Proteinuria:
Significance and Treatment

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Objectives

• To become familiar with the ways to measure proteinuria

• To recognize that proteinuria is associated with an increased risk of death and kidney failure

• To be able to modify the treatment of people with proteinuria to reduce the risk of cardiovascular events and kidney failure
Proteinuria: Measurement Considerations
A Small Amount of Protein in the Urine is Normal

• Small amount of low molecular weight proteins and albumin are excreted in the urine

• “Normal” daily protein excretion
  – Protein <150 mg /day
  – Albumin <30 mg/day
  – In reality, “normal” is actually lower than these cutoffs
Proteinuria is a common manifestation of kidney disease

- Causes:
  - Glomerular
  - Tubular
  - Overflow
Transient Proteinuria

• Common!

• Many situations/conditions can transiently increase urine protein levels:
  – Exercise
  – Febrile illness
  – Decompensated CHF
  – Urinary tract infection
  – Urologic or menstrual bleeding
  – Acute severe elevations in blood pressure or blood sugar

• It important to CONFIRM the presence of proteinuria by repeating the urine test 1 -2 weeks later
Methods of Urine Protein Measurement

• Qualitative – ignores urine concentration
  – Urine dipstick

• Quantitative - accounts for urine concentration
  – Albumin to Creatinine Ratio (ACR) on spot sample
  – Protein to Creatinine Ratio (PCR) on spot sample
  – 24 hour urine collection – the “gold standard”
Urine ACR versus PCR
Which one should I order?

• Both affected by day to day variability, circadian variability, posture and physical activity
  – Early morning specimens are preferred (ideally first void)
  – Be careful not to overinterpret small changes

• ACR recommended for screening and in diabetes
  – Included in CKD classification system

• PCR may be more useful in some cases
  – Where the main protein excreted is NOT albumin e.g. tubulointerstitial diseases
When should I order a 24 hour urine collection for protein?

- Disadvantages: cumbersome, prone to errors in collection

- Most accurate method if performed correctly

- Often used for follow up of glomerulonephritis treatment
  - Spot specimens (ACR, PCR) not validated

- Always include a 24 hour urine creatinine to assess the completeness of collection
# Albuminuria Definitions

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>“Normal”</td>
<td>Normal to mildly increased albuminuria</td>
<td>&lt; 30 mg/day ACR &lt; 3.0 mg/mmol</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>Moderately increased albuminuria</td>
<td>30 – 300 mg/day ACR 3 – 30 mg/mmol</td>
</tr>
<tr>
<td>Macroalbuminuria Overt proteinuria</td>
<td>Severely increased albuminuria</td>
<td>&gt;300 mg/day ACR &gt; 30 mg/mmol</td>
</tr>
<tr>
<td>Nephrotic-range proteinuria</td>
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<td>≥3.5 grams/day protein ACR &gt;220-300 mg/mmol</td>
</tr>
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</table>
Significance of Proteinuria (Albuminuria)
Albuminuria predicts adverse outcomes in CKD

• Increased risk of:
  – Cardiovascular events
  – Mortality
  – CKD progression
Loss of life expectancy due to CVD deaths with albuminuria

Gansevoort et al, Lancet 2013;382:339-52

- Urine ACR 3 – 30 mg/mmol
- Urine ACR ≥ 30 mg/mmol
Higher albuminuria associated with higher risk of ESKD

Kidney International 2011;79:1331-40
Higher albuminuria is associated with FASTER RATE of CKD Progression

<table>
<thead>
<tr>
<th>Kidney function</th>
<th>Proteinuria</th>
<th>Population</th>
<th>Adjusted progression</th>
<th>Yearly change in eGFR ml/min/1.73 m²</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(95% confidence interval)</td>
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<tr>
<td>eGFR&lt;30</td>
<td>Normal</td>
<td>13467</td>
<td>-0.65 (-0.71 to -0.60)</td>
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<tr>
<td></td>
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<tr>
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<tr>
<td></td>
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<tr>
<td>eGFR 45-59.9</td>
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<tr>
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<td>-2.05 (-2.40 to -1.71)</td>
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<td>Heavy</td>
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<tr>
<td>eGFR 60-89.9</td>
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<tr>
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Heavy = ACR > 30

Turin et al, JASN 2013;24:1661-7
Higher albuminuria is associated with **FASTER RATE** of CKD Progression

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<td>eGFR ≥ 90</td>
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</tr>
<tr>
<td>eGFR 15-29.9</td>
<td>Normal</td>
<td>104</td>
<td></td>
<td>0.67 (0.01 to 1.33)</td>
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<tr>
<td></td>
<td>Mild</td>
<td>191</td>
<td></td>
<td>0.06 (-0.44 to 0.57)</td>
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<tr>
<td></td>
<td>Heavy</td>
<td>199</td>
<td></td>
<td>-1.48 (-1.96 to -0.99)</td>
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Normal = ACR < 3

Turin et al, JASN 2013;24:1661-7
What’s more likely: Death or ESKD? Age has an important effect on Risk

<table>
<thead>
<tr>
<th>Age</th>
<th>ESRD Rate/1000 P-Yrs</th>
<th>Mortality Rate/1000 P-Yrs</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>ACR</td>
<td>ACR</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>High</td>
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<tr>
<td>18 - 54</td>
<td>0.5</td>
<td>5.2</td>
</tr>
<tr>
<td>55 - 64</td>
<td>0.8</td>
<td>5.1</td>
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<tr>
<td>65 - 74</td>
<td>0.8</td>
<td>6.2</td>
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<tr>
<td>≥ 75</td>
<td>0.6</td>
<td>2.3</td>
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</table>

Hallan et al, JAMA 2012;308:2349-60
Most patients with CKD are more likely to DIE from CVD than get kidney failure
CKD Definition: KDIGO 2012
Includes Assessment of Albuminuria

<table>
<thead>
<tr>
<th>GFR categories (mL/min/1.73 m²)</th>
<th>Description and range</th>
<th>Persistent albuminuria categories</th>
<th>Description and range</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Normal or high</td>
<td>A1 Normal to mildly increased</td>
<td>30 mg/g &lt; 3 mg/mmol</td>
</tr>
<tr>
<td>G2</td>
<td>Mildly decreased</td>
<td>A2 Moderately increased</td>
<td>30-300 mg/g 3-30 mg/mmol</td>
</tr>
<tr>
<td>G3a</td>
<td>Mildly to moderately decreased</td>
<td>A3 Severely increased</td>
<td>&gt;300 mg/g &gt;30 mg/mmol</td>
</tr>
<tr>
<td>G3b</td>
<td>Moderately to severely decreased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G4</td>
<td>Severely decreased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G5</td>
<td>Kidney failure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.
Proteinuria
Treatment Considerations
General Treatment Principles

- Identify and treat the underlying cause
- Cardiovascular risk factor modification
- Blood pressure control
- Antiproteinuric agents: ACE inhibitors, ARBs
- Considerations in the nephrotic syndrome
Manage cardiovascular risk factors

- **Lifestyle**
  - Quit smoking
  - Exercise
  - Weight (BMI 20 – 25)

- **Diet**
  - Salt restrict

- **Pharmacologic**
  - Lipids
  - Diabetes
  - Blood pressure
Blood Pressure Treatment

• Objectives:
  – Protect against cardiovascular risks of high BP
  – Delay progressive loss of kidney function

• Lifestyle intervention is important
  – Weight optimization, exercise, reduce alcohol intake, salt restriction
Blood Pressure Targets in CKD
Blood Pressure Targets in CKD
CHEP 2014

• **Nondiabetics**, regardless of urine protein level, target: $<140/<90$ mmHg
  – Post hoc analysis of some trials suggest lower target MAY benefit proteinuria – evidence insufficient to recommend lower target

• **Diabetics**, regardless of urine protein level, target: $<130/<80$ mmHg
  – Lower target is recommended mainly for STROKE risk reduction, but may also assist ESKD risk reduction
First line antihypertensives for people with proteinuria

- ACE inhibitors
- Angiotensin receptor blockers
Blood Pressure Targets in CKD
Not everyone can tolerate their “target”

- Individualize BP targets if necessary:
  - Inquire about medication side effects such as postural dizziness, check for postural hypotension
  - Use caution in the elderly
Antiproteinuric Medications: ACE inhibitors and ARBs

Consider various individuals with albuminuria:

<table>
<thead>
<tr>
<th></th>
<th>Diabetes</th>
<th>**No Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal BP</td>
<td>Treat</td>
<td>Individualize</td>
</tr>
<tr>
<td>High BP</td>
<td>Treat</td>
<td>Treat</td>
</tr>
</tbody>
</table>

** Treatment may also include specific interventions directed against the disease process e.g. Immunosuppressives for glomerulonephritis
Practical Tips for ACE inhibitor and ARB use

- **CHECK** creatinine and potassium at baseline and within 1 – 2 weeks of starting or uptitrating an ACEi or ARB

- If hyperkalemia develops or creatinine rises >30% therapy may need to be **STOPPED** and labwork should be repeated

- **HOLD** during episodes of acute kidney injury and during acute illness (“sick days”)
Practical Tips for ACE inhibitor and ARB use

- Mild to moderate hyperkalemia may be manageable without permanent discontinuation with: low potassium diet, diuretics, potassium binders

- In general, there is no “eGFR cutoff” below which patients do not benefit from these medications but stage 4 and 5 CKD are at higher risk of complications – closer monitoring required

CDA Clinical Practice Guidelines 2014
ACE inhibitor + ARB?
Two are not better than one!

• Use of an ACE inhibitor and ARB together is not recommended
  – No reduction in CKD progression
  – Increased risk of adverse events

Is there a specific “target” level for proteinuria during treatment?

• The cause is an important determinant of the answer to this question
  – In some cases, disappearance of proteinuria is an indicator that the disease has been adequately treated, e.g. minimal change disease, other glomerular diseases

• Observational studies, post hoc analysis of trials: the lower the level of urine protein achieved, the lower the risk of CKD progression
  – This is not the same as having a trial where proteinuria level is the target of treatment
Complications of Nephrotic Syndrome

- Edema
- Malnutrition
- Hypercoagulability
- Hyperlipidemia
- Increased risk of infection
Summary

• The most commonly used measure of urine protein is the urine ACR
  – Transient proteinuria can occur – confirmatory testing is needed
  – Be careful not to ”overinterpret” small changes in ACR

• Proteinuria is associated with an increased risk of kidney failure and death from cardiovascular disease

• The mainstays of proteinuria management include: cardiovascular risk factor modification, blood pressure control and ACE inhibitors/ARBs
Kidney Failure Risk Equation

Proteinuria is not just a disease marker, it influences disease progression