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Research Article

Assessing Climate Related Kidney Disease in Palm Beach County, Florida

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Introduction

The first reference to the possible existence of climate-related kidney disease was published in 2002 by a group of clinicians who observed an increasing prevalence of advanced Chronic Kidney Disease (CKD) among agricultural workers in the tropical coastal regions of El Salvador [1]. These patients were predominantly adult males who worked in sugar cane fields, and were without significant incidence of diabetes mellitus, hypertension or other particular risk factors for renal disease. Over the years since then, this phenomenon has become the subject of intense international study, and has been described more deeply in both clinical and epidemiologic terms [2-5]. As data accumulated, a series of international symposia have been held, and the name Mesoamerican Nephropathy (MeN) was tentatively given to this phenomenon, though several other names have also been suggested [6-8]. In El Salvador and Nicaragua [9], the prevalence of CKD is about 13-17% (compared to about 5% in the United States). This is concentrated in the tropical lowlands where sugar cane is grown as compared to the more temperate highlands where coffee is a dominant crop by a factor of 9:1 (18-19% in coastal communities, and <2% in high-altitude populations). The majority of affected workers are less than 60 years of age (57%). CKD-associated mortality in these countries is about 110/100,000, as opposed to <40/100,000 in Cuba, Costa Rica and Panama. The rate of End-stage Kidney Disease (ESKD) is about 1.4/1,000, with a male preponderance of 9:1; this is about four times the prevalence of ESKD in the United States (348/1M) [10]. These data suggest that sugar cane harvesters are at higher risk of CKD/ESKD than other agricultural workers or construction workers who also typically work outdoors in the heat [9].

In the half-decade from 2005 through 2009, male deaths from kidney disease rose in Costa Rica by 16%; in El Salvador, by 26%; in Guatemala by 27% and in Nicaragua by an astounding 41% [6]. The geographical foci of increased mortality correspond precisely to those areas where temperature change has been most extreme. Things have become worse since then. According to Sorensen and Garcia-Trabanino, over the past decade the CKD-related mortality rate in Guatemala rose 83%, CKD is attributed as the second leading cause of death in Nicaragua and El Salvador [11]. Among the clinical characteristics that have emerged, those affected by this syndrome tend to be working-age male adults (78.3%) with prolonged experience working in sugar cane fields. Exposure to prolonged extreme heat, accompanied by profuse sweating is typical (76.3%) and agrochemical exposure is high (95.7%). Typical symptoms include arthralgia (54.3%), asthenia (52.2%), cramps (45.7%) and fainting (30.4%). Renal symptoms include nocturia (65.2%), dysuria (39.1%) and foamy urine (63%) [2]. While patients who present with the disease have symptoms consistent with chronic kidney disease, etiology is often unknown. Numerous biochemical characteristics have also been noted [2]. These include macroalbuminuria (80.4%) which infrequently (<10%) reaches nephrotic levels; β-microglobulinuria (78.2%), NGAL (26.1%), hypermagnesuria (100%), hyperphosphatemia (50%), hypernatriuria (45.7%), hyperkaluria (23.9%), hypercalciuria (17.4%), polyuria (43.5%), hyponatremia (47.8%), hypocalcemia (39.1%), hypokalemia (30.4%) and hypomagnesemia (19.6%). Again, these are not specific for any particular renal etiology but rather demonstrate a range of tubular defects consistent with chronic interstitial disease. The only marker noted by Herrera et al that is more suggestive of an etiology is the prevalence of metabolic alkalosis (45.7%), from which one might infer the possibility of volume contraction, in distinction from most renal disease, where metabolic acidosis would tend to be a more likely finding.

Among risk factors identified for development of MeN, males are four times more prevalent than females, which is consistent with the greater proportion of male field workers. Also, lifetime exposure in the sugar cane fields (OR=5.86, p<0.1), pesticide inhalation (OR=3.31, $p<0.1$) and sugar cane chewing (OR=3.24, $p<0.1$) have been noted as risk factors [3]. Two studies on pathologic findings in these patients confirm that MeN is a form of nonspecific chronic tubulointerstitial disease, without evidence of immunologic processes of importance and that glomerular findings including glomerulosclerosis are secondary to the tubulointerstitial changes [4,5]. Climate change does not affect Central America alone. National Oceanographic and Atmospheric Administration (NOAA) has charted actual and anticipated temperature rise in Florida and the Southeastern United States [12]. The Center for Ocean and Atmospheric Prediction Studies at Florida State University (COAPS.FSU) provided temperature data for Florida for the last 120 years, and this information is refined to the level of county by quarter of the year and by zip codes since these have been available (1900-2019) [13]. The increasing prevalence of MeN is of particular interest in Palm Beach County, FL (PBC). PBC is the county with the highest agricultural production in dollars of any US county east of the Mississippi River [14]. With over 500,000 acres under cultivation, PBC leads the US in production of sugar cane, among other items of produce. The work force is largely a migrant work force, ethnically Central American, working alone, seasonally, and earning wages that fail to raise them from poverty [15]. As of 2018, there were more than 118,000 agricultural workers in PBC, accounting for 12.3% of the county's total workforce, most of whom were unaccompanied migrants (59%), with the majority earning less than $10,000 per year [16]. These workers' incomes are directly tied to the weight of their harvests. Thus, long hours and few breaks are rewarded financially. Typically, they might have limited access to high quality potable water, and be subject to repeated daily bouts of subclinical dehydration and muscle trauma. Access to medical care is limited by working locations and undocumented status. Given the evidence for MeN and the high concentration of sugar cane farming in Palm Beach County, Florida, we hypothesize that this county will have experienced higher rates of MeN over the past decade and that these higher rates are correlated with an increase in ambient temperature.

Methodology

For this retrospective study we analyzed all hospital discharge data for a ten-year period, from 2008 through 2017, in Palm Beach County, FL, from those zip codes around the southeastern perimeter of Lake Okeechobee, where sugar cane is the predominant crop. The zip codes used in the study include 33430, 33476 and 33493. Hospital discharge data was obtained from Florida's Agency for Health Care Administration (AHCA). All hospital admissions reviewed were from Lakeside Medical Center, in Belle Glade, FL, in zip code 33430, which is the only hospital in these three zip codes. We used ICD-9 (until October 2015) and ICD-10 codes (after October 2015) to identify all patients with discharge diagnoses related to either acute kidney injury or chronic kidney disease. ICD-9 codes included 584.9 and 585.x and ICD-10 codes included N17.9 and N.18.x. Cases of interest were patients of male gender, ages 18 to 64, ethnicity of Hispanic origin, with these ICD-9 and ICD-10 codes; we are unable to further distinguish Central American from other Hispanic origin. These cases were compared to the complementary groups by age, gender, and ethnicity. Exclusion criteria included all patients with any diagnosis in the hospital discharge dataset of pre-existing kidney disease or primary diseases likely to result in kidney disease including, including diabetes mellitus, primary or secondary hypertension, glomerulonephritis of any etiology or congenital renal disease such as polycystic kidney disease.

Data were analyzed to determine whether epidemiologic evidence might support the existence of climate-related kidney disease in the geographic area of interest. Thus, we examined data with respect to season and year of discharge, and by age (18 to 64), gender and ethnicity of patients. We made the general assumption that in these very rural agricultural areas, the predominance of working age males of Hispanic origin are likely to be Central American migrant agricultural workers for the most part. We correlated hospital discharge data with temperature data which was acquired from the COAPS.FSU data base. Figure 1 demonstrates the average maximum temperature for PBC, and the equation describes the observed pattern of temperature increase [13].

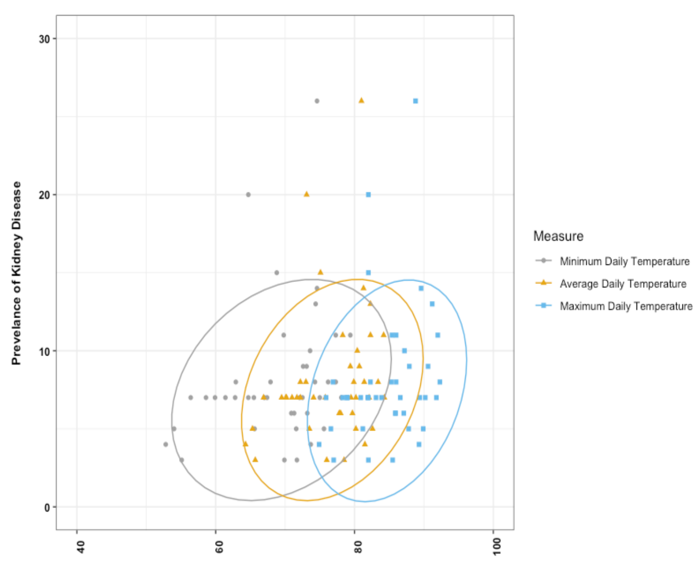

Figure 1: Scatter plot with ellipses for the number of kidney disease cases by temperature.

Statistical analysis comprised examination of the distribution and dispersion of data through descriptive numerical summaries and graphical tools. The Arithmetic Mean (AM) and Standard Deviation (SD) or the median and interquartile range are presented to one decimal place. To examine the effect on the number of renal disease as a function of quarter, year and temperature (minimum average daily temperature, maximum average daily temperature or average daily temperature), we created and tested three negative binomial regression models. We first examined the relationship between the number of renal disease cases as a function of minimum daily temperature, average daily temperature and maximum daily temperature. We found no significant association between minimum daily temperature and the prevalence of renal disease ($r(39) = 0.26$, $p = 0.092$), average daily temperature and the prevalence of renal disease ($r(39) = 0.25$, $p = 0.106$), and maximum daily temperature and the prevalence of renal disease ($r(39) = 0.24$, $p = 0.117$) (Figures 1 and 2). In our second analysis we created three Negative Binomial (NB) models to examine the change in the number of renal disease cases as a function of ambient temperature, year and quarter. The model was specified as follows:

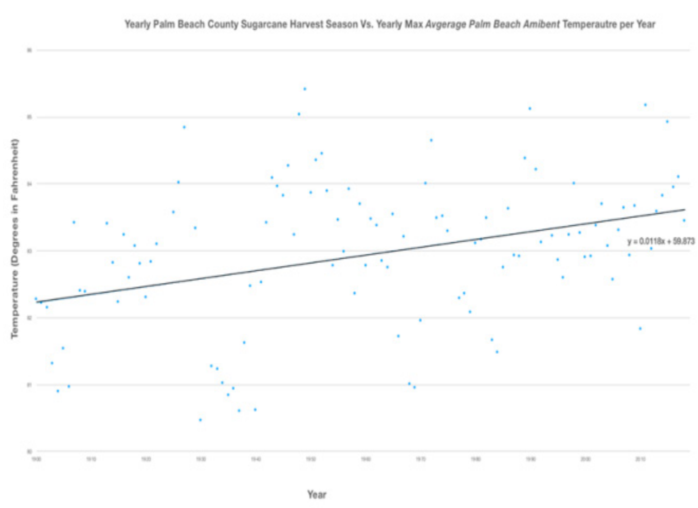

Figure 2: Temperature change in Palm Beach County, FL over 120 years.

$$\log_e (N_{renal}) = \beta_0 + \beta_1 temp + \sum_{0\leq n\leq 4}(\beta_{2+q} quarter_q) + \sum_{0\leq o\leq 10}(\beta_{6+o} year_o) + u.$$

Where: N designates the expected number of admissions for the specified renal disease renal. Temp is a variable representing daily temperature across all the days included in the study, specified as either maximum, minimum or average temperature. β_1 is the regression coefficient representing the effect of a 1°F increase in temp. Exp (β_1) is the calculated IRR for an increase in admissions per 1°F increase in temperature. Overall, β_1 temp represents the effect of temperature. β_{2+}quarter represents the effect of the quarter; using a categorical variable for each quarter (q). β_{6+o} year o represents the effect of the year, using a categorical variable for each year (o) within this study. β_0 and u represent estimated constants in the model; u is specifically included in NB models to account for extra variance.

Results

Demographic data reveal that among the study dataset there were 469 patients who met the inclusion criteria. Among subjects 56.1% were male (n= 263), 76.8% were black (n=360), and 85.3% were Hispanic (n=400). The average age was 56.4 (SD= 23.7). The number of renal disease cases did not vary significantly from year-to-year or by quarter (Table 1). We found no relationship between the number of renal disease cases as a function of maximum, minimum or average temperature, year or quarter.

Year	Quarter 1	Quarter 2	Quarter 3	Quarter 4	Median	IQR
2008	8	8	11	7	8	1
2009	7	6	13	20	10	14
2010	4	6	7	8	6.5	5.5
2011	3	8	7	7	7	5
2012	5	6	5	3	5	3.9
2013	5	10	4	5	5	3.5

2014	7	7	26	11	9	5.8
2015	7	7	14	3	7	4.1
2016	7	9	9	8	8.5	8
2017	7	7	11	15	9	8.2
2018	7	NA	NA	NA	NA	NA
Median	7	7	10	7.5	NA	NA
IQR	2	1.8	5.5	4.8	NA	NA
Source: Agency for Health Care Administration (AHCA).						

Table 1: The number of renal cases by quarter and year (2005-2017).

For additional insight we created three separate bivariate models for the number of renal disease cases as a function of gender (male vs female), ethnicity (Hispanic/Latino vs. other) or age. We discovered the following associations:

1) The rate of kidney disease for males (4.70: 95% CI 4.07,5.42) is 1.28 (95% CI 1.11,1.44) greater than for females (3.67:95% CI 3.13,4.32).

2) The rate of kidney disease for Hispanics (6.80: 95% CI 6.07,7.68) is 3.70 (95% CI 2.56,4.83) greater than for Non-Hispanics (1.85: 95% CI 1.39,2.45).

3) No significant association was found between kidney disease and age.

In our final analysis, we created a multivariate model for the number of renal disease cases as a function of gender (male vs female) and ethnicity (Hispanic/Latino vs other). A significant association was found ($p < 0.05$). We found that the rate of kidney disease for female Hispanics (3.27: 95% CI 2.76,3.89) is 3.27 times greater than for female Non-Hispanics (1.07: 95% CI 1.34,2.55). Additionally, the rate of kidney disease for male Hispanics (3.73: 95% CI 3.17,4.37) is 2.01 (95% CI 1.28,2.73) greater than for male Non-Hispanics (1.85: 95% CI 1.34,2.55) (Figure 3).

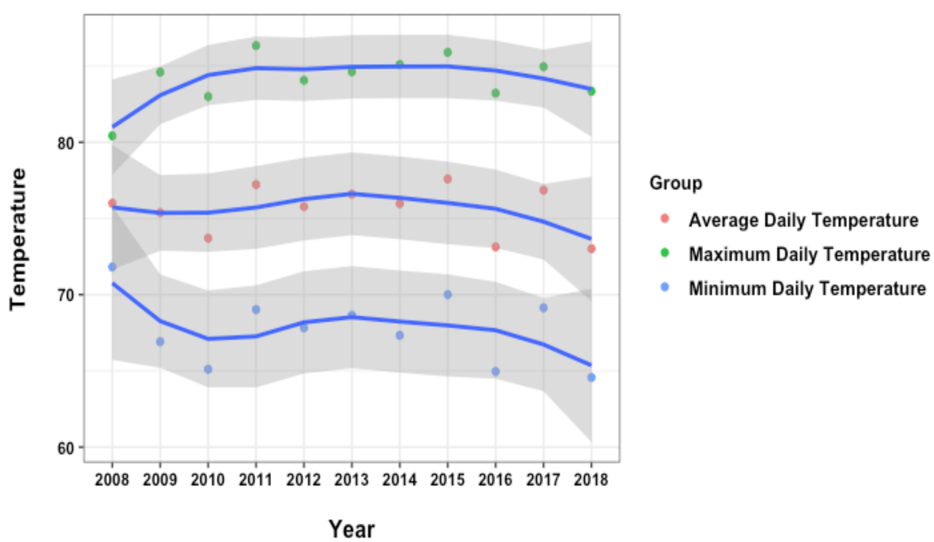

Figure 3: Line plot with smoothing of ambient temperature by year.

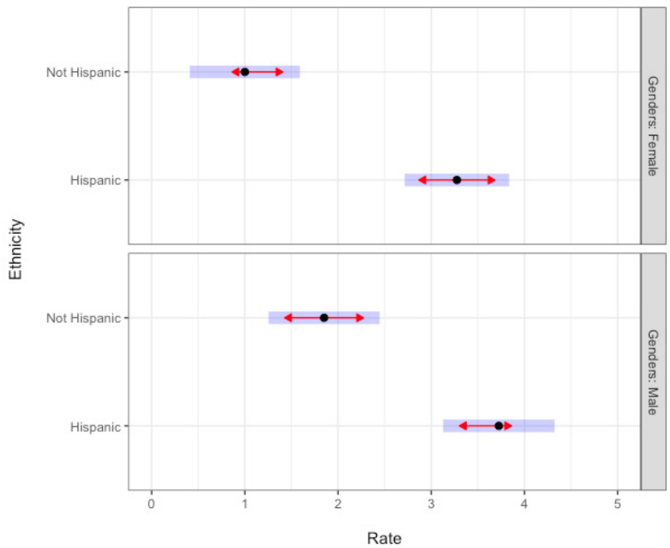

Figure 4: Pairwise comparisons for ethnicity and gender.

The blue bars are confidence intervals for the means, and the red arrows are for the comparisons among them. If an arrow from one mean overlaps an arrow from another group, the difference is not "significant," based on a Tukey adjustment.

Discussion

The original intent of this research was to seek evidence for occurrence of MeN among agricultural workers in rural PBC. This is an area of subtropical climate which is home to the largest harvests of sugar cane in the US. Thus, it seemed reasonable to expect that if MeN was occurring in the U.S., one might look for it in this setting, which is the U.S. setting most analogous to the locus of the first reports in Central America. While our hypothesis was not proven in that there was no increase in cases, no increase in temperature change observable at the zip code level from 2008-2017 and subsequently no correlation to temperature change, what did emerge from this study was that Hispanic populations had a 3.70 times higher risk for kidney related diagnoses with unknown etiology (OR=3.70; 95% CI 2.56,4.83), regardless of gender or age, and that male Hispanics were at greater risk than females (OR=1.28; 95%CI 1.11, 1.44). The absence of finding that local temperature averages were not increasing over the decade does not mean that this is not occurring. Indeed, different models lead to differing conclusions on the subject. Rather, it might mean that ten years is too short (restricted range) to detect such temperature increase in such a small geographical zone as three zip codes [17]. It is possible that different models of temperature might have yielded different results regarding analysis of incidence of kidney related diagnoses; this analysis has not been performed yet.

There was no way in our data set to determine occupation of patients. We hoped to extrapolate from the possibility of identifying a large percentage of agricultural workers among males of Hispanic or Central American ethnicity based on the demographics of the region as compared to the occurrence of kidney-related diagnoses, knowing that most of these workers are male, Hispanic, and in the 18-64 age range. US census data supports the idea that the Hispanic populations of two of the three subject zip codes have Hispanic populations greater than average in the state of Florida [18] (Table 2). But the degree of risk for kidney related diagnoses of the Hispanic population exceeds expectations based on their proportion of the total populations of the three zip codes, confirming that Hispanic ethnicity is a significant risk factor for kidney related diagnoses, and that males are at greater risk than females. Taken together, these finding suggest that MeN might not be restricted to Central America, but may also be occurring in PBC. The role of heat stress in kidney disease per se has not been examined deeply, but the geographic range of interest is widening, and in fact, is becoming global, with evidence of occurrence in Sri Lanka, India, southeast Asia, Saudi Arabia, Egypt, Sudan and Israel [19-22]. Two papers have explored the possibility of its occurrence in the USA [23-25].

	33430	**33476**	**33493**	**State of Florida**
Population Total	20058	6270	5185	21299325
% Male	0.488	0.566	0.806	0.489
% White, non-Hispanic/ Latino	0.077	0.101	0.179	0.535
% Hispanic/ Latino	**0.329**	**0.309**	**0.248**	**0.261**
% Black or African American	0.584	0.588	0.555	0.169
% Without health insurance, under age 65 years old	0.255	0.202	0.258	0.16
% Persons in poverty*	0.421	0.379	0.318	0.136
Data developed by the U.S. Census Bureau's SAIPE program, measuring family income compared to the poverty threshold. Definition of poverty is size of family unit (e.g. Six person family poverty threshold is $34,533).				

Table 2: US Census Bureau 2018 Data for three subject zip codes.

There is no clear certainty that ambient heat is the critical factor in the pathophysiology of this syndrome, even though our findings and those of other epidemiology studies point to its importance. Several reviews have hypothesized pathophysiologic schemata that reflect the multiple factors that are likely contributing to causality [11,26,27]. Among the environmental factors under investigation, apart from ambient temperature, are: cadmium and heavy metals in soils, ionicity and salinity of soils, hard water, agrochemicals, fluoride, illegal alcohol with risk of lead exposure, petrochemicals, excessive use of NSAIDs, illegal drugs, arsenic or algae in soils, use of illegally grown tobacco, and infections such as leptospirosis and malaria [20]. It is hypothesized that some combination of these factors, acting upon individuals in a setting of extremes of ambient heat who are also subject to recurrent dehydration and work-related muscle injury, might create episodes of low grade rhabdomyolysis, hyperosmolality, hyperthermia and extracellular volume depletion. These physiological insults in turn might trigger intrarenal vasoconstrictive effects of vasopressin; upregulation of fructose metabolism associated with anaerobic metabolism, release of pro-oxidants and chemokines; uricosuria and urate crystal formation; and low grade renal ischemia. The summative result of these events may trigger repeated, even daily, events of acute kidney injury, leading to chronic interstitial fibrosis, and, eventually, chronic kidney disease [11,26]. A key to understanding this hypothesis is that all of the potential triggers (agrochemicals, NSAIDs, etc.) have been present for a long time before MeN was described [20,25]; but rising ambient temperature might be a possible the trigger to have brought them together to cause this kind and degree of kidney damage.

There are several limitations of the present study to discuss. We were not able to identify migrant agricultural workers among the total patient population nor to identify any difference between this population and the rest of the local population in incidence or prevalence of kidney-related diagnoses. One of our initial assumptions was that we would be able to distinguish among these two populations (that is, male migrant agricultural workers of Hispanic/Central American origin versus residential population of the region). Although we tried to exercise caution about this with our inclusion criteria, we were limited by availability of data. And we were not able to quantify exposure to heat ("dose") except by ambient temperature data, but not with respect to individual exposures, or even exposure of patients with kidney-related diagnoses to patients without kidney-related diagnoses. Finally, for any given time interval, the number of patients with kidney-related diagnoses was small, making meaningful comparisons of significance more difficult.

Nonetheless, this paper represents one of the first studies to assess the relationship of ambient temperature and risk of kidney disease in the US. Confirmation of this hypothesis is needed in other parts of the country and further work is needed to identify pathophysiology more clearly. As this work is being done, we cannot assume that suitable treatment specific to this entity will be found that will benefit individual patients. Rather, the key is prevention. In this case, prevention can mean improvement in the working conditions of workers at current risk, and mitigation of ambient temperature rise to prevent future risk. Regarding the first of these, efforts have been initiated to reduce the risk of MeN among sugar cane workers in El Salvador [28], providing an initial template for action. Our study provides a methodology for further research into the phenomena of climate related disease that includes temperature.

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