Chronic Kidney Disease and Climate change

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Dr Johnson has funding with the NIH, DOD, and VA Merit. He is on the scientific board of Amway and XORT therapeutics. He has patents and patent applications related to uric acid and fructose metabolism and is a member of a startup company, Colorado Research Partners LLC that is developing inhibitors of sugar metabolism.
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

Fischer and Knutti
Nature Clim Change
2015;5:560

http://earthobservatory.nasa.gov/Features/WorldOfChange/decadaltemp.php
Iran city hits suffocating heat index of 165 degrees, near world record

The Kidney: An Organ hit hard by Dehydration

Classic Teaching

- Sweat--- loss of sodium and water
- Kidneys must concentrate the urine
- This occurs with some retention of urea and creatinine but was generally thought to be reversible
- However, a newly recognized type of chronic kidney disease is being observed among workers in hot regions of the world
An Epidemic of Chronic Kidney Disease

Map showing the distribution of Chronic Kidney Disease in Guanacaste and the Rest of Costa Rica. The graph on the right illustrates the increase in cases over time, with a significant rise in Guanacaste for both men and women compared to the Rest of Costa Rica.

- Guanacaste
- Rest of Costa Rica
Mesoamerican Nephropathy

- Occurs predominantly along the Pacific Coast.
- Primarily men working in sugar cane fields, but can occur with other occupations.
- Presents with asymptomatic elevation in creatinine, low grade proteinuria, and chronic tubulointerstitial nephritis.
- Also affects women, possibly children.
- 20,000 Deaths so far!
Mesoamerican Nephropathy is a Chronic Tubulointerstitial Disease

- Tubulointerstitial fibrosis
- Secondary glomerulosclerosis
- Glomerular ischemia
- Some inflammation
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
What are the other Candidates besides pesticides that might be causing Mesoamerican Nephropathy?

Proposed, but Little evidence: Environmental toxins

- NSAIDS (nonsteroidal agents)
- Heavy metals: Cadmium, Lead, Arsenic
- Aristolochic Acid (Balkans) – cause of Chinese Herb Nephropathy
- Leptospirosis and other infections

Most Important Risk Factor: Volume Depletion and Dehydration:

- Repeated kidney injury from recurrent dehydration, such as from Heat Stroke or Rhabdomyolysis
Central America: Site of High Solar Radiation Correlates with Site of CKD Epidemic
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_
Symptoms of Dehydration are Common in Sugarcane Workers

Temperature Variability; Hotter at Low Altitude, but variable

Garcia Trabanino et al. 2015
Disease Preferentially Occurs at Low Altitude

COASTAL

HIGH-ALTITUDE
Could Mesoamerican Nephropathy be a Dehydration Disorder?
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

Water Please!

TOTAL DURATION
5 weeks

8:00 AM
8:00 AM

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

Roncal-Jimenez et al Kidney Int. 2013
How Does Dehydration Cause Kidney Disease?
Vasopressin and Fructose May be Mediators for Dehydration Kidney Injury

↑ Vasopressin

↓

↑ Aldose Reductase

glucose

sorbitol

fructose

Oxidative stress, inflammation

Kidney Damage
Could Sugar-containing Rehydration Solutions Worsen Dehydration Induced Kidney Disease?

- Recurrent Dehydration Increases Serum Osmolarity
- Soft Drinks containing fructose
  - Aldose Reductase
  - Fructokinase
- Kidney Fructose Accumulation
- Oxidative Stress
- Kidney Injury

Vasopressin
Temperature Change in El Salvador

Rats are given one-third of normal water intake for 22 hours of each day, then given water or sugary beverage, or stevia water for two hours.

Rehydration with Soft Drinks Causes Kidney Damage in Dehydrated Rats

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)

Serum Creatinine

Morning: 0.81
Afternoon: 0.96

Serum Uric acid

Morning: 5.53
Afternoon: 6.61

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
Sugar cane Workers in Chinandega, Nicaragua Showed Marked Uricosuria in One of Four Urines

![Uric acid levels chart](chart.png)

- Urine Uric acid (mg/dl)
  - May 13th, 2013: > 100 mg/dl
  - Dec 5th, 2012: 40 mg/dl
  - Nov 26th, 2012: 30 mg/dl
  - May 10th, 2013: 80 mg/dl

Temperature and weather conditions:
- May 14th, 2013: 104°F
- May 25th, 2013: 85°F
- June 26th, 2013: 87°F
- Sept 27th, 2013: 70°F
- Dec 23rd, 2013: 65°F
# World “CKD HOT SPOTS” Chronic Interstitial Nephritis in Agricultural Workers

<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>
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<tr>
<td></td>
<td>Akola districts in Maharashtra</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>North Central Province</td>
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<tr>
<td>Mexico</td>
<td>Tierra Blanca, Vera Cruz</td>
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<td>Egypt</td>
<td>El Minya, Upper Egypt</td>
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<td>Saudi Arabia</td>
<td>Tabuk Area</td>
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<tr>
<td>Sudan</td>
<td>Rural Areas</td>
</tr>
<tr>
<td>Thailand</td>
<td>Northeastern</td>
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Sugar cane Workers in Chinandega, Nicaragua Showed Marked Uricosuria in One of Four Urines

Urine Uric acid (mg/dl)

> 100 mg/dl

May 13th, 2013

Dec 5th

Nov 26th

May 104 ˚F

May 14 72˚F

May 15 87˚F

May 16 92˚F

May 21 70˚F
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
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Thanks for your Attention