


Diabetic Kidney Disease
Tripti Singh MD
Department of Nephrology
University of Wisconsin

Disclosures 
I have no financial relationship with the manufacturers of any commercial product discussed during this CME activity

Objectives 
• How diabetes causes kidney disease
• Risk factors for development of diabetic kidney disease
• Prevent development of diabetic kidney disease

What is Diabetic Kidney disease?
Why do we care?

65 year old Mr. Z with type 2 diabetes for 20 years

- No follow up for 5 years
- HgA1c 10%
- 3.0 gram proteinuria (up from 900 mg 5 years ago)
- Serum Creatinine 1.1, eGFR >60ml/min
- BP 140/85
- PE: 1+ ankle edema



Image courtesy Google Images

65 year old male with type 2 diabetes for 20 years with serum creatinine 1.1 (eGFR>60ml/min) and 3000 mg of proteinuria

Does Mr. Z have diabetic kidney disease?

Diabetic Kidney disease

Presumptive diagnosis that kidney disease is caused by diabetes

- Micro/macro-albuminuria
- Decreased GFR
- Pathologic features of diabetic nephropathy



Definitions Albuminuria

Category	Spot Collection (mg/g creatinine)	24-Hour Collection (mg/24 h)	Timed Collection (µg/min)
Normoalbuminuria Normal	<30	<30	<20
Microalbuminuria Moderately increased	30-300	30-300	20-200
Macroalbuminuria Severely increased	>300	>300	>200

Because of variability in urinary albumin excretion, at least 2 specimens, preferably first morning void, collected within a 3- to 6-month period should be abnormal before considering a patient to have crossed 1 of these diagnostic thresholds. Exercise within 24 hours, infection, fever, congestive heart failure, marked hyperglycemia, pregnancy, marked hypertension, urinary tract infection, and hematuria may increase urinary albumin over baseline values.

2007 NKF KDOQI guidelines
2012 KDIGO Guidelines

Albuminuria and Proteinuria

Table 7 | Relationship among categories for albuminuria and proteinuria

Measure	Categories		
	Normal to mildly increased (A1)	Moderately increased (A2)	Severely increased (A3)
AER (mg/24 hours)	<30	30-300	>300
PBR (mg/24 hours)	<150	150-500	>500
ACR (mg/min)	<3	3-30	>30
PCR (mg/min)	<30	30-300	>300
PCR (mg/min)	<15	15-50	>50
PCR (mg/d)	<150	150-500	>500
Protein reagent strip	Negative to trace	Trace to +	+ or greater

2012 KDIGO Guidelines

Definitions Decreased Glomerular Filtration Rate

GFR categories in CKD		
GFR category	GFR (ml/min/1.73 m ²)	Terms
G1	≥ 90	Normal or high
G2	60-89	Mildly decreased*
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	< 15	Kidney failure

KDIGO 2012 Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease K1 2013

Staging of Diabetic Kidney Disease

GFR category (ml/min/1.73 m ²)	GFR category		Proteinuria albuminuria categories		
	Description and range		A1	A2	A3
G1	Normal or high	≥ 90			
G2	Mildly decreased	60-89			
G3a	Mildly to moderately decreased	45-59	Normal to mildly increased	Moderately increased	Severely increased
G3b	Moderately to severely decreased	30-44			
G4	Severely decreased	15-29	< 30 mg/dL or less	30-300 mg/dL	> 300 mg/dL
G5	Kidney failure	< 15			

65 year old male with type 2 diabetes for 20 years with serum creatinine 1.1 (eGFR>60ml/min) and 3000 mg of proteinuria

Mr. Z has G2A3 Diabetic Kidney Disease

Why do we care?

Very common

Very expensive

High mortality

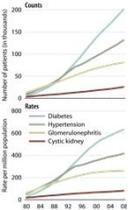


Image Courtesy: Google Images

Diabetic Kidney Disease

Very common

50% of ESRD patients have diabetic as cause of ESRD



January 1 point prevalent Medicare patients age 66 & older. Adj. age/gender/race prior hospitalization/comorbidities. Ref: 2010 patients, USRDS 2013

Diabetic Kidney disease

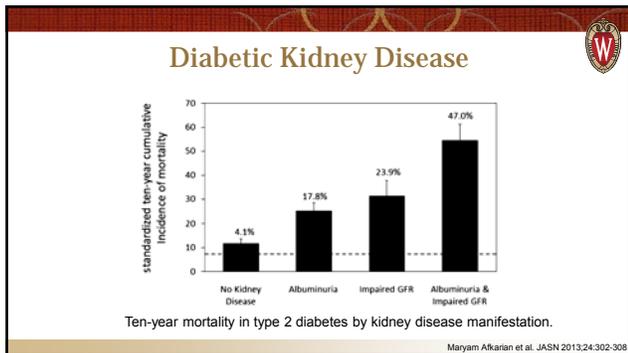
25 billion \$

Table 2. Per person and total costs attributable to CKD

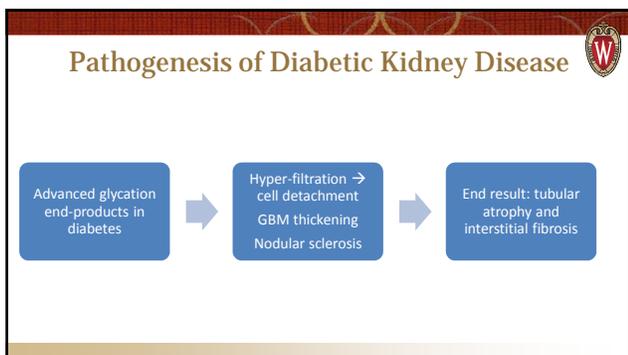
CKD Stage	Per Person Costs (\$5% CI) ^a	Estimated Medicare FFS Enrollees, 2010 (n) ^b	Total CKD Costs for Medicare FFS Enrollees (\$) ^c
1	1400 (–900 to 3870)	474,012	0.74 billion
2	1700 (530 to 2840)	2,700,432	4.56 billion
3	3500 (1780 to 4620)	10,726,317	37.18 billion
4	12,700 (6000 to 19,650)	563,787	7.17 billion

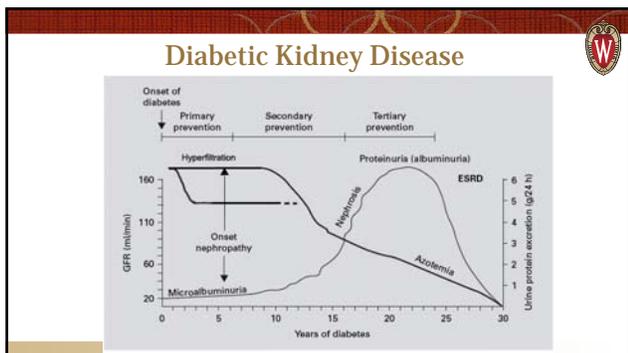
^aUpdated to 2010 dollars by using the medical care component of the Consumer Price Index. Each part of the two-part cost model is estimated also including controls for age, age-squared, sex, race/ethnicity, education, region of residence, and each of the following comorbid conditions: diabetes, hypertension, cancer, arthritis, pneumonia, back pain, chronic bronchitis, and asthma. CI, confidence interval.
^bBoosted using 95% CI by using 1000 iterations.
^cCalculated by using estimates of CKD prevalence for the population age 65 years or older to most closely approximate the Medicare population; prevalence estimated by using 1999–2004 NHANES data applied to 2010 Medicare enrollment data.
^dEstimates are the product of the per person cost point estimates and the number of enrollees.

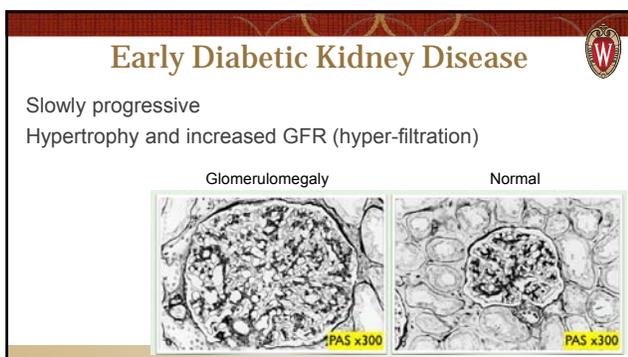
Honeycutt et al JASN Aug 1 2013



- ### Objectives
- How diabetes causes kidney disease?
 - What are the risk factors for development of diabetic kidney disease?
 - How to prevent development of diabetic kidney disease?

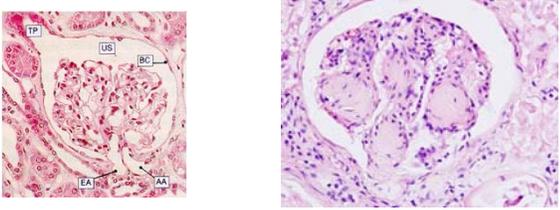








Kimmelstein Wilson Lesions



The slide features two histological images of Kimmelstein-Wilson lesions. The left image shows a glomerulus with labels TP, US, BC, EA, and AA. The right image shows a glomerulus with nodular mesangial sclerosis.

Late Diabetic Kidney Disease

Increased mesangial matrix → nodular mesangial sclerosis
GBM thickening



The slide features a histological image of a glomerulus in late diabetic kidney disease, showing nodular mesangial sclerosis and GBM thickening.

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Risk Factors for Diabetic Kidney Disease

Not every diabetic gets diabetic kidney disease



Google Images

Risk Factors for Diabetic Kidney Disease

Type 2 DM (10 years after diagnosis)
Prevalence of albuminuria **25%**
Elevated plasma creatinine > 2.0 mg/dL **5%**
Requirement for renal replacement therapy **0.8%**

Type 1 DM (30 years after diagnosis)
Albuminuria of 300 mg/d, serum creatinine level > 2 mg/dL, or dialysis or renal transplant: **25%**

Alder et al Development and progression of nephropathy in type 2 diabetes: UKPDS Kidney Int. 2003;63(1):225
Nathan et al DCCT/EDIC work group 2009 Jul 27;169(14):1307-1

Risk Factors for Diabetic Kidney Disease

- Genetic predisposition
 - Ethnicity
 - Family History of Diabetic Kidney Disease
- Poor glucose control
- Duration of Diabetes
- Hypertension
- Smoking

Genetics

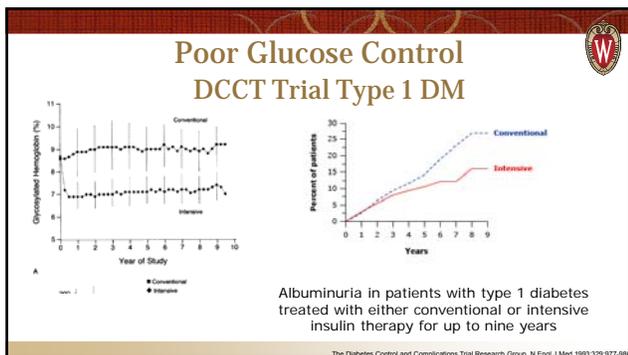
- Nephropathy occurs in families
- Risk of nephropathy increases 5 fold if a sibling has nephropathy
- Family history of hypertension increases risk
- Predisposition to diabetic nephropathy linked to polymorphism in angiotensinogen and angiotensin receptors (AT1R)

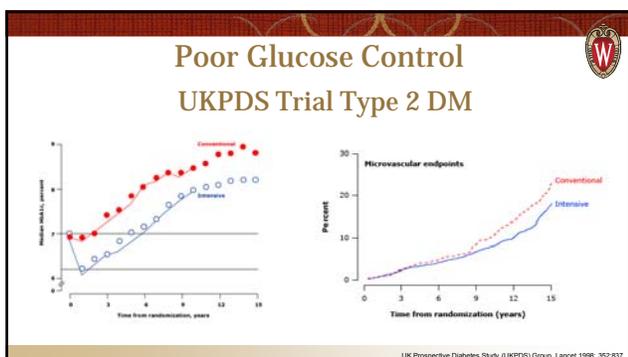
Salko et al. Nephropathy in siblings of African Americans with overt type 2 diabetic nephropathy. *AJKD* 2002 Sep;40(3):489-94.
Kobayashi et al. Genetic susceptibility to diabetic kidney disease: an update. *J Diabetes Complications* 2010 Oct;24(4):277-8.
Forsyth et al. Genetic susceptibility and the role of hypertension in diabetic nephropathy. *Curr Opin Nephrol Hypertens* 1997 Mar;6(2):154-9.

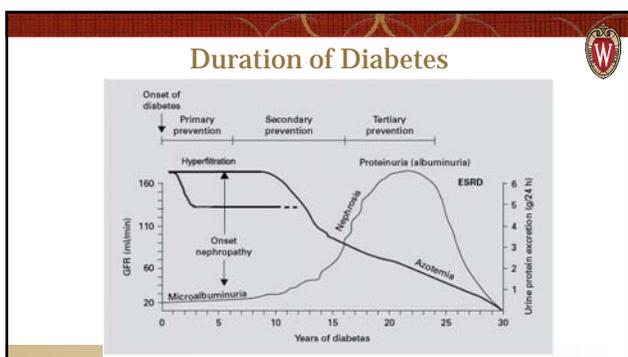
Gender and Ethnicity

- Men > women
- Increased incidence in
 - African Americans, Native Americans
 - Mexican Americans
 - Polynesians
 - Australian Aborigines
 - Caucasians

Smith et al. Racial differences in the incidence and progression of renal diseases. *KD* 1991 Nov;40(5):815-22.
Brancati et al. The excess incidence of diabetic ESRD among blacks. A population-based study of potential explanatory factors. *JAMA* 1992 Dec 2;268(21):3078-84.







Mr. Z with type 2 diabetes for 20 years

- No follow up for 5 years
- HgA1c 10%
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Risk factors in him?

Mr. Z with type 2 diabetes for 20 years

- Male
- Poor diabetes control HgbA1c 10%
- Duration of diabetes
- HTN BP 140/85
- ?Smoking

Risk factors in him?

Objectives

- How diabetes causes kidney disease?
- What are the risk factors for development of diabetic kidney disease?
- How to prevent/slow down development of diabetic kidney disease?



Mr. Z with type 2 diabetes for 20 years

- No follow up for 5 years
- HgA1c 10%
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What to do now?

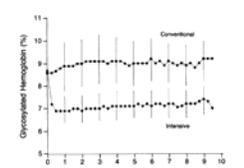


How to prevent/slow down progression of diabetic kidney disease?

- Tight Glycemic control
- Good BP control
 - ACE-I or ARB
- Quit smoking
- Weight loss
- Treatment of hyperlipidemia

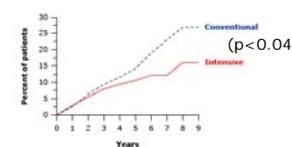


Tight Glucose Control Primary prevention



A

Legend: ● Conventional, ● Intensive



B

$p < 0.04$

Albuminuria in patients with type 1 diabetes treated with either conventional or intensive insulin therapy for up to nine years

The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993;329:977-86

Tight glucose control- primary prevention

22 years since the start of the DCCT trial, patients originally assigned to intensive glycemic control were significantly less likely to develop impaired renal function, defined as an estimated glomerular filtration rate less than 60 mL/min per 1.73 m² (3.9 versus 7.6 percent)

No. at Risk	Intensive Therapy	Conventional Therapy
0	721	720
5	654	657
10	584	617
15	472	594
20	413	506
25	308	461

The DCCT/EDIC Research Group. N Engl J Med 2011; 365: 2266-2277

Poor Glucose Control UKPDS Trial Type 2 DM

Intensive therapy associated with 12 percent reduction in the development of any diabetes-related endpoint (P = 0.03)

UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352:857

What to use for good glucose control in T2DM

- Metformin: eGFR of 30 ml/min/1.73m² if already on it. Starting metformin eGFR >45ml/min/1.73m² ¹
- Sulfonylurea: Risk of hypoglycemia
- Sodium glucose cotransporter-2 (SGLT2) inhibitors: Efficacy reduced and toxicity if eGFR<45 ml/min/1.73m²
- Insulin: High risk of hypoglycemia especially with CKD

¹ Kojouhar et al Metformin therapy and kidney disease: a review of guidelines and proposals for metformin withdrawal around the world. *Pharmacoeconomics Drug Saf.* 2013 Oct 22; 1(1): 1027-35

Angiotensin pathway inhibition in Type 1 DM

N= 207 in captopril group
 N= 202 in placebo group
 Average diabetes duration 22 years
 Proteinuria >500 mg/day
 Serum creatinine < 2.5 gm/dL
 Systolic BP = 135 mm Hg in the captopril group and 138 mm Hg in the placebo group

Lewis EJ et al. The Effect of Angiotensin-Converting Enzyme Inhibition on Diabetic Nephropathy. *N Engl J Med* 1993;329:1456-1461

Angiotensin pathway inhibition in Type 2 DM

1715 T2DM patients
 irbesartan (300 mg daily), amlodipine (10 mg daily), or placebo.

End point: doubling of serum creatinine, development of ESRD or death from any cause.

Follow-up was 2.6 years.

Treatment with irbesartan led to primary composite end point that was 20% lower than that in the placebo group (P=0.02) and 23% lower than that in the amlodipine group (P=0.006)

Lewis EJ, Hunsicker LG, Clarke WR, et al. *N Engl J Med* 2001; 345:861

Dual ACE-I and ARB in diabetic nephropathy

- 2 large randomized trials showed dual blockade led to increase in hyperkalemia, worsening eGFR and increased mortality

Yusuf S et al ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008; 358: 1547-1559.

Fried et al VANEPROND Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy. *N Engl J Med* 2011

Aldosterone Antagonists

- Meta-analysis (11 trials, 991 patients)
- Addition of spironolactone to ACEi/ARB
- Reduces Proteinuria by 0.80g (-1.27,-0.33)
- Increased Hyperkalemia RR=3.06 (1.26, 7.41)
- No improvement in eGFR



Naranjo et al. Clin J Am Soc Nephrol. 2009;4(3):542

Aldosterone Antagonists- who to use

- A subset of patients (40%) after initiation of ACE inhibitor or ARB therapy develop aldosterone breakthrough. Patients with aldosterone breakthrough may lose kidney function faster (median of -5.0 ml/min/yr vs -2.4 ml/min /yr)

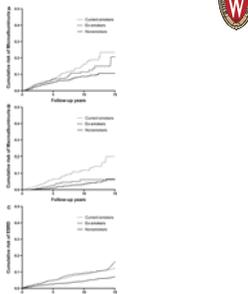
Bombardieri et al. The incidence and implications of aldosterone breakthrough. Nat Clin Pract Neph. 2007 Sep;3(9):486-92

Smoking Cessation

3613 patients with type 1 diabetes, participating in the Finnish Diabetic Nephropathy Study

The 12-year cumulative risk of ESRD

Current smokers 10.3 % ($P < 0.0001$)
 Ex-smokers 10.0 % ($P < 0.0001$)
 Non smokers 5.6 % (4.6-6.7)



Feodoroff, M. et al. Smoking and progression of diabetic nephropathy in patients with type 1 diabetes. Acta Diabetol (2016) 53: 525

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- PE: 1+ ankle edema

What to do now?

65 year old male with type 2 diabetes for 20 years

- HgA1c 10% - **better DM control**
- 3.0 gram proteinuria (up from 900 mg 5 years ago)- **ACE-I**
- Serum Creatinine 1.1, eGFR >60ml/min
- BP 140/85 **ACE-I**
- PE: 1+ ankle edema – **might need diuretics**
- **Low salt diet**
- **Lipid check**
- **Smoking cessation**

Thank you

Questions

LOVE YOUR kidneys

Contact: tsingh@medicine.wisc.edu
