- Fructose
- Sorbitol
- Glucose
- Fibronectin
- Collagen IV
- Mesangial cell

Source Undetermined
Unified field theorem for diabetic complications: oxidative stress rules

...or maybe it’s all inflammation?

Treatment of DM nephropathy:
Glucose control

Renal preglomerular vasodilation

Systemic hypertension

Glomerular hypertension

Hyperglycemia
Genetic factors
Δ metabolism of glom. cells

Glomerular sclerosis

from T. Hostetter
The Diabetes Control And Complications Trial (DCCT) 1993

1400 INDIVIDUALS WITH IDDM

CONVENTIONAL INSULIN THERAPY

INTENSIVE INSULIN THERAPY

CONTROL OF Sx’s.

NORMALIZE BLOOD SUGAR

Does long-term normalization of blood glucose levels in type 1 diabetes reduce the risk of development or progression of microvascular complications?
The Benefits of “Tight Control”: The DCCT

Intensive metabolic control dramatically reduced the risk of developing or worsening microvascular complications in type 1 diabetes.

The United Kingdom Prospective Diabetes Study (UKPDS), demonstrated very similar results in individuals with type 2 diabetes.
Intensive insulin Rx prevents diabetic nephropathy for years after (EDIC)

HbA1c levels after end of DCCT

Cumulative incidence of nephropathy

Arch Int Med; 2009;169(14):1307
The stages of diabetic nephropathy

Renal preglomerular vasodilation

Systemic hypertension

Glomerular hypertension

Hyperglycemia
Genetic factors
Δ metabolism of glom. cells

Glomerular sclerosis

Treatment of DM nephropathy: Hypertension control

from T. Hostetter
Effect of antihypertensives on progression of DM nephropathy

Rate of decline in GFR (ml/min/mo)

MAP post Rx (mmHg)

111
99
114

Source: Undetermined
Renal preglomerular vasodilation

Systemic hypertension

glomerular hypertension

Hyperglycemia
Genetic factors
Δ metabolism of glom. cells

glomerular sclerosis

Treatment of DM nephropathy: Effect of ACEIs and ARBs

from T. Hostetter
The normal glomerulus

Proximal convoluted tubule
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Basement membrane
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Extraglomerular mesangium
Macula densa
Afferent arteriole
Juxtaglomerular apparatus

ACEI or ARB
DM
Delaying nephropathy with ACE inhibitors

Lewis et al., NEJM 329:1456, 1993
Delay of diabetic nephropathy in type 2 patients with ARBs

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>RENAAL</td>
<td>Reduction of endpoints in non-insulin-dependent diabetes mellitus with the angiotensin II receptor antagonist losartan</td>
</tr>
<tr>
<td>IDNT</td>
<td>Irbesartan diabetic nephropathy trial</td>
</tr>
<tr>
<td>IRMA-II</td>
<td>irbesartan in patients with type II diabetes and microalbuminuria</td>
</tr>
</tbody>
</table>

ARB = angiotensin receptor blocker

NEJM, 2001
**Delay of diabetic nephropathy in type 2 patients with ARBs**

RENAAL and IDNT--
- pts with established overt nephropathy
- Age = 60 (IDNT)
- virtually all pts hypertensive; groups had similar BPs
- endpoints = 2x serum creatinine, ESRD, death
- 20-33% reduction in endpoints in ARB treated pts vs control or amlodipine-treated pts

IRMA-II
- reduction in proteinuria and rate of progression to overt nephropathy in type 2 pts with microalbuminuria
Treatment of DM nephropathy: Effect of dietary protein restriction

Renal preglomerular vasodilation

Systemic hypertension

Glomerular hypertension

Hyperglycemia
Genetic factors
Δ metabolism of glom. cells

Glomerular sclerosis

from T. Hostetter
Effect of dietary protein restriction on progression of DM nephropathy
Treatment of DM nephropathy: Effect of statins

Renal preglomerular vasodilation

↓

Systemic hypertension

↓

Glomerular hypertension

↓

Hyperglycemia

ROS

Genetic factors

Δ metabolism of glom. cells

Glomerular sclerosis

from T. Hostetter
Effects of lipid lowering on progression of diabetic nephropathy

Fried, et al., Kidney Int, 2001; 59:260
Renal preglomerular vasodilation

↓ Glomerular hypertension

↓ Glomerular sclerosis

- Systemic hypertension
- Hyperglycemia
- ROS
- Genetic factors
- Δ metabolism of glom. cells

Treatment of DM nephropathy: All together!

from T. Hostetter
Remission of microalbuminuria

Table 3. Results of the Cox Regression Analysis of Regression of Microalbuminuria with the Use of Time-Dependent Factors.∗

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonmodifiable</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (≤26 vs. &gt;26 yr)</td>
<td>1.6 (1.2–2.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>Incidence cohort (vs. prevalence cohort)‡</td>
<td>1.8 (1.2–2.6)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Modifiable</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid status†</td>
<td>2.4 (1.4–4.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Cholesterol &lt;198 mg/dl, triglycerides &lt;145 mg/dl</td>
<td>1.9 (1.0–3.8)</td>
<td></td>
</tr>
<tr>
<td>Cholesterol ≥198 mg/dl, triglycerides &lt;145 mg/dl</td>
<td>2.1 (1.2–3.5)</td>
<td></td>
</tr>
<tr>
<td>Cholesterol ≥198 mg/dl, triglycerides ≥145 mg/dl</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Glycosylated hemoglobin</td>
<td>1.9 (1.2–2.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>8.0–8.9 %</td>
<td>1.5 (1.0–2.3)</td>
<td></td>
</tr>
<tr>
<td>9.0–9.9 %</td>
<td>1.2 (0.8–1.9)</td>
<td></td>
</tr>
<tr>
<td>≥10.0%</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure§</td>
<td>1.4 (1.0–1.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>≥115 mm Hg</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

Graph showing likelihood of regression with number of factors at salutary levels.
The stages of diabetic nephropathy


American Diabetes Association
Remittive effect of pancreas Tx on DM nephropathy

<table>
<thead>
<tr>
<th>time after Tx</th>
<th>0 yr</th>
<th>5 yr</th>
<th>10 yr</th>
</tr>
</thead>
</table>

GBM

TBM

Mesangial fx. vol

Matrix fx. vol


Remittive effect of long term ACEI on chronic nephropathies

Ruggenenti, JASN10:997, 99
Remission of microalbuminuria results in fewer cardiovascular and kidney events.

TABLE 3
The risk of death from and hospitalization for renal and cardiovascular events, evaluated using the pooled logistic regression analysis

<table>
<thead>
<tr>
<th></th>
<th>Crude risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted risk (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Model 1</td>
</tr>
<tr>
<td></td>
<td>Model 2</td>
</tr>
<tr>
<td>Reduction of albuminuria</td>
<td></td>
</tr>
<tr>
<td>50% reduction</td>
<td>0.38 (0.16-0.91)</td>
</tr>
<tr>
<td>Nonreduction</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td></td>
<td>0.47 (0.17-0.98)</td>
</tr>
<tr>
<td></td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td></td>
<td>0.41 (0.15-0.96)</td>
</tr>
<tr>
<td>Stage of diabetic nephropathy</td>
<td></td>
</tr>
<tr>
<td>Remission</td>
<td>0.30 (0.09-0.89)</td>
</tr>
<tr>
<td>No change</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td></td>
<td>0.27 (0.08-0.91)</td>
</tr>
<tr>
<td></td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td></td>
<td>0.25 (0.07-0.87)</td>
</tr>
<tr>
<td></td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>Progression</td>
<td>2.31 (1.00-5.07)</td>
</tr>
<tr>
<td></td>
<td>2.45 (1.96-5.65)</td>
</tr>
<tr>
<td></td>
<td>2.55 (1.04-6.30)</td>
</tr>
</tbody>
</table>

Model 1 adjusted for sex and age, initial AER levels, and a history of cardiovascular disease. Model 2 adjusted for sex, age, initial AER levels, a history of cardiovascular disease, current smoking, A1C, total and HDL cholesterol, triglyceride, systolic and diastolic blood pressure, BMI, and the use of ACE inhibitors, angiotensin receptor blockers, or lipid lowering-drugs. ref., referent.
Clinical course — M.W. (34 yo female with type 1 DM for 33.5 yrs)

Estimated GFR (ml/min)

U Pro/creat

BP = 133/83

BP = 100/70

Stopped ACEI

Last eGFR = 47 ml/min
Diabetic Nephropathy: “You can't cure it so you have to endure it”

With current treatment, we can keep patients stable or in remission for years.....

But can we do better?
Management of Diabetic Nephropathy-Dx

• Screen for microalbuminuria and eGFR (1x/yr).

• Identify high risk patients.

• Monitor BP, blood glucose closely at home.

• Monitor for macrovascular disease.
Management of Diabetic Nephropathy-Rx

• Normalize BP. Target <130/80.

• Treat with ACE inhibitors or ARBs.

• Treat hyperlipidemia and hyperglycemia aggressively.

• Moderate protein restriction (0.8-1.0 gm/kg/day).

• Treat cardiovascular disease aggressively.

• Refer to nephrologist early in course of azotemia.
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Slide 12: American Diabetes Association
Slide 13: American Diabetes Association
Slide 14: American Diabetes Association
Slide 15: American Diabetes Association
Slide 17: American Diabetes Association
Slide 18: Standards of Medical Care in Diabetes—2010 DIABETES CARE, VOLUME 33, SUPPLEMENT 1, JANUARY 2010
Slide 19: Diabetes Care, 23:S69, 2000
Slide 20: American Diabetes Association
Slide 21: American Diabetes Association
Slide 22: Source Undetermined
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Slide 25: Source Undetermined
Slide 27: American Diabetes Association
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Slide 30: Source Undetermined
Slide 31: Source Undetermined
Slide 34: American Diabetes Association
Slide 35: Arch Int Med; 2009;169(14):1307
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Slide 44: Ruggenenti, JASN10:997, 99
Slide 45: Araki, et al., Diabetes. 2007 Jun;56:1727
Slide 46: Source Undetermined
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Slide 49: American Diabetes Association; Source Undetermined