Occupational Kidney Disease: Emerging Exposures

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Disclosures

• No relevant disclosures
Why the Kidney?

Blood with wastes

Kidneys

Ureters

Blood with filtered blood

Blood with wastes to the bladder

Bladder

Urethra

Filter

National Institute of Diabetes and Digestive and Kidney Diseases, NIH
Spectrum of Kidney Disease

- Acute kidney injury (AKI)
- Chronic kidney disease (CKD)
  - Defined by proteinuria and/or estimated glomerular filtration rate (GFR) < 60
  - End-stage renal disease (ESRD)
- Glomerulonephritis
- Nephrolithiasis/ urolithiasis
- Kidney injury biomarkers (?) clinical relevance

Established Occupational Exposures

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Associated Kidney Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heavy metals</td>
<td></td>
</tr>
<tr>
<td>Lead</td>
<td>Proximal tubular damage</td>
</tr>
<tr>
<td>Cadmium</td>
<td></td>
</tr>
<tr>
<td>Uranium</td>
<td>*Glomerulonephritis</td>
</tr>
<tr>
<td>Mercury*</td>
<td></td>
</tr>
<tr>
<td>Organic solvents</td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Silica</td>
<td>Tubulointerstitial damage Glomerulonephritis</td>
</tr>
<tr>
<td>Over-exertion</td>
<td>Rhabdomyolysis/ AKI</td>
</tr>
<tr>
<td>Blood-borne viruses</td>
<td>Variable</td>
</tr>
</tbody>
</table>
Emerging Occupational Exposures

- Melamine manufacturing
- Agricultural work
- Particulate matter exposure
- Infrequent urination

Melamine & Acute Kidney Injury

- Nitrogen-rich organic base
- Illegal adulterant to increase protein content
  - Pet food (2007)
  - Infant formula (2008)
  - Nutritional supplements?
- Acute exposure linked to bladder/ kidney stones and AKI
  - Complex with cyanuric acid or uric acid

Bhalla V et al, Kidney Int 2009
Gabriels G. et al, Nutr J 2015
Melamine & Occupational Exposure?

• Study of melamine tableware factory workers (n=44) vs. control factory workers (n=105)
• Highest levels of melamine in air, serum, and urine of melamine manufacturers (n=16)
  – Rise in urinary melamine during the workweek
• Urine [melamine] correlated with urine NAG
  – Higher rates of detectable urine β2-microglobulin in melamine manufacturers
  – No relationship with albuminuria or clinical events

Wu C, et al. JASN 2015
CKD of Unknown Cause ("CKDu")

- CKD affecting predominantly men in agricultural communities in Central America
  - "Mesoamerican nephropathy"
  - "CKDnT" ("non-traditional" causes)
- Similar condition reported in Sri Lanka, India, Egypt

CKDu in Nicaragua

- Town of Chicigalpa in Chinandega, Nicaragua
  - Northwest Nicaragua near El Salvador
  - Highest concentration of sugar cane plantations
  - Highest prevalence of CKDu
  - Rural community known as "The Island of Widows"
- Collaboration with La Isla Foundation & scientists at UNAN-Leon
CKDu in Nicaragua

- Leading cause of death among men in Chicigalpa (2002-2012)
  - 45% of deaths in men

CKDu: Proposed Etiologies

- Heat stress/ volume depletion
- Agrochemicals/ pesticides
- Endemic infections
- NSAID use
CKDu in Nicaragua

- Case-control analysis of heavy metal exposure identified no link with CKDu
- Cross-sectional study in Chicigalpa (n=424)
  - GFR < 60ml/min/1.73m² in 42% of men, 10% of women
  - No association with rare traditional risk factors
  - Among agricultural workers (n=151), low GFR associated with days cutting sugarcane, pesticide inhalation, and sugarcane chewing

Raines N et al. MEDICC Review 2014

CKD & Agriculture in the US

- Agricultural Health Study
  - Male pesticide applicators in NC and Iowa
  - Self-reported exposure to pesticides at enrollment used to calculate intensity-weighted lifetime days
  - N=55,580 with data for this analysis
- Linked to US Renal Data System (USRDS)
  - CMS database of all end-stage renal disease (ESRD) cases in the US
  - Sensitivity analysis excluded cases within 5 years of enrollment in AHS

Lebov et al, Occ Environ Med 2016
CKD & Agriculture in the US

- Cumulative exposure (self-reported) to several pesticides was linked to ESRD
  - Mostly herbicides (atrazine, pendimethalin, metolachlor, alachlor, paraquat) & permethrin
  - Some have been implicated in animal studies; none in studies of CKDu
- Pesticide exposure requiring MD visit or hospitalization was associated with ESRD

CKDu: Multifactorial Etiology?

- Heat stress/ volume depletion
- Agrochemicals/ pesticides
- Endemic infections
- NSAID use

Lebov et al, Occ Environ Med 2016
Particulate Matter Exposure: WTC

- Asbestos
- Benzene
- Pulverized glass
- Pulverized cement
- Silica
- Carbon
- Gypsum
- Heavy metals

Particulate Matter Exposure

- Air pollution has been linked to cardiovascular events & mortality (MESA)
- Exposure to inhaled particulate matter increases inflammation & oxidative stress
- WTC exposure has been linked to pulmonary, ENT, GI, and mental health issues
- Prior studies of WTC responders have not focused on CKD risk

Brook RD, et al. *Circulation* 2010
Araujo J. *Air Qual Atmos Health* 2011
WTC Health Program

• CDC/ NIOSH-funded program
• Seven screening/ treatment sites in NY/ NJ
• Mount Sinai WTC program also funded to study cardiovascular disease (WTC-CHEST)

WTC Exposure Assessment

• **Very High**: worked > 90 days, exposed to dust cloud, and worked at least some time on the pile
• **High**: rescue workers who were exposed to dust cloud but worked < 90 days or did not work on the pile
• **Intermediate**: rescue workers not exposed to the dust cloud and who either worked 40-90 days or did not work on the pile
• **Low**: worked < 40 days, were not exposed to dust from collapse, and did not work on the pile

Particulate Matter: WTC

• Preliminary analysis in WTC-CHEST correlated WTC exposure to albuminuria
• WTC-RENAL funded by CDC/ NIOSH in 2014
  – Nested cohort study within WTC-CHEST
    • Data on shared CVD/ CKD risk factors
  – Additional laboratory tests for CKD
    • Serum creatinine/ eGFR
    • Urine albumin: creatinine ratio

McLaughlin M et al.  Presented at ASN 2014
### WTC-RENAL Preliminary Results

<table>
<thead>
<tr>
<th></th>
<th>n=359</th>
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<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>55</td>
</tr>
<tr>
<td>40-60</td>
<td>297 (83%)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>62 (18%)</td>
</tr>
<tr>
<td><strong>Male sex</strong></td>
<td>289 (81%)</td>
</tr>
<tr>
<td><strong>African-American race</strong></td>
<td>40 (11%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>158 (44%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>41 (11%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>163 (45%)</td>
</tr>
<tr>
<td>Never smoker</td>
<td>256 (71%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Body mass index (kg/m²)</th>
<th>31 (49%)</th>
</tr>
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<tbody>
<tr>
<td>Mean</td>
<td>175</td>
</tr>
<tr>
<td>&gt;30</td>
<td></td>
</tr>
<tr>
<td>Waist circumference (inches)</td>
<td>41.1</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>119</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>76</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>189</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>121</td>
</tr>
<tr>
<td>hs- C reactive protein (mg/l)</td>
<td>2.9</td>
</tr>
<tr>
<td>HbA1c glycosylated hemoglobin (%)</td>
<td>5.9</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.01</td>
</tr>
<tr>
<td>Urine albumin: creatinine (ug/mg)</td>
<td>17</td>
</tr>
</tbody>
</table>
WTC-RENAL Preliminary Results

• Expected associations between GFR, albuminuria, and Framingham Risk Score
  – Last participant enrolled this month…..

• Contacted by WTC responders with established kidney disease
  – Possible pattern of immune complex diseases
  – Obtaining IRB approval for a registry
“Taxicab Syndrome”

- Linked to kidney stones & other urologic conditions
  - Infrequent urination
  - Decreased fluid intake
- Infrequent urination documented in other occupations
  - Nurses & OR personnel

Linder BJ et al. Urolithiasis 2013
Acknowledgements

• WTC-RENAL
  – CDC/ NIOSH U01
  – Mary Ann McLaughlin/ Cynara Maceda

• Nicaragua
  – Student research team
  – Mount Sinai Global Health/ Phil Landrigan
  – Robert Wright

What is the most common renal manifestation of heavy metal toxicity?

• A. Rhabdomyolysis & acute kidney injury
• B. Immune complex glomerulonephritis
• C. Proximal tubular dysfunction
• D. End-stage renal disease
Occupational exposure to melamine has been associated with:

- A. Acute kidney injury
- B. Increased urine biomarkers
- C. Chronic kidney disease
- D. Kidney stones

Which of the following is NOT hypothesized to contribute to CKDu?

- A. Hypertension
- B. Heat stress
- C. Pesticides
- D. NSAIDS