KI REPORTS
KIReports.org

Seasonal Changes in Kidney Function in CKD of Uncertain Etiology

Sahil Arora[1], Priyamvada PS[1], Jayaprakash Sahoo[2], Balasubramaniyan Vairappan[3] and Sreejith Parameswaran[1]

[1]Department of Nephrology, Jawaharlal Institute of Post Graduate Medical Education and Research, Puducherry, India; [2]Department of Endocrinology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India; and [3]Department of Biochemistry, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India

Correspondence: Priyamvada PS, Department of Nephrology, Jawaharlal Institute of Post Graduate Medical Education and Research, Puducherry 605006, India. E-mail: priyamvadaps@gmail.com

Received 1 June 2021; revised 4 August 2021; accepted 9 August 2021; published online 18 August 2021

Kidney Int Rep (2021) **6,** 2918–2921; https://doi.org/10.1016/j.ekir.2021.08.011

Chronic kidney disease of uncertain etiology (CKDu) is a term used to describe kidney disease without traditional risk factors.[1] Disease clustering is reported from Central America, corresponding with the warmest areas along the Pacific coast and Srilanka.[2] The Indian CKD registry reported CKDu as the second common cause of CKD in India, accounting for 16% of cases.[3] We have described a new CKDu hotspot, Tondaimandalam nephropathy, from the northern coastal districts of Tamil Nadu, India.[4] The other CKDu hotspots from India include the Uddhanam, Andhra Pradesh, and Narsinghpur and Badamba blocks of Odisha.[5,6] The changes in kidney function associated with seasons are often considered physiological and have not been extensively evaluated. We have undertaken a preliminary observational study to assess the changes in kidney function from the warmest to the coolest season of the year among prevalent CKDu patients with CKD stages 3 and 4.

RESULTS

Baseline Characteristics

A total of 69 patients with CKDu were recruited. The summer and winter temperature and humidity were 41 °C (interquartile range 41–41) vs. 31 °C (interquartile range 31–31.75), and 56% vs. 74%, respectively. The baseline characteristics are given in Table 1. None of the patients progressed to end-stage kidney disease. Two patients developed acute kidney injury during the study period.

Seasonal Variations in Kidney Function

The changes in blood and urine parameters across the seasons are summarized in Table 2. The antihypertensive requirement increased from summer to winter ($P = 0.020$). The urine angiotensinogen-creatinine ratios showed a significant negative correlation with urine ammonium-creatinine ratios (Spearman $\rho = -0.585$ [summer, $P < 0.001$] and −0.786 [winter, $P < 0.001$]). Both stages 3 and 4 showed higher bicarbonate ($P < 0.038$) and urine ammonium-creatinine ratios in winter ($P < 0.001$); the urine angiotensinogen-creatinine ratios were higher in summer ($P < 0.001$) (Figure 1; Supplementary Table S1).

DISCUSSION

We observed that summers were associated with more acidosis, higher uric acid levels, low urine ammonium excretion, and increased angiotensinogen levels without estimated glomerular filtration rate or osmolarity changes. A few small, single-center studies have reported seasonal changes in the glomerular filtration rate in healthy and hypertensive individuals without CKD.[7,8] To our knowledge, there are no previous publications on seasonal changes in subjects with prevalent CKDu.

Even though there were no documented heat strokes, the participants are likely exposed to low levels of chronic heat exhaustion. Uric acid is generated during heat stress owing to nucleotide release from the muscles.[9,S1] The subjects had higher uric acid levels in summer in this study, possibly a surrogate marker of ongoing heat stress. Exposure to an ambient temperature of 39.5 °C induces mitochondrial dysfunction and tubular inflammation without osmolarity or creatinine change.[S2] Further increments in core temperature by another degree resulted in more pronounced differences, including increased osmolarity and creatinine.

Table 1. Baseline characteristics at recruitment (March 2019)

Parameter	Value
Age[a], yr	55 (48.5–61.5)
Median prerecruitment follow-up[a], mo	30 (15–35)
Male-female ratio	3.3:1
Residence in a rural area, *n* (%)	56 (81)
Occupation, *n* (%)	
Agriculture	12 (17)
Outdoor manual work other than agriculture	25 (36)
Unemployed	32 (46.3)
Comorbidities, *n* (%)	
Hypertension	33 (47.82)
Hypothyroidism	4 (5.80)
Gout	2 (2.90)
CVA	2 (2.90)
CAD	2 (2.90)
Other comorbidities	8 (11.60)
RAAS blockade, *n* (%)	5 (7.2)
Uric acid–lowering agents, *n* (%)	6 (8.6)
Creatinine[a], mg/dl	2.54 (2.16–3.04)
eGFR[b], ml/1.73 m^2	25.9 (24.5, 28.6)
Urine PC ratio[a], mg/g	0.31 (0.18–0.68)
Systolic blood pressure[a], mm Hg	128 (110–140)
Diastolic blood pressure[a], mm Hg	80 (70–90)
BMI[b]	23.7 (21.0, 25.5)
Intact PTH[a], pg/ml	115.3 (58.9–195.7)
Bicarbonate[a], mEq/l	23.1 (22.2–23.9)
pH[b]	7.37 (7.32, 7.40)
Uric acid[b], mg/dl	8.06 (7.51, 8.62)

BMI, body mass index; CAD, coronary artery disease; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; IQR, interquartile range; PC, protein-creatinine; PTH, parathyroid hormone; RAAS, renin-angiotensin-aldosterone system.
[a]Median with IQR.
[b]Mean with 95% CI.

Table 2. Seasonal changes in kidney function

Parameter	Summer	Winter	*P* value
Weight[a], kg	59.6 (57, 62.1)	60 (57.3, 62.7)	.297
Water intake[b], L	2 (1–2.5)	2 (1–2)	.713
Systolic blood pressure[b], mm Hg	129 (115–140)	129 (118–142)	.923
Diastolic blood pressure[b], mm Hg	80 (70–89)	79 (70–86)	.556
Sodium bicarbonate dose[b], mg	1500 (1000–1500)	1500 (1000–1500)	.757
Blood parameters			
Osmolarity[b], mOsm/kg	290 (286–292)	291 (285–295)	.076
Sodium[b], mEq/l	138 (135–139)	137 (135.5–139)	.457
Potassium[b], mEq/l	4.34 (3.81–4.78)	4.38 (3.7–4.9)	.553
Chloride[b], mEq/l	103 (99.5–105.5)	102 (98.1–105)	.091
Uric acid[a], mg/dl	8.4 (7.8, 8.9)	7.8 (7.4, 8.3)	.041
pH[b]	7.36 (7.32–7.36)	7.36 (7.32–7.36)	.260
Bicarbonate[b], mEq/l	23.2 (21.7–25.5)	25 (23–27)	.002
Bicarbonate <22 mEq/l, *n* (%)	22 (31.9)	13 (18.8)	.049
Base excess[b], mEq/l	–0.9 (–4.5 to 1.6)	0.1 (–2 to 1.9)	.026
Serum creatinine[b], mg/dl	2.73 (2.15–3.37)	2.66 (2.16–3.33)	.247
eGFR[b], ml/min per 1.73 m^2	23.60 (17.38–32.19)	25.37 (17.57–31.65)	.161
Urine parameters[b]			
Urine urea, mg/dl	674 (525–908)	733 (526–992)	.174
Urine osmolarity, mOsm/kg	334 (278–441)	354 (292–400)	.260
Urinary Na, mEq/l	83 (64–104)	84 (57–104)	.751
Urinary K, mEq/l	28 (18–41)	29 (20–41)	.741
Urine Cl, mEq/l	83 (64–109)	88 (62–107)	.673
Urine angiotensinogen (μg/L) / creatinine (mg/dl)	30.1 (9.3–127)	4.5 (2.8–8.8)	.002[c]
Urine ammonia (μmol/L) / creatinine (mg/dL)	9.96 (7.00–17.01)	21.03 (15.23–33.54)	<.001[c]

eGFR, estimated glomerular filtration rate; IQR, interquartile range.
[a]Mean with 95% confidence interval.
[b]Median with IQR.
[c]Adjusted for proteinuria and eGFR.

Both high–anion gap and non–anion gap acidosis have been described in the setting of heat stroke.[9] In the present study, the lower bicarbonate levels in summer were not compensated by urine ammonium excretion. In the acute Mesoamerican nephropathy, significant interstitial inflammation and elevated serum inflammatory markers in the absence of serum osmolarity changes has been reported.[S3] Subclinical tubular damage may be occurring in the summer months, leading to abnormal tubular functions resulting in a lower ammonium excretion. A low urine ammonium excretion is an independent and better prognostic factor for CKD progression than venous bicarbonate levels.[S4–S7] The low NH_4^+ excretion reflects a functional failure of the acid transporters in the tubule. The resultant shift in the NH_4^+-NH_3 dissociation equilibrium leads to an increased tissue availability of NH_3, enhancing the renal toxicity by activating complement pathways.[S5,S6] Even though urine ammonium excretion has a better predictive value, the levels do not exhibit a linear relationship with venous bicarbonate, endogenous acid production, or glomerular filtration rate.[S4] In the present study, urine ammonium levels did not correlate with venous pH or bicarbonate concentrations.

We observed that urine angiotensinogen levels were higher in summer after adjustments for GFR and proteinuria. In nonproteinuric individuals, angiotensinogen appearing in the urine represents the intrarenal renin activation rather than the systemic levels. Metabolic acidosis is associated with increased intrarenal renin-angiotensin-aldosterone system activation to increase the acid excretion in kidneys.[S8,S9] However, this does not translate to elevated H^+ excretion in patients with CKD because of structural and functional kidney damage.[S9,S10] Another potential reason might be uric acid–induced intraglomerular hypertension, which may activate the intrarenal renin-angiotensin-aldosterone system.[1,S9]

Even though blood pressures were comparable between seasons, we observed that the antihypertensive

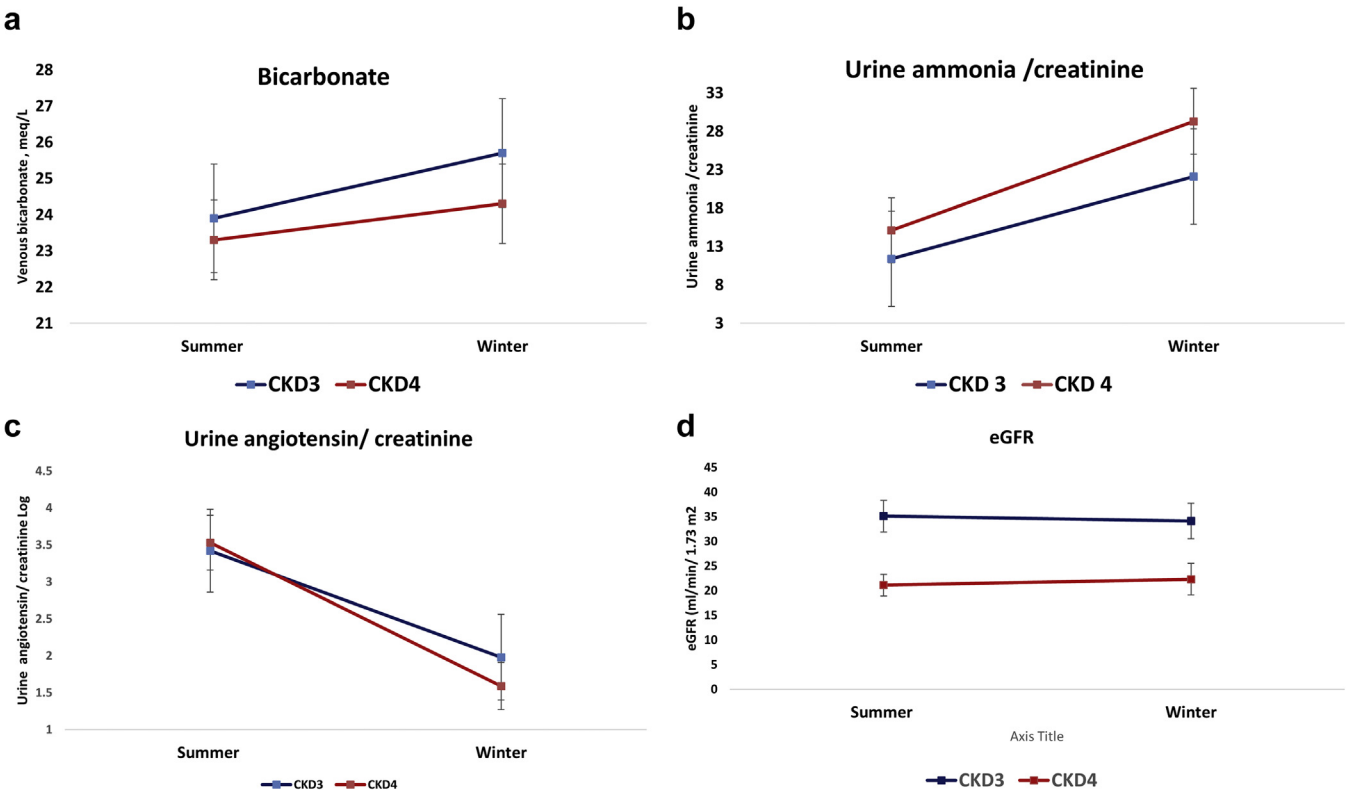

Figure 1. The seasonal changes in bicarbonate, urine ammonium-creatinine ratio, angiotensinogen-creatinine ratio, and eGFR from summer to winter among CKD 3 and 4. All comparisons done with mixed methods. Urine angiotensinogen/creatnine values expressed as natural logarithms.
Both CKD stages 3 and 4, bicarbonate ($P = 0.038$), and urine ammonium-creatinine ratio ($P < 0.001$) were higher in winter, whereas urine angiotensinogen-creatinine ratios were higher in summer ($P < 0.001$). No differences were observed in eGFR between seasons.
Trajectories for bicarbonate ($P = 0.594$), urine angiotensinogen-creatinine ratios ($P = 0.301$), and urine ammonium-creatinine ratios (0.528) were similar across CKD stages 3 and 4.

requirements were higher in winter. The blood pressures tend to be lower in summer, more marked in lower latitudes, with more prolonged sun exposure.[S11,S12] A decline of blood pressure in ESRD cohorts has been documented in the summer months without any appreciable changes in total fluid volume.[S13,S14] Lower temperatures cause increased sympathetic activity and vasoconstriction, whereas vasodilatation occurs in the summer months, resulting in lower blood pressures.

The strengths of the study include recruitment of prevalent CKDu patients with stable drug prescriptions and kidney function. There were no confounders, such as renin-angiotensin-aldosterone system blockers or other drugs, to account for acidosis and urinary angiotensinogen levels. However, we do not have data on the daily dietary acid load, lactate, muscle enzymes, or uric acid excretion. Likely, the observed changes might not be confined to CKDu alone; similar seasonal changes might be operational in kidney diseases resulting from etiologies and in the healthy population. There are no control arms, including these groups, which acts as a limitation.

In conclusion, the findings from this study point toward the existence of a distinct influence of seasons on kidney function in CKDu, which needs further field studies with larger sample sizes, with controls.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

This study received funding from the Jawaharlal Institute of Post Graduate Medical Education and Research, Puducherry, India. All procedures performed in studies involving human participants were per the ethical standards of the Indian Council of Medical Research and the institution, at which the studies were conducted (IRB approval no: JIP/IEC/2018/382) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Material and Methods

Table S1. The seasonal changes across CKD stages 3 and 4

Supplementary References.

REFERENCES

1. Lunyera J, Mohottige D, von Isenburg M, Jeuland M, Patel UD, Stanifer JW. CKD of uncertain etiology: A systematic review. *Clin J Am Soc Nephrol*. 2016;11(3):379–385. https://doi.org/10.2215/CJN.07500715.
2. Abraham G, Agarwal SK, Gowrishankar S, Vijayan M. Chronic kidney disease of unknown etiology: hotspots in India and other Asian countries. *Semin Nephrol*. 2019;39(3):272–277. https://doi.org/10.1016/j.semnephrol.2019.02.005.
3. Rajapurkar MM, John GT, Kirpalani AL, et al. What do we know about chronic kidney disease in India: first report of the Indian CKD Registry. *BMC Nephrol*. 2012;13:10. https://doi.org/10.1186/1471-2369-13-10.
4. Parameswaran S, Rinu PK, Kar SS, et al. A newly recognized endemic region of CKD of undetermined etiology (CKDu) in South India—"Tondaimandalam Nephropathy.". *Kidney Int Rep*. 2020;5(11):2066–2073. https://doi.org/10.1016/j.ekir.2020.08.032.
5. Gummidi B, John O, Ghosh A, et al. A systematic study of the prevalence and risk factors of CKD in Uddanam, India. *Kidney Int Rep*. 2020;5(12):2246–2255. https://doi.org/10.1016/j.ekir.2020.10.004.
6. Mahapatra H, Inamdar N. Chronic kidney diseases of unknown etiology (CKDu) hot spot at Narsinghpur and Badamba blocks in costal districts of Odisha, India. *Indian J Nephrol*. 2021;31(3):327–328. https://doi.org/10.4103/ijn.ijn_56_20.
7. Ephraim RKD, Asamoah CA, Abaka-Yawson A, Kwadzokpui PK, Adusei S. Climate change causes changes in biochemical markers of kidney disease. *BMC Nephrol*. 2020;21(1):542. https://doi.org/10.1186/s12882-020-02186-w.
8. Masugata H, Senda S, Inukai M, et al. Seasonal variation in estimated glomerular filtration rate based on serum creatinine levels in hypertensive patients. *Tohoku J Exp Med*. 2011;224(2):137–142. https://doi.org/10.1620/tjem.224.137.
9. Dematte JE, O'Mara K, Buescher J, et al. Near-fatal heat stroke during the 1995 heat wave in Chicago. *Ann Intern Med*. 1998;129(3):173–181. https://doi.org/10.7326/0003-4819-129-3-199808010-00001.