CLIMATE CHANGE and KIDNEY DISEASE

ACOI 2018
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No disclaimers!
Map of Palm Beach County, Florida
Agriculture in Palm Beach County

• Highest production of any county east of the Mississippi River
• Over 500,000 acres under cultivation
• Leads the nation in production of sugar cane, sweet corn, bell peppers
• Leads the state in production of rice, lettuce, cabbages, radishes, Chinese vegetables, celery
Agricultural Workers in Palm Beach County

- >118,000 individuals
- 12.3% of labor force
- >67,000 (59%) unaccompanied migrants
- 41% unaccompanied seasonal
- 42% earn <$5,000/yr
- >50% earn <$10,000/yr

The Work

- Long hours, income tied to harvest weight
- Suboptimal access to potable water
- Good access to commercial beverages
- Access to NSAIDs
- Muscle injury under stress
- Subclinical rhabdomyolysis
- Repeated episodes of subclinical AKI
- Migrant populations
- Limited access to medical care
Temperature Projections for FL and SE USA

Figure 17.3: Observed annual average temperature for the Southeast and projected temperatures assuming substantial emissions reductions (lower emissions, B1) and assuming continued growth in emissions (higher emissions, A2). For each emissions scenario, shading shows the range of projections and the line shows a central estimate. The projections were referenced to observed temperatures for the period 1901-1960. The region warmed during the early part of last century, cooled for a few decades, and is now warming again. The lack of an overall upward trend over the entire period of 1900-2012 is unusual compared to the rest of the U.S. and the globe. This feature has been dubbed the "warming hole" and has been the subject of considerable research, although a conclusive cause has not been identified. (Figure source: adapted from Kunkel et al., 2013).
Variations of the Earth's surface temperature for:

- the past 140 years

Figure 1.
Global temperature shifts over the past 140 years. The zero line represents the 30-year average temperature from 1961 to 1990, which the World Meteorological Organization has designated to be the base for climatology.

Source: Fourth Assessment of the Intergovernmental Panel on Climate Change (IPCC).

Atmospheric Carbon Dioxide Concentrations
From ice cores and direct measurements

Figure 2.
Atmospheric CO₂ concentrations as measured from ice cores and direct measurements. Source: Fourth Assessment of the IPCC.

https://climatecenter.fsu.edu/images/docs/ClimateChange-factsheet.pdf
Kidney Failure in the Cane Fields!

Epidemic of Kidney Disease Among Migrant Agricultural Workers Across the County
That has been the reality in tropical agricultural zones around the world for almost 2 decades.
Nefropatía terminal en pacientes de un hospital de referencia en El Salvador

Ramón García Trabanino,¹ Raúl Aguilar,² Carlos Reyes Silva,¹
Manuel Ortiz Mercado¹ y Ricardo Leiva Merino³


Terminal nephropathy in patients of a reference hospital in El Salvador
Clinical Characteristics of “nontraditional” CKD in Salvadoran farming communities

- Poverty
- Agrochemical exposure (95.7%)
- Agricultural work (78.3%)
- Male (78.3%)
- Profuse sweating during work (76.3%)
- Malaria (43.5%)
- NSAID use (41.3%)

Clinical Characteristics of “nontraditional” CKD in Salvadoran farming communities

<table>
<thead>
<tr>
<th>General symptoms:</th>
<th>Renal symptoms:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Arthralgia (54.3%)</td>
<td>• Nocturia (65.2%)</td>
</tr>
<tr>
<td>• Asthenia (52.2%)</td>
<td>• Dysuria (39.1%)</td>
</tr>
<tr>
<td>• Cramps (45.7%)</td>
<td>• Foamy urine (63%)</td>
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<tr>
<td>• Fainting (30.4%)</td>
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</tbody>
</table>

Clinical Characteristics of “nontraditional” CKD in Salvadoran farming communities

Renal markers:
- Macroalbuminuria (80.4%)
- β-microglobuoin (78.2%)
- NGAL (26.1%)
- Hypermagnesuria (100%)
- Hyperphosphatemia (50%)
- Hypernatriuria (45.7%)
- Hyperkaluria (23.9%)

Renal signs:
- Hypercalciuria (17.4%)
- Polyuria (43.5%)
- Metabolic alkalosis (45.7%)
- Hyponatremia (47.8%)
- Hypocalcemia (39.1%)
- Hypokalemia (30.4%)
- Hypomagnesemia (19.6%)

Risk Factors for CKD in a Nicaraguan Agricultural Community

• Agricultural worker
• Male:female > 4:1
• Proteinuria < 10%
• Lifetime days cutting sugarcane during dry season (OR 5.86)
• Pesticide inhalation (OR 3.31)
• Sugarcane chewing (OR 3.24)

Histopathology of Chronic Kidney Disease of Unknown Etiology in Salvadoran Communities. MEDICC Review, April 2014, 16(2)
The most important and striking lesion, interstitial fibrosis accompanied by glomerular damage, and classic tubular atrophy, led to the histopathological diagnosis of chronic interstitial nephritis, since it increased directly with CKD stage. . . Our findings are consistent with a multifactorial etiology for this disease.

Lopez-Marin L, Chavez Y, et al. Histopathology of Chronic Kidney Disease of Unknown Etiology in Salvadoran Communities. MEDICC Review, April 2014, 16(2)
Figure 1. Light microscopy findings in kidney tissue from the Nicaragua biopsy study. Global glomerulosclerosis of varying degree (stars in A [periodic acid-Schiff (PAS)-methenamine staining from patient 1], B [Ladewig staining from patient 9], and D [PAS staining from patient 9]) and (A, B) moderate to severe glomerular hypertrophy (black arrow) were found in all patients. Signs of glomerular ischemia with thickening of Bowman’s capsule or wrinkling of capillary walls (arrowheads in A, C [PAS staining from patient 6], and D) were found in all but 1 patient. (B) Mild to moderate interstitial fibrosis (white arrow) and (C, D) tubular atrophy of varying degree (black arrows) were seen in most patients. (C, D) Arteries were in most cases normal (white arrows) or only mildly changed. Scale bars = (A, C) 100 μm, (B, D) 200 μm.
Figure 2. (A) Transmission electron microscopy image from patient 10 shows cytoplasm of a podocyte (c) containing vacuoles (arrowhead). (B) Image from patient 17 shows lipofusin-like bodies (lfb) in cytoplasm of a podocyte. (C) Image from patient 6 shows cell debris in Bowman’s space (*), probably derived from podocytes because it was mostly found within the glomerular tuft between capillary loops and Bowman’s capsular epithelium showed no apparent pathology. (D) Image from patient 17 shows widespread foot-process effacement (arrowhead) and a focally swollen endothelium (*). Abbreviations: c, capillary space; n, nucleus. Scale bars = (A) 5 μm, (B-D) 1 μm.

Chronic glomerular changes could be the result of compensatory mechanisms due to nephron loss ... periglomerular fibrosis indicating ischemia, changes consistent with hypertension [and ] immune complex glomerulonephritis could be excluded ... Podocyte effacement not correlated with albuminuria ...

Prevalence of CKD in Central America

• Coastal El Salvador 13-17% (♂:♀ = 4:1) (v. US 5%)
• 38% with HTN, no other risk factors
• Age < 60: ♂ 57%; ♀ 28%
• Nicaragua ~13%; ♂ > 57 y/o: 53%
• Coastal regions > highlands 9:1
• CKD-associated mortality in Nicaragua & El Salvador 110/100,000 (<40/100,000 in Cuba, Costa Rica, Panama)
• ESRD 1410/1M, ♂: ♀ = 9:1
• Typically, no proteinuria, some hypertension, rare diabetes
• Risk: Sugar cane cutters > construction workers > farmers

Figure 1. | Temperature trends in Central America. The average maximum temperatures (Tmax) in Central America over the last 60 years (left panel) correspond closely with sites of the CKD epidemic, such as Chichigalpa and Quezaltenango in Nicaragua, San Alejo and the Bajo Lempa region in El Salvador, or Guanacaste in Costa Rica. Those areas are also generally colocated with the climatologically warmest zones (left panel). Maximum temperatures are also increasing, especially in Guatemala and El Salvador (right panel). Data from the US National Oceanic and Atmospheric Administration, Earth System Research Laboratory, Boulder, Colorado (public domain). Average daily Tmax at observing sites are averaged into monthly, and then into annual mean values. Data are then objectively interpolated to a half degree grid. The left panel shows the 60-year (1951–2010) annual average, and the right panel shows the total linear trend change over the period 1945–2014.
Figure 3. | **Changing temperatures in El Salvador.** Mean temperatures have increased by about 0.8°C during this period in El Salvador, which results in a significant (30%-75%) increase in the frequency of extremely hot days (>99th percentile) (image from Berkeley Earth [http://berkeleyearth.lbl.gov/regions/el-salvador], public domain).
Figure 5

Prevalence of kidney disease in Quetzalguaje compared with the USA using the NHANES 1999–2006 data

CKD in quetzalguaje vs the US by age, males

<table>
<thead>
<tr>
<th>AGE</th>
<th>Quetzalguaje</th>
<th>USA</th>
<th>Quetzalguaje</th>
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CKD in quetzalguaje vs the US by age, Females

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Sources: Adapted from O'Donnell et al. (2011).
Figure 2
Chronic Kidney Disease & Unspecified Renal Failure Mortality Rates by Age & Sex (x 100,000 pop.) in selected countries. 2001 (A) and 2008 (B)

Figure 2A, year 2008

Figure 2b, year 2008

[Graph showing mortality rates by gender (femenino and masculino) for Costa Rica, Cuba, El Salvador, Guatemala, Nicaragua, and Panama.]
MESOAmerican nephropathy
report from the first international research workshop on MeN

november 28-30, 2012 hotel barcelo palma real, san jose, costa rica

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Central American Institute for Studies on Toxic Substances (IRET)
Universidad Nacional (UNA), Costa Rica

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Kristina Jakobsson
Rebekah Lucas
David Wegman

bringing together knowledge, research questions, and initiatives related to chronic kidney disease of unknown origin in Mesoamerica
Among the conclusions . . .

Case Definition

- Persons with abnormal kidney function by internationally accepted standards, living in Mesoamerica and with no other known causes for CKD, typically with no hypertension and no edema on physical exam; defining standard diagnostic methods (history, imaging, blood and urine markers, kidney biopsy), and longitudinal follow up
Among the results . . .

Social Determinants

- **Occupational exposures:** Industry → job/task → exposure (inhalation/ingestion/dermal) → absorbed dose
- **Environmental exposures:** Region → media → exposure (inhalation/ingestion/dermal) → absorbed dose
- **Susceptibility:** Absorbed dose → biologically effective dose → AKI → CKD
Questions of the International Symposium

• What do we know?
  • Hydration, hard work & heat

• What do we need to know?
  • Type, quality, quantity & timing of fluid intake by workers
  • Diet, salt intake
  • Heat illness history, exposure levels, historical data, childhood exposures, NSAID use, alcohol exposure

• How do we find out what we need to know?
  • Development of qualitative & quantitative methods, intervention protocols & trials, database accrual & mining
Among the results . . .
Proposed priorities for exploring causative hypotheses

- **Highly likely:** Heat stress, dehydration, NSAIDs, duration of exposure
- **Possible** (high priority): arsenic, fructose, nephrotoxic meds, leptospirosis
- **Possible** (lower priority): genetic and epigenetic factors, low birth weight, prenatal/perinatal/childhood exposures, ages of exposure
- **Unlikely:** pesticides, urinary tract diseases, STIs
- **Little known:** calcium/minerals in drinking water, medication contamination, homeopathic meds, locally produced alcohol, inhalants, UV
- **Unlikely:** lead, mercury, cadmium, uranium, aristolochic acid
Fig. 2 Multiple potential causes for CKD-mfo. Colour code: blue probable causes; yellow less probable causes; white causes that have not been investigated.
Figure 2. Frequency of measured exposures from studies across different regions. (A) Exposures measured in studies from all regions; (B) exposures measured in studies from South Asia; (C) exposures measured in studies from Central America. BMI, body mass index.
The Biggest Problem with Mesoamerican Nephropathy . . .
. . . It’s Global
Escalating chronic kidney diseases of multi-factorial origin in Sri Lanka: causes, solutions, and recommendations

Sunil J. Wimalawansa

Figure 4. Sri Lankan nephropathy. (A) and (B) An epidemic of CKD is occurring in the dry zone of the north central region of Sri Lanka. (C) The region is exceptionally hot, with average temperatures of approximately 30°C. While the relationship of CKD with higher average annual temperatures is evident, it is interesting that the most northern part of Sri Lanka is also hot but does not appear to be a site of the CKD epidemic. However, this is an area where little investigation has been done, and it remains possible to be a site of underreporting. (A) and (B) courtesy of Channa Jayasumana (106). (C) is from the Centre for Climate Change Studies, Department of Meteorology, Colombo, Sri Lanka (http://www.meteo.gov.lk/index.php?option=com_content&view=article&id=13&Itemid=132&lang=en). CKDu, CKD of unknown etiology.
Figure 5. Confirmed site (Andhra Pradesh) and suspected sites of CKD epidemics of unknown etiology in India. Average number of heat wave days (Avg HW days) between March and July (hottest time of the year) in India, based on the number of heat wave days over the 50-year period. Andhra Pradesh has had some of the longest heat waves, with one recorded at 35 days. Other suspected sites of CKD of unknown etiology, such as the Akola district of Maharashtra and the central Odisha region, are also sites with high number of heat waves. In contrast, Goa does not show this pattern.Courtesy: Editor Mausam—India Meteorological Department. Reprinted from reference 5, with permission.
Figure 6. Worldwide annual maximum temperature changes. Change in annual maximum temperature from 1945 to 2014 (top panel) and the average annual maximum temperature during 1951–2010 (bottom panel). From the US National Oceanic and Atmospheric Administration, Earth System Research Laboratory, Boulder, Colorado (public domain). Data definition as shown in Figure 1. EQ, equator; Tmax, annual maximum temperature.
## Confirmed and suspected sites of heat stress-associated nephropathy

<table>
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<th>Confirmed</th>
<th>Suspected</th>
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<tbody>
<tr>
<td><strong>Central America</strong></td>
<td><strong>South Asia</strong></td>
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<tr>
<td>• Costa Rica</td>
<td>• India</td>
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<tr>
<td>• El Salvador</td>
<td>• Thailand</td>
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<tr>
<td>• Guatemala</td>
<td>• Middle East</td>
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<tr>
<td>• Nicaragua</td>
<td>• Saudi Arabia</td>
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<tr>
<td><strong>South Asia</strong></td>
<td><strong>Africa</strong></td>
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<tr>
<td>• India</td>
<td>• Egypt</td>
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<tr>
<td>• Sri Lanka</td>
<td>• Sudan</td>
</tr>
<tr>
<td><strong>North America</strong></td>
<td><strong>North America</strong></td>
</tr>
<tr>
<td>• Mexico</td>
<td>• Mexico</td>
</tr>
<tr>
<td>• California Central Valley</td>
<td>• California Central Valley</td>
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</tbody>
</table>

Most frequently studied CKDu etiology risk factors by region

- Central America
  - Age
  - Gender
  - Agrochemical use
  - Occupation
  - Heat stress

- South Asia
  - Heavy metals
  - Occupation
  - Family history
  - Agrochemical use
  - Smoking

- Other regions
  - Body mass index
  - Heavy metals
  - Age
  - Dietary exposure
  - Heat stress

Pathophysiology of CKDu

- Rising ambient temperature (*aka* global warming)
- Recurrent low levels of dehydration
- Agrochemical and/or heavy metal exposure
- Recurrent muscle injury → rhabdomyolysis
- NSAID use
- Vasopressin
- Fructose
- Increased core temperature
The Combined Effect of High Ambient Temperature and Antihypertensive Treatment on Renal Function in Hospitalized Elderly Patients

Iftach Sagy1,2,3,*, Alina Vodonos1,2,*, Victor Novack1,2,3, Boris Rogachev2,3,4, Yosef S. Havin2,3,4, Leonid Barski2,3
1 Clinical Research Center, Soroka University Medical Center, Beer-Sheva, Israel, 2 Internal Medicine Division, Soroka University Medical Center, Beer-Sheva, Israel, 3 Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel, 4 Department of Nephrology, Soroka University Medical Center, Beer-Sheva, Israel

More heat, worse CKD -- Worse CKD, more heat vulnerability

Fig 2. The cumulative increase in serum creatinine (mg/dL) for the addition of each clinical characteristic. The additional p-value for each parameter is presented in brackets. ACE/ARBs—angiotensin-converting-enzyme inhibitor or angiotensin receptor blockers, CKD—chronic kidney disease
Are they drinking enough? What are they drinking?

- Access to potable water often restricted by circumstance
- Is available water clean?
- Can it be carried or transported?
- Are containers safe?
- Are workers drinking enough?
- Are they drinking in anticipation of thirst, or in response to thirst?
- What about preference for fructose-sweetened colas?
- What about home made alcohol?
Role of agrochemicals & heavy metals?

- Related to concentrations in soil?
- Related to renal concentrating mechanisms in relative dehydration?
- Facultative/permissive rather than primary etiologic role?
- Demonstration so far equivocal, inconsistent in Mesoamerican zones
- But evidence of increased incidence of ESRD in US among pesticide applicators

Role of muscle stress and access to NSAIDs?

- Apparent unrestricted access
- Keeps workers working
- Known problem, difficult to quantify
- Exacerbation of prerenal status
- Exacerbation of repeated subclinical rhabdomyolysis
The role of fructose?

• Increased proximal tubular resorption of glucose rich fluid in setting of decreased renal perfusion
• Increased activation of aldose reductase pathway, increased conversion of glucose to sorbitol & fructose, exacerbated by relative renal ischemia
• Better access to soda than potable water?
• Increased activation of fructokinase → ATP depletion → ischemic-like cellular shock → uric acid generation → inflammation & oxidative stress
• Renal vasoconstriction, glomerular hypertrophy, microvascular lesions, tubulointerstitial inflammation & fibrosis, albuminuria & glomerulosclerosis

Vasopressin response in Heat Stress

• The Survival Hormone?
• Suppresses nonrenal water loss (skin, respiration) as well as urinary
• Increased Na⁺ reabsorption
• Stress response: BP maintenance, ↑ serum glucose, ↑ fat accumulation, ↑ protein conservation

• Role of non-osmotic stimulation?
• Role in heat stress nephropathy?

Figure 2. | Mechanism for heat stress nephropathy. Repeated heat stress and water shortage, especially when coupled with overexertion, can lead to several pathophysiologic processes, including low grade or overt rhabdomyolysis, hyperosmolarity, hyperthermia, and extracellular volume depletion. These processes can result in several mechanisms that can lead to AKI, including the acute effects of vasopressin on renal tubules, endogenous fructose metabolism in the proximal tubule via the fructokinase system, the development of uricosuria and urate crystal formation, hypokalemia-induced renal vasoconstriction and injury, and a generalized reduction in renal blood flow that may also cause ischemic damage. Repeated AKI, in turn, may lead to chronic tubulointerstitial disease.

Role of core temperature?
Thermoregulation

- We perspire up to 2 L/hr
- Blood flow to skin can increase from ~300 ml/min to ~7500 ml/min – up to 50% of cardiac output
- Sweat loss > fluid replacement → hyperosmotic hypovolemia
- Increased inotropic & chronotropic demand, increased SNS & RAAS stimulation

- What’s missing: assessment of thermoregulatory challenges, body temperature changes, $O_2$ consumption in workers, or in renal perfusion/output/function per day/week/season

<table>
<thead>
<tr>
<th>Process</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>Heart disease</td>
<td>Insufficient cardiac output, reduced blood volume to skin</td>
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<td></td>
<td>Lower efficiency in heat loss</td>
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<tr>
<td>Nephropathy/impaired water and sodium reabsorption</td>
<td>Dehydration</td>
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<td></td>
<td>Decreased sweat production</td>
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<tr>
<td></td>
<td>Decreased perfusion to skin</td>
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<tr>
<td>Endocrine diseases</td>
<td>Decreased sweat production</td>
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<td></td>
<td>Impaired heat elimination/production regulation</td>
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<tr>
<td>Drugs</td>
<td>Anticholinergic drugs</td>
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<td>Decreased sweat production</td>
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<td>Decreased cardiac output</td>
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<td>Skin disorders</td>
<td>Lower efficiency in heat loss</td>
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Adapted from Sankoff.²⁸

Proposed mechanisms of heat shock protein intervention in apoptotic pathways. Both HSPA1 and HSPB1 blocked MOMP upstream of mitochondria by inhibiting JNK and JNK activation, respectively. In addition, both HSPs were reported to directly interfere with Bax activation and translocation, and HSPA1 was shown to prevent stress-induced MCL-1 degradation. Furthermore, HSPB1 activated AKT leading to inactivation of BH3-only proteins. HSPA1 and HSPB1 were found to delay cytochrome c release, whereas HSPB1 bound cytochrome c and thus prevented apoptosome formation. Interference with apoptosome activity has been demonstrated for both HSPA1 and HSPB1. Finally, both HSPs inhibited the full activation of executioner caspases. HSPA1 impaired death receptor signaling at the DISC, whereas HSPB1 augmented NF-κB activation by promoting the degradation of IκB. Note that for simplicity, different death receptor signaling platforms have been unified into one. Activating or inhibitory interactions are depicted using arrows or flat lines, respectively. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
Figure 1. Summary of physiological adaptations induced by heat acclimation.
Hypothesis: Heat stress, Core temperature and CKD

- HSPs deeply conserved through evolution
- Not designed for chronicity or severity of heat change
- Exhaustion of adaptation
- Exhaustion of thermoresistance
- Exhaustion of modulation of mediators of inflammation
- Increased oxidative and inflammatory damage
- Accelerated development of tubulointerstitial fibrosis, concomitant changes of tubular function and reciprocal changes of tubuloglomerular balance as described
Critique of the hypothesis

• Largely inferential (plant and animal data, short term human data in firefighters, athletes)
• Analogies in sepsis and shock syndromes
• Paucity of human data available on chronic heat exposure
• No human experimental confirmation possible
• No therapeutic intervention conceivable
Naming the Problem

- Chronic Kidney Disease of unknown etiology (CKDu)
- Agrochemical Nephropathy
- Chronic Agricultural Nephropathy
- MesoAmerican Nephropathy (MeN)
- Chronic Kidney Disease of multifactorial origin (CKD-mfo)
- Chronic Interstitial Nephritis in Agricultural Communities (CINAC)
- Heat Stress Nephropathy (HSN)*
- Global Warming Nephropathy
Climate Change and the Emergent Epidemic of CKD from Heat Stress in Rural Communities: The Case for Heat Stress Nephropathy


Abstract
Climate change has led to significant rise of 0.8°C–0.9°C in global mean temperature over the last century and has been linked with significant increases in the frequency and severity of heat waves (extreme heat events). Climate change has also been increasingly connected to detrimental human health. One of the consequences of climate-related extreme heat exposure is dehydration and volume loss, leading to acute mortality from exacerbations of pre-existing chronic disease, as well as from outright heat exhaustion and heat stroke. Recent studies have also shown that recurrent heat exposure with physical exertion and inadequate hydration can lead to CKD that is distinct from that caused by diabetes, hypertension, or GN. Epidemics of CKD consistent with heat stress nephropathy are now occurring across the world. Here, we describe this disease, discuss the locations where it appears to be manifesting, link it with increasing temperatures, and discuss ongoing attempts to prevent the disease. Heat stress nephropathy may represent one of the first epidemics due to global warming. Government, industry, and health policy makers in the impacted regions should place greater emphasis on occupational and community interventions.

Mesoamerican Nephropathy or Global Warming Nephropathy?

Carlos A. Roncal-Jimenez a, Ramon Garcia-Trabanino b, Catharina Wesseling c, Richard J. Johnson a

a Division of Renal Diseases and Hypertension, University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, USA; b Scientific Board, Department of Investigation, Hospital Nacional Rosales, San Salvador, El Salvador; c Unit of Occupational Medicine, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

Abstract

Background: An epidemic of chronic kidney disease (CKD) of unknown cause has emerged along the Pacific Coast of Central America. The disease primarily affects men working manually outdoors, and the major group affected is sugarcane workers. The disease presents with an asymptomatic rise in serum creatinine that progresses to end-stage renal disease over several years. Renal biopsies show chronic tubulointerstitial disease. While the cause remains unknown, recent studies suggest that it is driven by recurrent dehydration in the hot climate. Potential mechanisms include the development of hyperosmolality with the activation of the aldose reductase-fructokinase pathway in the proximal tubule leading to local injury and inflammation, and the possibility that renal injury may be the consequence of repeated uricosuria and urate crystal formation as a consequence of both increased generation and urinary concentration, similar to a chronic tumor lysis syndrome. The epidemic is postulated to be increasing due to the effects of global warming.

Summary: An epidemic of CKD has led to the death of more than 20,000 lives in Central America. The cause is unknown, but appears to be due to recurrent dehydration. Potential mechanisms for injury are renal damage as a consequence of recurrent hyperosmolality and/or injury to the tubules from repeated episodes of uricosuria. Key Messages: The epidemic of CKD in Mesoamerica may be due to chronic recurrent dehydration as a consequence of global warming and working conditions. This entity may be one of the first major diseases attributed to climate change and the greenhouse effect.
Kidney Diseases in Agricultural Communities: A Case Against Heat-Stress Nephropathy

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The beginning of the 21st century has seen the emergence of a new chronic tubulo-interstitial kidney disease of uncertain cause among agricultural communities in Central America and Sri Lanka. Despite many similarities in demography, presentation, clinical features, and renal histopathology in affected individuals in these regions, a toxic etiology has been considered mainly in Sri Lanka, whereas the predominant hypothesis in Central America has been that recurrent acute kidney injury (AKI) caused by heat stress leads to chronic kidney disease (CKD). This is termed the heat stress/dehydration hypothesis. This review attempts to demonstrate that there is sparse evidence for the occurrence of significant AKI among manual workers who are at high risk, and that there is little substantial evidence that an elevation of serum creatinine < 0.3 mg/dl in previously healthy people will lead to CKD even with recurrent episodes. It is also proposed that the extent of global warming over the last half-century was not sufficient to have caused a drastic change in the effects of heat stress on renal function in manual workers. Comparable chronic tubulo-interstitial kidney disease is not seen in workers exposed to heat in most tropical regions, although the disease is seen in individuals not exposed to heat stress in the affected regions. The proposed pathogenic mechanisms of heat stress causing CKD have not yet been proved in humans or demonstrated in workers at risk. It is believed that claims of a global warming nephropathy in relation to this disease may be premature and without convincing evidence.

KEYWORDS: chronic interstitial nephritis in agricultural communities; CKDu in Sri Lanka; heat-stress nephropathy
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CKDu: A Perfect Storm

When chronic kidney disease (CKD) rates began to climb in poor agricultural communities in Central America and elsewhere, at least a decade ago, no one could have predicted the devastation wrought since then by what appears to be a new form of nephropathy. An epidemic that in a country such as El Salvador has catapulted end-stage renal disease to third place among causes of hospital deaths, first place among men.

Termed alternately CKD of nontraditional causes, CKD of unknown etiology, agricultural nephropathy, or chronic agrochemical nephropathy, Mesamerican epidemic nephropathy, and CKD of uncertain etiology—its effects are the same and its characterization similar in the countries where it has emerged. Most often described histopathologically as chronic tubulointerstitial nephropathy, this CKD has thus far been studied in El Salvador, Nicaragua, Costa Rica, Mexico, Sri Lanka, Egypt, and India. We prefer CKD of uncertain etiology (CKDU), since initial research findings point to multifactorial causation in nearly all cases.

And it is the multifactorial mystery that has generated a perfect storm, in which social determinants such as deep-rooted poverty appear to combine synergistically with harsh, sometimes inhuman, working conditions and exposure to environmental toxins to produce a silent killer that is most often diagnosed when kidney damage already requires renal replacement therapy. This is too late for most of these subsistence farmers and agricultural laborers, since the cost of such treatment is simply out of reach, and they often have little access to the range of specialties required to manage their disease.

The brewing storm is complicated by the fact that the people and communities affected are in developing countries, the least able to provide the infrastructure and financial resources for urgently needed health services such as dialysis and transplantation. In the best of cases, governments and health ministries have sounded the alarm and taken action within their means; in the worst of cases, people who suffer are not only threatened by illness, but their protests are also repressed by misguided government authorities.

Researchers have yet to agree on the trigger for CKDUs or the exact configuration of its risk factors. The debates are heated, and many vested interests surely will be touched upon as they proceed, making full disclosure by researchers more ethically essential than ever. Critical to move forward is coordinated research agendas that respect differing results and new professional climates. The race is not to be first or to be right after all, but to halt the loss of lives. In this context, public health actions are required to intervene to protect lives, even before the final results are in on CKDU’s causal relationships, if they ever are. This means exercising the precautionary principle when necessary, and clearly implies the need for greater attention and cooperation from international agencies such as PAHO and WHO, as well as health ministries, research centers, NGOs, labor, industry, and foundations.

We hope this issue of MEDECC Review contributes to advancing collaboration in this alarming epidemic, by publishing the latest findings on CKDUs and its global impact. In addition to Original Research and Perspectives by authors in five countries, we are grateful to the major figures in public health and nephrology who found the time to express their superb viewpoints in the pages that follow. We call your attention to the sections available online only: in particular the Special Abstracts Section on CKDUs, intended as a repository for articles related to the disease published in peer-reviewed journals, and for which we invite additions to update readers (see www.medcc.org/meedirect review). Also noteworthy are online reprints of several important documents stemming from regional meetings, as well as the Concept Paper and Resolution approved by PAHO’s Executive Committee, providing a framework to address the epidemic.

"Dr Miguel Márquez, one of the hemisphere’s public health luminaries and a member of MEDECC Review’s Editorial Board, passed away on February 3. Born in Ecuador in 1924, he studied medicine at the University of Caracas, went on to earn a masters degree at the University del Valle in Caliambra, and to work for many years in the Pan American Health Organization (PAHO) in human resources for health and other key fields. He served as PAHO/WHO country representative in both Nicaragua and Cuba, the latter through 1996.

"He was a founding member of the journal’s Editorial Board, generously contributing his wisdom and profound experience. He authored or co-authored over 80 major publications, including the UNPDD’s Human Development in Cuba (Spanish, three editions); [and] a book on the Cuban health system (Sala para toda, si es posible).

"This hemisphere has lost a great man, a defender of vulnerable populations and the importance of strengthening health systems to serve them."

For the full note from our publisher on Dr Márquez’s life, see http://medcc.org/?p=5175"

We congratulate two of our Editorial Board members for recent achievements: Dr Francisco Rojas Ochoa, recognized by the Cuban medical sciences publishing community for his decades of dedication to medical and public health research and debate, most recently as editor of the Revista Cubana de Salud Pública, a post he has now retired. And accolades to Dr Paul Herrera, recently awarded the Carlos J. Finlay Medal, the highest honor in Cuban public health.

Our thanks to The Ford Foundation and The Atlantic Philanthropies, a limited life foundation, for supporting this special issue.

The entire MEDECC Review team is grateful for the wise counsel and exceptional editorial contribution to this issue provided by Guest Editor Dr Wendy Hoi, whose life’s work offers an example of scientific rigor at the service of disadvantaged people.-jlp

The Editors
The Human Dimension
An island of widows: the human face of Mesoamerican endemic nephropathy

Figure 1 | The patient’s red dialysate drainage bags.

Figure 2 | Exterior view of the clean room.

Figure 3 | An ambulance arrived to transport the patient to the hospital.
Poverty: The Common Denominator of CKD’s Global Threat

Guillermo Garcia-Garcia MD FACP FASN

“I think that we are an important voice speaking on behalf of the world’s most vulnerable people today—the sick and dying among the poorest of the poor. The stakes are high. Let’s therefore speak boldly so that we can feel confident that we have fulfilled our task as well as possible.”

—Jeffrey Sachs

Chronic kidney disease (CKD) is increasingly recognized as a global public health problem and is a key determinant of poor health outcomes. Reports from Europe, Australia, Asia, Africa, and Latin America confirm a high prevalence of CKD. While the magnitude of CKD has been better defined in developed countries, increasing evidence indicates that the burden of CKD is as great or even greater in developing countries. Disadvantaged communities—i.e., those from low socioeconomic status, racial and ethnic minority, and indigenous backgrounds—suffer from marked increases in incidence, prevalence, and complications of CKD. The fact that even in developed countries, racial and ethnic minorities bear a disproportionate burden of the disease suggests there is much to learn beyond the traditional risk factors contributing to CKD and its associated complications.

The lack of renal registries means that there are no reliable statistics about CKD prevalence in most of the developing world. However, it is known that diabetes and hypertension are the leading causes of chronic kidney disease in all developed and many developing countries. In contrast, infectious diseases continue to play an important role as a cause of end-stage renal disease in low-income countries, secondary to poor sanitation, inadequate supply of safe water and high concentrations of disease vectors.

As reported in this issue, the elevated prevalence of CKD in unspecified cause in various developing countries reminds us of the relationship between poverty and ill health, in which other factors, environmental exposures to heavy metals or other toxins and pollutants may play a significant role in the development of CKD. The elevated prevalence of CKD of unspecified cause that has been reported in male farmers in various developing countries confirms this relationship. Indeed, in Nicaragua, increased CKD rates in male farmers aged 60 years were found to be associated with pesticide exposure, dehydration, alcohol consumption, and exposure to heavy metals.

Costa Rica has reported a higher incidence of chronic renal disease among young sugarcane workers, with clinical and histological findings of chronic interstitial nephritis. In El Salvador, a high-prevalence of CKD (17%) was found among male farmers exposed to toxic pollutants. In Mexico, in one third of incident dialysis patients, the etiology is unknown.

Studies in Sri Lanka have found an association between pesticide poisoning and pollutants with repeated episodes of acute renal failure and CKD. In India and Pakistan, a large percentage of CKD cases are of undetermined etiology and environmental factors have been postulated in causation of the disease.

Additionally, the use of traditional herbal medications is common and frequently associated with CKD among the poor. Nephrotoxicity resulting from their use has accounted for 37.5% of cases of acute tubular necrosis in Nigeria. In East Africa, about 11% of cases of acute renal failure have been attributed to traditional herbal medicines. In South Asia, use of herbal medicines and infections are among the commonest causes of acute renal failure. Traditional remedies have rarely been analyzed and the active nephrotoxic components have not been isolated and characterized in most cases.

The association of poverty and disease could explain the increased burden of CKD in these populations. Poverty negatively influences these major determinants of health: healthy behaviors, health care access and environmental exposure—all of which contribute to health care disparities through a number of mechanisms. First, the poor are much more susceptible to disease because of lack of access to clean water and sanitation, information about preventive behaviors and adequate nutrition. Second, they often lack access to medical care and are much less likely to seek it, because of greater distance from health care providers, lack of resources needed to pay for health expenditures and their lack of education on how best to respond to illness. Third, environmental exposure to heavy metals and other pollutants, as well as lifetime exposure to poverty, increase their risk of kidney disease. Additionally, genetic or biochemical predisposition may be involved in cases with accelerated CKD progression in the setting of poverty, as seen in nondiabetic patients with focal segmental glomerulosclerosis.

In summary, poverty is associated with poor health outcomes, including CKD. A concerted attack against these diseases—by increased community outreach, better education, improved economic opportunity and access to preventive medicine for those at risk—could end the relationship between CKD and poverty in these communities. Investments in health therefore merit a special place within the strategies for poverty and disease reduction now under way in many low-income countries. 

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I think that we are an important voice speaking on behalf of the world’s most voiceless people today—the sick and dying among the poorest of the poor. The stakes are high. Let’s therefore speak boldly so that we can feel confident that we have fulfilled our task as well as possible.

Jeffrey Sachs
Current state of evidence for heat stress nephropathy in US


Is this on our doorstep?  
Our Research Plan

- One day study of agricultural workers in Palm Beach and Dade Counties
- Before work and after work assays of
  - Age, gender
  - Capillary blood (fingerstick) creatinine
  - Dipstick urinalysis
  - Weight
  - Core temperature (ear thermistor)
  - Capillary cystatin C
  - Work hours
- Limitations
  - Adequate N?
  - Access to immigrant migrants
  - Extrapolation from 1-day data to CKD
  - Comorbid confounders
  - Lack of follow up
Response to the challenge

• Levels of response:
• Treat the individual
• Prevention in the individual
• Local treatment systems
• Local prevention mechanisms
• Regional and national policy
  • Work conditions
  • Water policy
  • Energy policy
  • Carbon footprint
How should we respond to Heat Stress Nephropathy? -- 1

- Treatment for the individual patient:
  - High index of suspicion
  - Screening and assessment
  - Treat hypertension (avoid diuretics)
  - Treat CKD
  - Monitor for development of hyperglycemia, hyperuricemia
  - Prepare for ESRD if necessary
How should we respond to Heat Stress Nephropathy? -- 2

• Prevention for the individual patient:

• Adequate hydration, quantity, quality, access
• Minimize NSAIDs
• Restrict NaCl
• Reduce high fructose corn syrup
• Moderate work hours according to ambient heat
• Screening
• Treat hypertension
How should we respond to Heat Stress Nephropathy? -- 3

• *Local:*

  • Public health infrastructure
  • Medical care infrastructure
  • Monitoring and care of work force
  • Work place regulations
  • Hours of exposure to ambient temperature
  • Potable water availability, quality and quantity
  • Exposure to NaCl-laden foods, high fructose drinks
  • Availability of medical care
  • Local energy policy
How should we respond to Heat Stress Nephropathy? -- 4

• *Regional/National:*

  • Public health adequacy for prevention
  • Health care infrastructure
  • Energy policy
  • Climate change policy
  • Carbon emissions
  • Carbon capture
*Estimated US Costs of Kidney Disease for Undocumented Immigrants

• Tax base of ~$15B (income and sales)
• Numerous barriers to care (bureaucratic, social, financial, educational)
• ~6,500 with ESRD
• Greater prevalence among young, nondiabetic males
• Many state and local variations in care provision and payment (twice weekly, thrice weekly, city or state safety net, or emergent only)
• Reimbursement:cost ratio ~ 2.5:1.5
• Up to $400k/yr in Denver 2013
• Cost ~$1B?

How should we respond to Heat Stress Nephropathy? -- 5

• Planetary:
  • Enlightened response to global climate change
  • Understanding and acceptance of science
  • International cooperation (for local benefits)
  • Change energy direction
  • Change energy infrastructure
  • Reduce carbon emissions
  • Increase carbon capture
Carbon Footprint

Remember, "Objects in mirror are closer than they appear."
Impact of Climate Change on Human Health

- Injuries, fatalities, mental health impacts
- Asthma, cardiovascular disease
- Heat-related illness and death, cardiovascular failure
- Malaria, dengue, encephalitis, hantavirus, Rift Valley fever, Lyme disease, chikungunya, West Nile virus
- Forced migration, civil conflict, mental health impacts
- Extreme heat, more extreme weather
- Environmental Degradation, rising temperatures
- Changes in Vector Ecology, increasing allergens
- Water and Food Supply Impacts, water quality impacts
- Cholera, cryptosporidiosis, campylobacter, leptospirosis, harmful algal blooms
- Respiratory allergies, asthma
- Malnutrition, diarrheal disease
Figure 2.3 Estimated annual counts of heat-related deaths in people aged 65 years and over, by 0.5° grid cell, for BCM2 in 2050, with no adaptation assumed.

Mortality counts shown for 0.5 degree grid cells.
Table 2 – Epidemiological studies of the impact of high temperatures and heat waves.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study population</th>
<th>Period</th>
<th>Renal impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sernertza et al.</td>
<td>General population</td>
<td>July 1995</td>
<td>20% increase in hospital admissions due to kidney disorders (p = 0.027).</td>
</tr>
<tr>
<td>Kovats et al.</td>
<td>General population</td>
<td>1994-2000</td>
<td>Hospital admission due to kidney disorders (AKI or lithium) significant increase only in children under 5 for each degree above 21°C [imputed statistical data]</td>
</tr>
<tr>
<td>Fouillet et al.</td>
<td>General population</td>
<td>1–20 August 2003</td>
<td>High mortality rate due to genitourinary disorders (&gt;361 deaths)</td>
</tr>
<tr>
<td>Conti et al.</td>
<td>Population over the age of 74</td>
<td>16 July–31 August 2006</td>
<td>Increased mortality rate due to kidney disorders</td>
</tr>
<tr>
<td>Rey et al.</td>
<td>General population</td>
<td>1971–2003</td>
<td>Significantly high renal mortality rate of 3% associated with temperatures above 95°F for 3 consecutive days. General: RR 1.255 (95% CI 1.033–1.519) Over the age of 65: 1.196 (95% CI 1.036–1.380) Men aged 15–65 years: RR 1.786 (95% CI 1.619–2.739)</td>
</tr>
<tr>
<td>Hansen et al.</td>
<td>General population</td>
<td>1995–2006</td>
<td>Admission due to AKI if temp. ≥35°C for &lt;3 days: General: RR 1.255 (95% CI 1.033–1.519) Over the age of 65: 1.196 (95% CI 1.036–1.380) Men aged 15–65 years: RR 1.786 (95% CI 1.619–2.739)</td>
</tr>
<tr>
<td>Knowlton et al.</td>
<td>General population</td>
<td>15 July–1 August 2006</td>
<td>Admission due to AKI: RR 1.11 (95% CI 1.08–1.15) Admission due to NNS: RR 1.05 (95% CI 1.02–1.07)</td>
</tr>
<tr>
<td>Green et al.</td>
<td>General population</td>
<td>1999–2005 (May–September)</td>
<td>7.4% increase in AKI (95% CI 4–10.9)</td>
</tr>
<tr>
<td>Fletcher et al.</td>
<td>General population</td>
<td>1991–2004 (July–August)</td>
<td>Admission due to AKI: OR 1.09 (95% CI 1.07–1.12)</td>
</tr>
<tr>
<td>Bal et al.</td>
<td>General population</td>
<td>2005–2012</td>
<td>Admission due to kidney disorders: RR 1.478 (1.005–2.174) (p &lt; 0.05)</td>
</tr>
<tr>
<td>Gronlund et al.</td>
<td>Population over the age of 65</td>
<td>1992–2006</td>
<td>1 increase in hospital admissions due to kidney disorders: Moderate heat: 4.3% (95% CI 2.9–4.9) Extreme heat: 9.3% (95% CI 4.3–14.3) Heat wave: 23.2% (95% CI 14.2–32.8)</td>
</tr>
</tbody>
</table>

AKI: acute kidney injury; 95% CI: 95% confidence interval; N: nephritis; Pop.: population in millions of people; NS: nephrotic syndrome; RR: relative risk.

The studies of high temperatures and heat waves are shown where the results involve data on renal morbidity, although there are only 2 studies in which this was the only objective.

a Compared with the 2000–2002 period.
b Temperature above 95°F: maximum and minimum temperatures above the 95th percentile of national temperatures.

c The objective of the study was only the impact on renal morbidity.
d RR was higher in men; among them, those aged 15–65 years were at a greater risk. By age, the group with the highest RR was men over the age of 65.

l Moderate heat: temperature above the 90th percentile; extreme heat: temperature above the 95th percentile; heat wave: temperature above the 95th percentile for at least 48 hrs.
How our health is harmed by climate change

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Upcoming Events & Opportunities

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August 18: Goddard Forum Advancing One Health in Pennsylvania
This forum brings together professionals, stakeholders, and leaders from diverse sectors to advance the Pennsylvania One Health Action Plan.
Medical Societies Consortium on Climate and Health

• The mission of the Consortium is to organize, empower and amplify the voice of America’s doctors to convey how climate change is harming our health and how climate solutions will improve it.
Medical Societies Consortium on Climate and Health

• American College of Physicians (ACP)
• American Academy of Family Physicians (AAFP)
• American Academy of Pediatrics (AAP)
• American College of Obstetricians and Gynecologists (ACOG)
• National Medical Association (NMA)
• American Academy of Allergy Asthma and Immunology (AAAAI)
• American College of Preventive Medicine (ACPM)
• American Podiatric Medical Association (APMA)
• American Geriatrics Society (AGS)
• Society of General Internal Medicine (SGIM)
• Academy of Integrative Health and Medicine (AIHM)
• American Association of Community Physicians (AACP)
• California Chapter of American College of Emergency Physicians
• American Telemedicine Association (ATA)
• Society of Gynecologic Oncology (SGO)
• American Medical Women’s Association (AMWA)
• American College of Lifestyle Medicine (ACLM)
• American Medical Association (AMA)
• American Psychiatric Association (APA)
• ***American College of Osteopathic Internists (ACOI)***
• American Academy of Dermatology (AAD)
There is no question in my mind that the earth will be a paradise in 200-250 years.
The only question is whether there will be any humans to enjoy it.