Mesoamerican Nephropathy

A CKD of unknown etiology in Central America
Mesoamerican Nephropathy

- Occurs predominantly along the Pacific Coast.
- Primarily men working in sugar cane fields, but can occur with other occupations.
- Also affects women, possibly children.
- 20,000 Deaths so far!
This is an epidemic and it affects both men and women.

CKD Mortality in Men in Costa Rica

<table>
<thead>
<tr>
<th>Year</th>
<th>Guan</th>
<th>CR</th>
<th>Guan</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970s</td>
<td>4.40</td>
<td>3.60</td>
<td>38.50</td>
<td>8.40</td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CKD Mortality in Women in Costa Rica

<table>
<thead>
<tr>
<th>Year</th>
<th>Guan</th>
<th>CR</th>
<th>Guan</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970s</td>
<td>2.3</td>
<td>2.6</td>
<td>10.7</td>
<td>5.00</td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Wesseling et al 2015 Occup Environ Medicine
Clinical Manifestations

- Not due to Hypertension or Diabetes
- Asymptomatic Rise in Creatinine
- Low grade proteinuria
- Blood pressure normal
- Hypokalemia and Hyperuricemia common
- Biopsies show Chronic Tubulointerstitial Disease
Sugarcane Workers are Especially at Risk for CKD

Sugar Cane Workers Show a Fall in their Kidney Function During the Harvest Season

<table>
<thead>
<tr>
<th>Role</th>
<th>eGFR Loss (ml.min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seed Cutter</td>
<td>8.6</td>
</tr>
<tr>
<td>Cane Cutter</td>
<td>5</td>
</tr>
<tr>
<td>Irrigator</td>
<td>7.4</td>
</tr>
<tr>
<td>Factory Worker</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Laws et al Int J Oc Envir Health 2015
Pesticides are Likely not the Cause of Mesoamerican Nephropathy

- Disease occurs in occupations that do not use pesticides (miners, construction workers, fishing industry, port workers)
- During the season, those cutting sugarcane are at higher risk for kidney damage than those who are applying the pesticides
Sugarcane Cutters, not Pesticide Applicators, are at Increased Risk

Changes in NGAL During Harvest

<table>
<thead>
<tr>
<th></th>
<th>Start</th>
<th>End</th>
<th>Start</th>
<th>End</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pesticide</td>
<td>7</td>
<td>6.9</td>
<td>7.6</td>
<td>19.3</td>
</tr>
<tr>
<td>Applicator</td>
<td>7</td>
<td>6.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sugarcane Cutter</td>
<td>7</td>
<td>6.9</td>
<td>7.6</td>
<td>19.3</td>
</tr>
</tbody>
</table>

Laws et al AJKD 2015
What are the other Candidates besides pesticides that might be causing Mesoamerican Nephropathy?

<table>
<thead>
<tr>
<th>Proposed, but Little evidence: Environmental toxins</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ NSAIDS (nonsteroidal agents)</td>
</tr>
<tr>
<td>▪ Heavy metals: Cadmium, Lead, Arsenic</td>
</tr>
<tr>
<td>▪ Aristolochic Acid (Balkans)– cause of Chinese Herb Nephropathy</td>
</tr>
<tr>
<td>▪ Leptospirosis and other infections</td>
</tr>
</tbody>
</table>

Most Important Risk Factor: Volume Depletion and Dehydration:

▪ Repeated kidney injury from recurrent dehydration, such as from Heat Stroke or Rhabdomyolysis
Sugar Cane Workers are Exposed to Extreme Heat

- Work starts at 5:30 am
- By 9:30 am they are working under heat conditions that exceeds the recommendations of the OSHA (Occupational Safety Health Administration)

Crowe et al Am Indus Med 56:1157; 2013
Disease Preferentially Occurs at Low Altitude

COASTAL

HIGH-ALTITUDE

Peraza et al; Am J Kid Dis 2012 59:531
Temperature Variability; Hotter at Low Altitude, but variable

Garcia Trabanino et al. 2015
Urinary Concentration Occurs During Shift
Symptoms of Dehydration are Common in Sugarcane Workers

Could Mesoamerican Nephropheny be a Dehydration Disorder?
The Classic Teaching is that Dehydration Results in Reversible Kidney Disease

- Sweat--- loss of sodium and water
- Results in “Pre-renal” dysfunction
- High BUN/Cr Ratio
- Concentrated urine

Renal Function is REVERSIBLE
Can Heat Induced Dehydration cause CKD?

**GROUPS**
- Controls
- Heat: + water
- Heat: water at night
  (Heat = Dehydrated)

Heating at 39.5 °C
30 min every hour

No heating

**TOTAL DURATION**
5 weeks

Roncal-Jimenez et al  Kidney Int. 2013
Recurrent Dehydration Causes Chronic Kidney Disease in Laboratory Mice

Roncal-Jimenez et al. Kidney Int. 2013
How Does Dehydration Cause Kidney Disease?
Renal Consequences of Dehydration

- Dehydration
  - Water loss > Salt Loss

  - Serum Osmolarity
    - ↑

  - Vasopressin
    - ↑

  - Aldose Reductase
    - ↑

  - Urinary Concentration
    - glucose
    - sorbitol
Vasopressin and Fructose May be Mediators for Dehydration Kidney Injury

↑ Vasopressin

↑ Aldose Reductase

- glucose
- sorbitol
- fructose

Oxidative stress, inflammation

Kidney Damage
Rats Given Fructose in the Drinking Water Develop Kidney Damage

Dehydration Results in Increased Fructose Generation in the Kidney

↑ Aldose Reductase

glucose
sorbitol
fructose
ATP
AMP
Uric acid, oxidants

Dehydration Increases Kidney Fructose

Roncal-Jimenez et al. Kidney Int. 2013
Mice that cannot metabolize fructose (fructokinase knockout) are Protected from Dehydration associated CKD

Roncal-Jimenez et al Kidney Int. 2013
This suggests Mesoamerican Nephropathy might be a Fructose Dependent Disease

Roncal-Jimenez et al Kidney Int 2013
Could Sugar-containing Rehydration Solutions Worsen Dehydration Induced Kidney Disease?

- Recurrent Dehydration Increases Serum Osmolarity
  - Aldose Reductase
  - Soft Drinks containing fructose
  - Fructokinase
  - Kidney Fructose Accumulation
  - Oxidative Stress
  - Kidney Injury
  - Vasopressin
Rehydration with Soft Drinks Causes Kidney Damage in Dehydrated Rats

Sanchez-Lozada et al  Submitted
While these studies suggest a role for dehydration in kidney damage, there is a Possibly More Important Mechanism for Mesoamerican Nephropathy!
Acute Kidney Injury may occur from a Sudden Increase in Uric acid during cancer chemotherapy (tumor lysis syndrome)
Mesoamerican Nephropathy: A Uric acid Disorder?

- Heat and Exercise
- Subclinical Rhabdomyolysis
  - Release of DNA, RNA
  - Lactic acid
- Increase in Uric acid
- High Urine Uric acid
  - Urine acidification
  - Crystal mediated AKI
Sugarcane Workers Show a Rise in Serum Uric Acid and Creatinine while working (during shift)

Pilot Data in El Salvador Sugarcane Workers, Garcia-Trabanino, Env Res in press
Urine pH falls during shift which increases risk for uric acid crystal formation.

Pilot Data in El Salvador Sugarcane Workers, Ramón Garcia-Trabanino, submitted.
Urate crystals are Common in the Urine of Sugarcane workers during the sugarcane harvest

Pilot Data in El Salvador Sugarcane Workers, Roncal-Jimenez AJKD
Urine Uric Acid Appears to Rise but when corrected for pH the rise is dramatic

Afternoon

Morning

Pilot Data in El Salvador Sugarcane Workers, Roncal-Jimenez AJKD
Sugarcane Workers Develop Large Urine Sediments

<table>
<thead>
<tr>
<th>AM</th>
<th>PM</th>
<th>Supernatant U-UA mg/dl</th>
<th>Sedim+PBS UA mg/dl</th>
<th>Uric Acid mg/dl Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAPH-66-1-AM</td>
<td></td>
<td>37.6</td>
<td>2.6</td>
<td>40.2</td>
</tr>
<tr>
<td>BAPH-66-1-PM</td>
<td></td>
<td>53.7</td>
<td>6.9</td>
<td>60.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AM</th>
<th>PM</th>
<th>Supernatant U-UA mg/dl</th>
<th>Sedim+PBS UA mg/dl</th>
<th>Uric Acid mg/dl Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTB-60-1-AM</td>
<td></td>
<td>88.2</td>
<td>43.7</td>
<td>131.9</td>
</tr>
<tr>
<td>MTB-60-1-PM</td>
<td></td>
<td>106.2</td>
<td>22.7</td>
<td>128.9</td>
</tr>
</tbody>
</table>
Given that Mesoamerican Nephropathy may be due to heat stress, is there a role of Global Warming and Water Shortage in this Disease?
Mean temperatures have increased 0.8 degree C since 1880, with two-thirds of the change since 1975.

Global Warming is responsible for 75% of moderate heat extremes throughout the globe.

Iran city hits suffocating heat index of 165 degrees, near world record

Temperature Change in El Salvador

Central America: Site of High Solar Radiation Correlates with Site of CKD Epidemic

- Chichigalpa
- Quezalguaque
- Guanacaste
Sugar cane Workers in Chinandega, Nicaragua Showed Marked Uricosuria in One of Four Urines

<table>
<thead>
<tr>
<th>Date</th>
<th>Urine Uric acid (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nov 26th</td>
<td>40.0</td>
</tr>
<tr>
<td>Dec 5th</td>
<td>45.0</td>
</tr>
<tr>
<td>May 13th, 2013</td>
<td>&gt; 100 mg/dl</td>
</tr>
</tbody>
</table>
### Record Temperature in nearby San Miguel, El Salvador, May 14th, 2013

- **May 13**

<table>
<thead>
<tr>
<th>May 13</th>
<th>Supernatant</th>
<th>Sediment</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61.9</td>
<td>20.2</td>
<td>82.2</td>
</tr>
<tr>
<td>2</td>
<td>97.7</td>
<td>36.4</td>
<td>134.1</td>
</tr>
<tr>
<td>3</td>
<td>153.6</td>
<td>7.9</td>
<td>161.5</td>
</tr>
<tr>
<td>4</td>
<td>113.7</td>
<td>19.8</td>
<td>133.5</td>
</tr>
<tr>
<td>5</td>
<td>114.0</td>
<td>15.3</td>
<td>129.3</td>
</tr>
<tr>
<td>6</td>
<td>97.8</td>
<td>9.0</td>
<td>106.8</td>
</tr>
<tr>
<td>7</td>
<td>147.5</td>
<td>55.9</td>
<td>203.5</td>
</tr>
<tr>
<td></td>
<td>112.3</td>
<td>23.5</td>
<td>135.8</td>
</tr>
</tbody>
</table>
Summary: Mechanism for Mesoamerican Nephropathy

Exercise, Heat and Recurrent Dehydration

- Low grade Muscle Injury with release of DNA/RNA and Production of Uric acid
- Lactate generation, volume contraction, Urinary acidification
- Proximal Tubular Injury with activation of Aldose Reductase and Fructokinase

 ↑Serum Osmolarity

Rehydration with soft drinks

Increased Fractional Excretion of Uric acid With Crystalluria

Noncrystalline and crystalline effects of uric acid

Repeated Acute Kidney Injury Chronic Kidney Disease
<table>
<thead>
<tr>
<th>Country</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>India, south</td>
<td>Andhra Pradesh (Uddanam Coast)</td>
</tr>
<tr>
<td></td>
<td>Goa</td>
</tr>
<tr>
<td></td>
<td>Chimakurthy mandal</td>
</tr>
<tr>
<td></td>
<td>Akola districts in Maharashtra</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>North Central Province</td>
</tr>
<tr>
<td>Mexico</td>
<td>Tierra Blanca, Vera Cruz</td>
</tr>
<tr>
<td>Egypt</td>
<td>El Minya, Upper Egypt</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>Tabuk Area</td>
</tr>
<tr>
<td>Sudan</td>
<td>Rural Areas</td>
</tr>
<tr>
<td>Thailand</td>
<td>Northeastern</td>
</tr>
</tbody>
</table>
Sri Lanka Nephropathy

Climate Zone

<table>
<thead>
<tr>
<th>Wet Zone</th>
<th>Intermediate Zone</th>
<th>Arid Zone</th>
<th>Dry Zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaffna</td>
<td>Mannar</td>
<td>Trincomalee</td>
<td>Arid Zone</td>
</tr>
<tr>
<td>Yavunliya</td>
<td>Anuradhapura</td>
<td>Polonnaruwa</td>
<td>Dry Zone</td>
</tr>
<tr>
<td>Batticaloa</td>
<td></td>
<td></td>
<td>Intermediate Zone</td>
</tr>
<tr>
<td>Kandy</td>
<td>Nuwara Eliya</td>
<td></td>
<td>Wet Zone</td>
</tr>
<tr>
<td>Colombo</td>
<td>Ampara</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hambantota</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CKD Sites

Not Reported
1 - 99
100 - 499
500 - 999
>= 1000

Average Temperatures

Average Annual Temperature

Source: Department of Meteorology
Low Water Increases Risk for CKD (NHANES 2005-2006)

Low vs. high water intake*

<table>
<thead>
<tr>
<th>Source of Water</th>
<th>Risk (Odds Ratio) for CKD [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total water from all beverages &amp; food</td>
<td>2.52 [0.91, 6.96]</td>
</tr>
<tr>
<td>Plain water</td>
<td>2.36 [1.10, 5.06]</td>
</tr>
<tr>
<td>Water from beverages other than plain water</td>
<td>0.87 [0.30, 2.50]</td>
</tr>
</tbody>
</table>

*Low (<20th percentile) water intake, high (>80th percentile) water intake.

Sontrop et al, Am J Nephrol 2013
Low Urine pH Predicts CKD

Risk for CKD [95% CI]

P<0.02

1811 Adults followed 7.7 yrs in Japan

Low pH increases risk

Low urine pH (5.0-5.5) versus high urine pH (6.5-7.0)

95% CI, 95% confidence interval; OR, odds ratio.

Nakanishi et al  Kidney BP Res 2012; 35:77
Heat Stress Associated CKD: The first epidemic due to Global Warming

- An Epidemic of CKD is occurring in Central America
- The primary risk factor is recurrent dehydration
- Recurrent dehydration and heat stress causes CKD in animals
- The injury may be a consequence of vasopressin, endogenous fructose, and uricosuria
- These pathways may be involved in other types of AKI and CKD
- Global warming, water shortage, and increased intake of sugary beverages may have a role in why CKD is increasing
Special Thanks

And to all collaborators, especially

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