AGING KIDNEY IN HIV DISEASE

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Kidney, Aging and HIV

- In general population, kidney disease disproportionately affects the elderly.

- Evidence that this process is accelerated in HIV:
  - 10-fold risk of ESRD compared with age-matched controls
  - 5-fold risk of proteinuria, an important sign of kidney injury

- However, the standard test of kidney function, creatinine, is derived from muscle mass; creatinine is slow to detect in CKD in elderly and HIV

- We need new methods to detect early kidney injury and reduced kidney function in HIV patients
Age and CKD in General Population

NHANES 1999-2004

Coresh J et al. JAMA 2007
CKD and Complications in General Population

- CKD
- CVD
- Death
- Kidney failure
- Hospitalizations
- Cognitive dysfunction
- Fractures
- Health Status/QoL
- Energy/Frailty
- Successful aging
Age and CKD in the HIV Population

VA Registry

Choi AI et al. Kidney International 2007
CKD and Cardiovascular Disease in VA Registry (N= 17,264)

7%- eGFR< 60
31%- proteinuria

<table>
<thead>
<tr>
<th>Risk of Adverse Cardiovascular Outcomes (HR; 95% CI)</th>
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<tbody>
<tr>
<td>Normal N=11,420</td>
</tr>
<tr>
<td>Cardiovascular Disease N= 833 events</td>
</tr>
<tr>
<td>Multivariate Adjusted*</td>
</tr>
<tr>
<td>Heart Failure N= 377 events</td>
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<tr>
<td>Multivariate Adjusted*</td>
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</table>

Multivariable-adjusted models control for age, sex, race, and time-updated hypertension, diabetes mellitus, chronic obstructive lung disease, dyslipidemia, smoking, CD4 count, HIV viral load, ART. “Normal” defined as albuminuria level0 mg/dL with an eGFR 60 mL/min per 1.73 m2. “Both conditions” defined as an eGFR 60 mL/min per 1.73 m2 with an albuminuria level 30 mg/dL.

Choi AI et al. Circulation 2010
Cystatin C

- Cystatin C is an alternate test of kidney function
- Unlike creatinine, not related to muscle mass so has advantages in elderly and HIV population
- FDA approved, widely available, but rarely used clinically
- To understand prevalence and outcomes of kidney disease in elderly and HIV, we need to add cystatin C
Creatinine Quintiles and Mortality Risk

*Significant adjusted hazard ratio

Mortality rate per year (%)

Cystatin C Quintiles and Mortality Risk

Kidney Disease Accelerated in HIV

FRAM, NHANES Comparison of Cystatin C

16-year acceleration in kidney decline

HIV+ - FRAM (dash line)
HIV+ - NHANES III (solid line)

Shlipak MG, Unpublished
## Kidney Function in HIV vs. Controls

**FRAM Study**

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>p-value</th>
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<tbody>
<tr>
<td></td>
<td>HIV (n = 519)</td>
<td>Control (n = 290)</td>
</tr>
<tr>
<td>Creatinine (mg/L)</td>
<td>0.87 ± 0.21</td>
<td>0.85 ± 0.19</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>110 ± 26</td>
<td>106 ± 23</td>
</tr>
<tr>
<td>Cystatin C (mg/dL)</td>
<td>0.92 ± 0.22</td>
<td>0.76 ± 0.15</td>
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</tbody>
</table>

Distribution of Cystatin C in HIV and Control Patients in FRAM

CysC > 1.0:
HIV+: 32%
No HIV: 4%

Adj. OR= 10.0
(95% CI: 4.4-22.0)

Adjusted for sex, age, ethnicity, tobacco use, hypertension, diabetes; systolic blood pressure, glucose, HDL, LDL, triglyceride, C-reactive protein, and uric acid levels, BMI, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use; albumin-creatinine ratio, proteinuria, current illicit drug use and total lean body mass

What Do These Findings Mean?

- HIV-infected persons have elevated cystatin C, but similar creatinine levels compared with HIV- persons.

- This implies either:
  - a) epidemic of unrecognized kidney disease in HIV
  - b) cystatin C levels biased and not useful in HIV

- To date, only very small GFR studies completed in HIV
Kidney Function and Mortality in HIV Infection

- 5 years of follow-up of FRAM for mortality
- Comparison of cystatin C and creatinine with mortality risk
- Albuminuria and mortality

Choi AI et al. Am J Kidney Dis 2010
## Creatinine, cystatin C, and Albuminuria with Mortality

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>Adjusted Odds Ratio</th>
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<tbody>
<tr>
<td>Linear eGFRcr (per 10 ↓)</td>
<td></td>
<td>1.05 (0.95, 1.15)</td>
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<tr>
<td>Linear eGFRcys (per 10 ↓)</td>
<td></td>
<td>1.20 (1.09, 1.32)</td>
</tr>
<tr>
<td>CKD (eGFR&lt;60) by Creatinine</td>
<td>46 (5%)</td>
<td>1.40 (0.60, 3.20)</td>
</tr>
<tr>
<td>CKD (eGFR&lt;60) by Cystatin C</td>
<td>104 (11%)</td>
<td>2.30 (1.30, 3.80)</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>199 (22%)</td>
<td>2.20 (1.30, 3.70)</td>
</tr>
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</table>
5 Year Mortality Risk by Cystatin C and Albuminuria Categories

Population Attributable Risk for Albuminuria and Cystatin C= 17%

Choi AI et al. Am J Kidney Dis 2010
Future Directions in Aging
Kidney Research
Our Framework/Paradigm

C. Clinical CKD
- Creatinine elevated

D. ESRD
- Renal replacement therapy
Our Framework/Paradigm

B. Preclinical
- Cystatin C elevated
- Creatinine normal

C. Clinical CKD
- Cystatin C elevated
- Creatinine elevated

D. ESRD
- Renal replacement therapy
Our Framework/Paradigm

A. Onset of Specific Injury within the Nephron
- Increase in kidney injury biomarkers
  - Creatinine normal
  - Cystatin C normal

B. Preclinical
- Increase in kidney injury biomarkers
  - Cystatin C elevated
  - Creatinine normal

C. Clinical CKD
- Increase in kidney injury biomarkers
  - Cystatin C elevated
  - Creatinine elevated

D. ESRD
- Renal replacement therapy
Novel Markers of Kidney Injury
A Non Invasive Kidney Biopsy?

NIA-funded R01: The Aging Kidney in HIV-Infection: Biomarkers for early detection of injury (PI-Shlipak)
Novel Markers of Kidney Injury
A Non Invasive Kidney Biopsy?

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**Tubule Injury**
- Urine NGAL
- Urine KIM-1
- LFABP
- Urine IL-18
  Other biomarkers
- Urine Cystatin C
- NAG
- Fetuin A (exosomes)

**Endothelial Injury**
- Pentraxin-3
- Serum ICAM-1
- Serum VCAM-1

**Glomerular Injury**
- Urine albumin excretion

**Mineral Metabolism**
- PTH
- 1,25(OH)2 vitamin D
- 25 (OH) vitamin D
- FGF-23
- Ca, Phosphate

**Loop of Henle Injury**
- Uromodulin
- Uropontin

**Interstitial Fibrosis**
- Urine TGF-β1
Determinants of Kidney Injury in HIV

- **Virus** (HIV, HCV)
- **Antiretroviral medications**
- **Traditional kidney risk factors** (diabetes, hypertension)
- **Age**
Future Directions for Aging Kidney Research

- Biomarkers for detection of early injury - virus, medications, risk factors
- Clinical strategies for measuring kidney function - creatinine and/or cystatin C
- Risk/benefit trade-off of medications
- Understand health consequences of CKD in HIV population - beyond cardiovascular disease, ESRD, and death
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