Use of Laboratory Tests in Kidney Disease

Overview

- Review functions of the kidney and related tests
- Discuss specific tests and issues relating to interpretation

Tests of kidney function
What does a kidney do?

- Blood flow to kidney is about 1.2 L/min (1/5 of Cardiac output)
- About 10% of blood flow is filtered across the glomerular membrane (100 – 120 ml/min/1.73m²)
  - Tests: urea, creatinine, creatinine clearance, eGFR, Cystatin C
Tests of kidney function

Kidney Functions – cont’d

Selectively secretes into or re-absorbs from the filtrate to maintain

- Salt Balance
  - Tests: Na⁺, Cl⁻, K⁺, Aldosterone, Renin

- Acid Base Balance
  - Tests: pH, HCO₃⁻, NH₄⁺, Acid loading, Urinary Anion Gap

Kidney Functions – cont’d

Selectively secretes into or re-absorbs from the filtrate to maintain

- Water Balance
  - Tests: specific gravity, osmolarity, water deprivation testing, Antidiuretic hormone

- Retention of nutrients
  - Tests: proteins, sugar, amino acids, phosphate

- Secretes waste products
  - Tests: urate, oxalate, bile salts
Kidney Function – cont’d

Endocrine Function

- Target organ
  - Parathyroid hormone (Ca²⁺, Mg²⁺)
  - Aldosterone (salt balance)
  - ADH (water balance)

- Production
  - Erythropoietin
  - 1, 25 dihydroxycholecalciferol

Calcium Metabolism

Renin Angiotensin System
Aldosterone

ADH

Tests that predict kidney disease

- eGFR
- Albumin Creatinine Ratio (aka ACR or Microalbumin)
Tests of Glomerular Filtration Rate

- Urea
- Creatinine
- Creatinine Clearance
- eGFR
- Cystatin C

Glomerular Filtration Rate (GFR)

- Volume of blood filtered across glomerulus per unit time
- Best single measure of kidney function

Glomerular Filtration Rate (GFR) – cont’d

- Patient’s remain asymptomatic until there has been a significant decline in GFR
- Can be very accurately measured using “gold-standard” technique
Glomerular Filtration Rate (GFR) – cont’d

Ideal Marker
- Produced endogenously at a constant rate
- Filtered across glomerular membrane
- Neither re-absorbed nor excreted into the urine

Urea
- Used historically as marker of GFR
- Freely filtered but both re-absorbed and excreted into the urine
- Re-absorption into blood increased with volume depletion; therefore GFR underestimated
- Diet, drugs, disease all significantly effect Urea production

<table>
<thead>
<tr>
<th>Increase</th>
<th>Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume depletion</td>
<td>Volume Expansion</td>
</tr>
<tr>
<td>↑ Dietary protein</td>
<td>Liver disease</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Severe malnutrition</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td></td>
</tr>
<tr>
<td>Blood in G-I tract</td>
<td></td>
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</tbody>
</table>
Creatinine

- Product of muscle metabolism
- Some creatinine is of dietary origin
- Freely filtered, but also actively secreted into urine
- Secretion is affected by several drugs

Serum Creatinine

**Increase**
- Male
- Meat in diet
- Muscular body type
- Cimetidine & some other medications

**Decrease**
- Age
- Female
- Malnutrition
- Muscle wasting
- Amputation

Creatinine vs. Inulin Clearance
Creatinine Clearance

- Measure serum and urine creatinine levels and urine volume and calculate serum volume cleared of creatinine
- Same issues as with serum creatinine, except muscle mass
- Requirements for 24 hour urine collection adds variability and inconvenience

Cystatin C

- Cystatin C is a 13 KD protein produced by all cells at a constant rate
- Freely filtered
- Re-absorbed and catabolized by the kidney and does not appear in the urine

eGFR

- Increasing requirements for dialysis and transplant (8 – 10% per year)
- Shortage of transplantable kidneys
- Large number at risk
### eGFR – cont’d

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR mL/min/1.73m²</th>
<th>Prevalence³</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney Damage with Normal or ↑ GFR</td>
<td>&gt;90</td>
<td>478,500</td>
</tr>
<tr>
<td>2</td>
<td>Kidney Damage with Mild ↓ GFR</td>
<td>60 – 89</td>
<td>435,000</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30 – 59</td>
<td>623,500</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15 – 29</td>
<td>29,000</td>
</tr>
<tr>
<td>5</td>
<td>Kidney Failure &lt;15 or dialysis</td>
<td></td>
<td>14,900</td>
</tr>
</tbody>
</table>

### eGFR – cont’d

<table>
<thead>
<tr>
<th>Serum creatinine (mg/dL, µmol/L)</th>
<th>Mortality Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.8 – 0.99 (71 – 88)</td>
<td>10</td>
</tr>
<tr>
<td>1.1 – 1.29 (97 – 114)</td>
<td>12</td>
</tr>
<tr>
<td>1.3 – 1.49 (115 – 132)</td>
<td>16</td>
</tr>
<tr>
<td>1.5 – 1.69 (133 – 149)</td>
<td>22</td>
</tr>
<tr>
<td>1.7 – 1.99 (150 – 176)</td>
<td>30</td>
</tr>
<tr>
<td>2.0 – 2.49 (177 – 220)</td>
<td>41</td>
</tr>
<tr>
<td>≥2.5 (≥221)</td>
<td>54</td>
</tr>
</tbody>
</table>

*Data from Shulman et al.¹*

### The Old Standard: Serum Creatinine

![Graph showing the relationship between serum creatinine and eGFR](image)
Problem

- Need an easy test to screen for early decreases in GFR that you can apply to a large, at-risk population
- Can serum creatinine be made more sensitive by adding more information?

eGFR by MDRD Formula

- Mathematically modified serum creatinine with additional information from patients age, sex and ethnicity

\[
eGFR = 30849.2 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times \begin{cases} 
1 & \text{if female} \\
0.742 & \text{if male} 
\end{cases}
\]

Screening Test – cont’d

- The Results
eGFR – cont’d

- eGFR calculation has been recommended by National Kidney Foundation whenever a serum creatinine is performed in adults

Guidelines & Protocols Advisory Committee

Identification, Evaluation and Management of Patients with Chronic Kidney Disease

Recommendations for:
- Risk group identification
- Screening
- Evaluation of positive screen
- Follow-up

Identify High Risk Groups

- Diabetes
- Hypertension
- Heart Disease
- Family History
- High Risk Ethnic Group
- Age > 60 years
Screen High Risk Groups

- eGFR
- Urinalysis
- Albumin / Creatinine Ratio

Follow-up based on Screen Results

- Kidney Ultrasound
- Specialist Referral
- Cardiovascular Risk Assessment
- Diabetes Control
- Smoking cessation
- Hepatitis / Influenza Management

Creatinine Standardization in British Columbia

- Based on Isotope dilution /mass spectrometry measurements of creatinine standards
- Permits estimation and correction of creatinine and eGFR bias at the laboratory level.
Importance of Standardization

- Low bias creatinine:
  - Causes inappropriately increased eGFR
  - Patients will not receive the benefits of more intensive investigation of treatment.

- High bias creatinine:
  - Causes inappropriately decreased eGFR
  - Patients receive investigations and treatment which is not required. Wastes time, resources and increases anxiety.

High 143.3
Low 116.0
Mean 124.6
Poor Creatinine Precision

- Incorrect categorization of patients with both “normal” and decreased eGFR.

Total Error

- TE = % bias + 1.96 CV
- Goal is <10% (requires bias ≤ 4% and CV ≤ 3%)

Proteinuria

- In health:
  - High molecular weight proteins are retained in the circulation by the glomerular filter (Albumin, Immunoglobulins)
  - Low molecular weight proteins are filtered then reabsorbed by renal tubular cells
Proteinuria – cont’d

- Glomerular:
  - Mostly albumin, because of its high concentration and therefore high filtered load
- Tubular:
  - Low molecular weight proteins not reabsorbed by tubular cells (e.g. alpha-1 microglobulin)
- Overflow:
  - Excessive filtration of one protein exceeds reabsorptive capacity (Bence-Jones, myoglobin)

Albumin Creatinine Ratio (Microalbumin)

- Normal albumin molecule
- In health, there is very little or no albumin in the urine
- Most dip sticks report albumin at greater than 150 mg/L
Urinary Albumin – cont’d

- Detection of low levels of albumin (even if below dipstick cut-off) is predictive of future kidney disease with diabetes
- Very significant biologic variation usually requires repeat collections
- Treatment usually based on timed urine albumin collections

Urinalysis

- Dipstick
  - Protein
    - Useful screening test
    - Dipstick more sensitive to albumin than other proteins
    - Large biologic variation

Urinalysis – cont’d

- Dipstick – cont’d
  - Hemoglobin
    - Glomerular, tubular or post-renal source
    - Reasonably sensitive
    - Positive dipstick and negative microscopy with lysed red cells
Urinalysis – cont’d

- Dipstick – cont’d
  - Glucose
    - Reasonable technically, however screening and monitoring programs for diabetes are now done by blood and Point-of-Care devices

Specific Gravity

- Approximate only
- Measurement of osmolarity preferred when concentrating ability being assessed

pH

- pH changes with time in a collected urine
- Calculations to determine urine ammonium levels and response to acid-loading generally required to assess for renal tubular acidosis
Microscopic Urinalysis

Epithelial Cells
- Squamous, Transitional, Renal
  - All may be present in small numbers
  - Important to recognize possible malignancy
  - Comment on unusual numbers

Renal Tubular Epithelial

Red Cells
- May originate in any part of the urinary tract
- Small numbers may be normal
- There is provincial protocol for the investigation of persistent hematuria
Red Cells

White Blood Cells

- Neutrophils often present in small numbers
- Lymphocytes and monocytes less often
- Marker for infection or inflammation

Neutrophils
Casts

- Hyaline and granular casts not always pathologic, clinical correlation required
- Red cell casts always significant, usually glomerular injury
- WBC casts also always significant, usually infection, sometimes inflammation
- Bacterial casts only found in pyelonephritis
- Waxy casts found in significant kidney disease

Hyaline Cast

Granular Cast
Tests for Renal Tubular Acidosis

- Urinary Anion Gap
  \((Na^+ + K^+) - Cl^-\)
- In acidosis the kidney should excrete NH4\(^+\) and the gap will be negative

RTA – cont’d

- If NH4\(^+\) is not present (or if HCO3\(^-\) is present) the gap will be neutral or positive, implying impaired kidney handling of acid load.

Urine Anion Gap = \((Na^+ + K^+) - Cl^-\)

RTA – cont’d

Ammonium Chloride Loading
- Load with ammonium chloride
- Hourly measurements of urine pH
- Normal at least one pH below 5.5
Tests of Kidney Concentrating Ability

To differentiate
- Psychogenic polydipsia
- Central diabetes insipidus
- Nephrogenic diabetes insipidus

Overnight Water Deprivation Testing

(Serum osmolarity <295 monitor patient weight hourly)
- Collect urine hourly from 0600 for osmolarity
- Baseline serum osmolarity, Na⁺, ADH
- When osmolarity plateaus repeat above tests and administer ADH

Interpretation

If urine concentrates (osmolarity >600 and serum osmolarity below <295)
- Normal physiology (? psychogenic polydipsia)
No Urine Concentration
No Response to ADH

- Nephrogenic diabetes insipidus

No Urine Concentration

Positive response to ADH

- Central diabetes insipidus