Kidney Disease and Hypertension in Diabetes: Early diagnosis and Aggressive Management are Key

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Numbers of Patients on Dialysis-USA: 1992

Numbers of Patients on Dialysis-USA: 2002

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Common Causes of Chronic Kidney Disease

- Diabetes Mellitus
- Hypertension
- Glomerulonephritis
### Kidney Disease 2011 Data

- About 14% of the USA Population has chronic kidney disease as defined as GFR of <60 ml/min or elevated urine albumin level.
- Most CKD patients die of heart disease before reaching ESRD.
- About 593,000 patients on dialysis or with a kidney transplant.
- About 427,000 - Dialysis and 86,000 - Transplant; 91,000 on transplant waitlist.
- Death Rates are 20% per year for dialysis population and the number of end stage patients rises about 1-3% each year.
- Medicare spent 31 Billion dollars in 2010 which is 6.2% of the medicare budget.

### Diagnose Kidney Disease Early

#### Calculate estimated Glomerular Filtration Rate

- **Cockroft-Gault Formula**
- **MDRD Formula**
- **CKD-EPI Formula**

#### Measure Urine Albumin/Protein Level

### Estimated Creatinine Clearance

\[
\frac{(140 - \text{age}) \times \text{Weight (kg)} \times 0.85}{\text{Serum Cr} \times 72} \text{ (if female)}
\]
A 70-year-old Woman Who Weighs 55 Kg (121 Lbs.) with a Creatinine of 1.5

You might think her GFR is about 50–70 ml/min

\[
\frac{(140 - 70)}{1.5} \times \frac{55}{72} \times 0.85 \text{ (for a female)}
\]

= 30.3 ml/min

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**Importance of Knowing GFR**

- Complications of renal disease (e.g., anemia, renal osteodystrophy, malnutrition, and volume regulatory disorders) are seen with increasing frequency at Stage 3 kidney disease (GFR <60ml/min)
- Deleterious relationship between chronic kidney disease (CKD) and cardiovascular disease is seen at stage 3
- Risk for Contrast Dye Nephropathy
- Drug dose adjustments

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**ALWAYS CALCULATE eGFR**
Albuminuria/Proteinuria Are Independent Risk Factors for Progression of Kidney Disease and Development and Progression of Cardiovascular Disease

**Albuminuria**

- Normal renal excretion is about 200 mg/day of total protein (up to 20 mg is albumin)
- Levels of albumin > 20 mg/24 hours is abnormal
- Microalbuminuria by Albumin/Creatinine Ratio: 30–300 mg/g
- Macroalbuminuria by Albumin/Creatinine Ratio: >300 mg/g

**Spot Urine Albumin or Protein/Creatinine Ratio Closely Correlates with 24 Hour Urine**

Albuminuria/Proteinuria Are Independent Risk Factors for Progression of Kidney Disease and Development and Progression of Cardiovascular Disease

Schwab Arch Int Med 1987
Increasing Albuminuria and Decreasing GFR Correlate with Increased Cardiovascular and Renal Events in Type 2 Diabetes


Mortality is directly Associated with GFR and Albumin/Creatinine Ratio


Excess Mortality in Type 2 Diabetes is Due to Kidney Disease


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Albuminuria appears to be a marker for generalized inflammation and endothelial dysfunction.

In a Patient with Cardiovascular Disease it is very important to screen for Kidney Disease.

In a Patient with Kidney Disease, it is very important to screen for Cardiovascular Disease.

Prevention of Kidney Disease
Everyone with Diabetes should take an ACE inhibitor to prevent the development of kidney disease.

1. Yes
2. No

No primary prevention of diabetic kidney disease by enalapril or losartan in Type 1 Diabetes


<table>
<thead>
<tr>
<th>End Point</th>
<th>Enalapril</th>
<th>Losartan</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Measured fractional excretion</td>
<td>0.385±0.164</td>
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<td>Mean change at 3 yr</td>
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<td>P-value</td>
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</table>
There was Primary Prevention with Trandolapril in Type 2 Diabetes


But:
1) Other large studies do not show any benefit.
2) 70% or more of type 2 DM patients will not develop kidney disease.
3) There is no study showing that waiting until a patient develops albuminuria and then treating is detrimental.

There is no unique Indication for ACE Inhibitors or ARBs for Primary Prevention of Kidney Disease in Diabetic Patients.

ACE Inhibitors and ARBs are definitely Indicated for Patients with Albuminuria

Prevention of Kidney Disease

- Aim for blood pressure of <130/80
- Stop smoking
- Tight Blood Glucose Control
  - A1c <7%
- Avoid high protein diet (>1.5 to 2 g/kg/day)
- No Indication for ACE Inhibitor or ARB for Primary Prevention of Kidney Disease
Treatment of Kidney Disease

Is there a role for Low Protein diets?

- Low Protein Diet (<0.8 g/kg/day)
- High protein intake is associated with worsening renal disease
- In animal studies, a sustained low protein diet lowers glomerular pressures and can slow progression
- Low protein diets have not been shown to be effective in humans. Possibly because it is very hard to stay on a low protein diet
TREATMENT

- Blood Pressure  <130/80
- Lower Urine Albumin
- Stop Smoking
- Tight Glucose Control  - A1c < 7.0%

ACE inhibitors and ARBs are ideal medications for protecting kidney function because they lower blood pressure, lower urine albumin level, and increase GFR.

1. True
2. False
The greater the initial decline in GFR after starting Losartan, the slower the rate of decline in long term GFR.


Lowering Urine Albumin (or Total Urine Protein) Level is a Major Goal in Slowing Progression of Kidney Disease.

ACE Inhibitors or Angiotensin Receptor Blockers Should be Administered to Patients with Increased Urine Albumin/Protein even with Normal Blood Pressure.

ACEs and ARBs Appear To Be Synergistic

Diabetic Medicine 24:466, 2007
ONTARGET Trial Suggests that ACEs and ARBs are not Synergistic

VA Nephron D and VALID

VA Nephron D – Type 2 Diabetes, GFR 30-90 ml/min, and >300 mg/g of albuminuria
- Stopped due to hyperkalemia and acute kidney injury

VALID – Type 2 Diabetes, Serum Creatinine 1.8 mg/dl to 3.5 mg/dl, >500 mg of urine protein
- To be completed by December, 2014

Use Of ACE Inhibitors/ARBS

- All patients with increased urine albumin (or total protein) should be on an ACE-inhibitor or an Angiotensin Receptor Blocker even if the patient has excellent blood pressure
- In general, avoid combination of ACE-I and ARB.
- Consider using combination in patients with kidney disease and heart failure and possibly in patients with high levels of proteinuria (>1 gram)
Other Medications that Lower Albuminuria/Proteinuria

Renin-Angiotensin-Aldosterone System

DO NOT USE IN COMBINATION WITH ACE-I or ARB

Beneficial for BOTH Cardiac and Kidney Disease.

Appears to be safe in combination with ACE-I or ARB.
Aldosterone Causes Many Deleterious Effects

Other Medications that Lower Albuminuria/Proteinuria that are not Part of the RAAS

Nondihydropyridine Calcium channel Blockers Lower Urine Protein
Hypertension

**What is the Initial Drug Choice for Hypertension Control?**

- It doesn’t matter unless there is increased urine protein. It often takes 3 or more drugs to achieve BP goals. Choose most effective anti-hypertensive.

  - Choose a medication on the following:
    - Cost
    - Age
    - Co-morbidities
    - Side Effects

- If increased urine protein then choose an ACE Inhibitor or ARB.

- Although an ACE Inhibitor is a reasonable first choice in diabetic patients as there is activation of the RAAS.

**Blood Pressure Goals**

- <130/80

- <125/75 in patients with proteinuria

- **American Diabetes Association Goal is Now**
  - <140/80
ACCORD Blood Pressures

ACCORD Trial: No benefit of Tight BP Control on Cardiovascular Outcomes

Intensive BP Control (systolic <130) did Not Improve Cardiovascular Outcomes

INVEST Study

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Low Blood Pressures Appear to Increase Cardiovascular Mortality

Cooper-DeHoff RM et al JAMA 304: 61-68 (2010)

ACCORD Blood Pressure Outcomes - Improvement for Stroke Outcomes


Mathematical Analysis Suggests that Systolic Blood Pressure <120 Does Not Improve Outcomes Except for Stroke


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Goal Depends in Part on Co-Morbid Conditions/Concerns

- Cardiac Disease
- Stroke Risk
- Kidney Disease

DIAGNOSIS

The blood pressure measurement that has been shown to best predict development of complications of hypertension is:

1. Home blood pressure
2. Office blood pressure
3. 24-hour blood pressure monitoring
4. Arterial line blood pressure measurement
Office Blood Pressure

- Considered to be the most accurate
- Usually only taken 1-3 times/year
- White Coat Hypertension may confound data
- Office BP machines are usually accurate but need to be calibrated on a routine basis.

Home Blood Pressure

- Accuracy may be a problem
- Home BP machines may be inaccurate and need to be evaluated at a doctor’s office
- If accurate, likely the best way to diagnose and monitor BP

Home Blood Pressure Monitoring Predicts Events Better than Office Measurements

24 Hour Ambulatory Blood Pressure

- Detailed Recording
- Very Helpful for Diagnosing White Coat Hypertension
- Discover Unrecognized Hypertension
- Dippers versus Non-dippers

Non-Dippers have Higher Mortality

Consider Causes Of Hypertension Other than Essential Hypertension

- Primary Hyperaldosteronism
- Renal Artery Stenosis
Primary Hyperaldosteronism

- Common in Diabetic Patients with Resistant Hypertension
- Hypokalemia May be a Sign
- Aldosterone Inhibition May Lead to Significant Reduction in Blood Pressure

Renal Artery Stenosis

- Surgical Intervention may not improve outcomes as compared to medical management
- Surgical Intervention may be indicated in patients with persistently high blood pressure who are taking many medications

ASTRAL Study - Blood Pressure

ASTRAL Study - Blood Pressure

Hypertension Recommendations

- Consider cost
- Use Home Blood Pressure Monitoring
- Simplify Regimen for Patient Compliance
  - Dosing Schedule
  - Number of Medications
- Education: Discuss pathophysiology with patients
- Exercise, weight loss, diet, smoking cessation, and salt restriction are paramount
- Consider Primary Hyperaldosteronism as Cause for Hypertension
- Select Medications and Goals Based on Comorbidities
  - Cardiovascular Disease
    - Beta Blockers; ACE Inhibitors; Aldosterone Antagonists
  - Kidney Disease
    - RAAS System inhibitors

Treatment of Kidney Disease

- Blood pressure control to at least <130/80
- Blood Glucose Control – A1c <7%
- Lower albuminuria/proteinuria
- Dietary interventions as indicated:
  - Low Salt intake and avoid high protein intake
  - Little to no role for low protein diet
- Stop smoking

Many Patients Start Dialysis without Seeing a Nephrologist

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