# Dehydration and malaria augment the risk of developing chronic kidney disease in Sri Lanka

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## ABSTRACT

Chronic kidney disease (CKD) of unknown etiology (CKDu) is a serious health issue in Sri Lanka. One-to-one age and sex-matched two sample comparative study was carried out in the Medawachchiya divisional secretariat area of the North Central Province (NCP) of Sri Lanka, by randomly selecting 100 CKDu patients and 100 age and sex-matched subjects from non-CKDu affected families from the same area. An interviewer-administered questionnaire was used for the collection of data pertaining to occupation, medical history and lifestyle. Data were analyzed using a conditional linear logistic model. Working for >6 h in the field per day, exposure to sun, drinking water only from well, consumption of <3 L of water per day, and having a history of malaria were found to be having significant ($P < 0.05$) likelihood toward the development of CKDu. Treatment of water prior to consumption had a significant protective effect against CKDu. Dehydration, history of malaria and drinking untreated well water from are likely contribute to the development of CKD of unknown etiology among the inhabitants of NCP, Sri Lanka.

**Key words:** Chronic kidney disease, dehydration, malaria, risk factors, water

## Introduction

The incidence of chronic kidney disease (CKD) in the world is on the rise. The prevalence of CKD in developed countries is relatively high, being 13-16%[1-3] in the United States, 6-16% in Australia and Japan,[3,4] and 10.2% among the European populations.[5] The existing data on the prevalence of CKD in developing countries is scanty, but a prevalence between 2% and 16% is claimed, according to screening studies.[6-10] The most frequent known causes of CKD in both developed and developing countries are diabetes mellitus and hypertension.[6,7,11] However, unusual forms of CKD, of which the exact cause(s) has not been identified as yet, have been reported from certain parts of the world, including Sri Lanka. Balkan endemic nephropathy reported among the inhabitants living along the tributaries of river Danube in the Balkan region, CKD in Nicaragua affecting sugarcane/banana farmers and fishing and mining communities, and chronic interstitial nephropathy of unknown causes in Tunisia (CINu) are such internationally reported scenarios of CKD of unknown etiology (CKDu). In Sri Lanka, CKDu is reported from certain parts of the country, including the North Central Province (NCP) and North Western and Uva provinces, and is reported to be spreading into Central and Southern provinces. The prevalence of CKDu in the NCP is higher than in other provinces, and is concentrated in the Medawachchiya, Padaviya, Dehiattakandiya, Girandurukotte, Medirigiriya and Nikawewa areas.

The majority of the CKDu affected inhabitants were males belonging to the farming community (Aturaliya TNC, 2006, unpublished data). Pathological

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studies carried out on biopsy samples of affected kidneys have shown the presence of tubulointerstitial type of disease, with least inflammation, suggesting a toxin-mediated damage. An increase in serum creatinine levels along with decrease in the kidney length and an increase in the parenchymal echogenecity were reported in CKDu patients (Kaviratna, 2012, unpublished data).

According to epidemiological studies, being a farmer, using pesticides, drinking well water, family history of renal dysfunction, regular use of ayurvedic treatment, and a history of snake bite were reported as possible risk factors leading to CKDu in the NCP.[12] Studies on geographical distribution of CKDu patients with the geographical information mapping system have convinced that while former discrete foci persist, new foci may emerge with time. Each endemic area identified hitherto was found to be located in close proximity to a reservoir of an irrigation system and thereby a likelihood of irrigated water being drained into shallow wells of affected households located below the level of reservoirs/canals is indicated.[13]

Presence of fluoride[14] and heavy metals[15] in the groundwater sources of the NCP, exposure to nephrotoxic mycotoxins,[16] distinctive hydrochemical properties of drinking water consumed by affected people,[17] ochratoxin A in food[18] and cyanobacterial blooming leading to toxin production in stagnant water are theories proposed to support probable environmental toxins as causative factors of CKDu. The exact scientific bridge between the hypothesized epidemiological and environmental risk factors and the pathogenesis of CKDu is yet to be built.

The highly endemic areas are composed of normal individuals besides the affected, implying that unaffected individuals inherit more protective factors or affected individuals are exposed more to the risk factors. Therefore, in-depth study of occupational, habitual and health factors that had not been addressed in earlier studies is required.

The objective of the current study was to investigate the possible risk factors associated with the etiology of CKDu in NCP of Sri Lanka.

## Subjects and Methods

Medawachchiya, the most heavily endemic area of CKDu in the NCP and in Sri Lanka, was selected as the study area for the current research. This area is administered by the Medawachchiya divisional secretariat, which is further divided into 37 grama niladhari (GN) divisions, the smallest administrative units (Planning division; Madawachchiya divisional secretariat, 2009/2010, unpublished data).

A random sample of 100 CKDu patients was selected from the pool of CKDu patients attending the renal care unit of the Medawachchiya base hospital. All these patients were inhabitants of the Medawachchiya divisional secretariat administrative unit and were diagnosed with CKDu. Their diagnoses were confirmed by the presence of proteinuria, elevated levels of serum creatinine and abdominal ultrasound scan reports. Patients with known causes of CKD, including diabetes mellitus, long-standing hypertension, glomerular nephritis, urolithiasis, congenital kidney diseases, history of snake bite and leptospirosis were excluded from the study. The majority (58%, $n = 100$) of the selected patients were in stage 3 of CKD according to the guidelines of National Kidney Foundation/Kidney disease outcomes quality initiative guidelines [Table 1].

Age and sex-matched normal subjects ($n = 100$) were drawn from families not having CKDu living in four randomly selected GN divisions of the Medawachchiya divisional secretariat administrative unit of the NCP of Sri Lanka. The normal subjects were confirmed as not having CKDu, subsequent to clinical examination by an experienced medical officer and also after testing their blood and urine samples. Their blood pressure, fasting blood glucose and serum creatinine were normal, and proteinuria was absent.

Ethical clearance for the study was obtained from the Research, Ethical Review and Higher Degrees Committee of the Faculty of Medicine, University of Peradeniya, Sri Lanka. Administrative clearance for the study was

**Table 1: Basic demographic data of CKDu patients and normal subjects and stage of the kidney disease of CKDu patients in accordance with NK, K/DOQI guidelines**

| Characteristic | Percentage (*n*=100) | |
|---|---|---|
| | CKDu patients | Normal subjects |
| Age (years, mean±SD) | 47.8±9.6 | 47.7±9.2 |
| Male (*n*=59) | 47.9±9.9 | 48.0±9.9 |
| Female (*n*=41) | 47.7±9.1 | 47.2±8.2 |
| BMI (kg $m^{-2}$, mean±SD) | 21.3±3.3 | 23.9±2.9 |
| Male (*n*=59) | 20.6±3.2 | 24.1±2.6 |
| Female (*n*=41) | 22.3±3.3 | 23.7±3.4 |
| Stage of CKD (GFR mL/min/1.73 $m^2$) | | |
| 1 (≥90) | - | |
| 2 (60-89) | 16 | |
| 3 (30-59) | 58 | |
| 4 (15-29) | 24 | |
| 5 (<15) | 2 | |

NK, K/DOQI: National Kidney Foundation/Kidney disease outcomes quality initiative, SD: Standard deviation, BMI: Body mass index, CKDu: Chronic kidney disease of unknown etiology, CKD: Chronic kidney disease, GFR: Glomerular filtration rate

obtained from the Regional Director of Health Services of Anuradhapura, and the District Medical Officer, Medawachchiya hospital. Written informed consent of all the study subjects was obtained prior to their participation.

An interviewer-administered questionnaire was used to gather information on demography, occupational background, lifestyle and medical history. Data were entered, doubled-checked and analyzed using SAS version 9.1 (2005, New Jersy, USA).[19]

## Results

The majority of the CKDu patients and normal subjects (73% CKDu patients and 52% normal subjects) were found to be occupied in farming either full time or part time. Some (25%, of the CKDu patients and 40% of the normal subjects) were found to be employed in other sectors, such as construction work, civil service, defense service, trade, etc., Significantly higher percentages of CKDu patients worked >6 h/day under the sun ($P = 0.003$) and consumed <3 L of water per day. The subjects who worked under such conditions had 8 times (odds ratio [OR]: 8.556, confidence interval [CI]: 2.270-11.411) and 4 times (OR: 4.215, CI: 1.062-6.219) higher probabilities of developing CKDu, respectively [Table 2]. Some of the CKDu patients and normal subjects (16% of CKDu patients and 2% of normal subjects) mentioned that they experienced dysuria on the days they worked in the paddy fields under the sun.

Well as the drinking water source was found to be having a significant likelihood ($P < 0.05$) toward the development of CKDu. Subjects who consumed well water were 7 times more likely to develop CKDu when compared with those who did not consume water from wells (OR: 7.667, CI: 1.676-10.479). The majority of CKDu patients (76%) consumed water brought only from wells while the majority of normal subjects (49%) obtained water from multiple sources, including wells, springs, tubewells, etc., Only 26% of the normal subjects used well water as their solitary source of water for drinking and culinary purposes. Majority of the normal subjects (69%) used water subjected to boiling, boiling and percolating through a filter, and directly percolating through a filter, prior to consumption. Majority of the CKDu patients (51%) consumed water without subjecting it to any treatment. Following a treatment method was found to be statistically significant ($P < 0.02$, OR: 5.863, CI: 3.029-7.688), indicating a protective effect against CKDu. Having a history of malaria increased the likelihood of developing CKDu by a factor of 4 (OR: 4.894, CI: 1.183-6.206) among CKDu patients when compared with normal subjects.

Being a farmer ($P = 0.117$), cultivating in paddy fields ($P = 0.314$), exposure to pesticides ($P = 0.082$), spraying pesticides without safety precautions ($P = 0.745$), consumption of black tea ($P = 0.795$), consumption of fresh water fish with skin ($P = 0.062$) or without skin ($P = 0.583$) didn't show any significant likelihood toward the development of the disease in linear logistic model analysis.

**Table 2: Results of occupational, lifestyle and health parameters analyzed with age and sex-matched conditional linear logistic model**

| Variable | Model *P* value | OR (95% CI) |
|---|---|---|
| Farmer | 0.117 | 2.448 (0.444-4.442) |
| Cultivating in paddy fields | 0.314 | 1.013 (0.003-2.520) |
| Exposure to pesticides | 0.082 | 3.018 (0.141-4.213) |
| Pesticide spraying without safety precautions | 0.745 | 0.106 (0.263-3.462) |
| Working>6 h in the field under sun | 0.003* | 8.556 (2.270-11.411) |
| Consumption of well water only | 0.006* | 7.667 (1.676-10.479) |
| Consumption of treated water | 0.016* | 5.863 (3.029-7.688) |
| Water intake<3 L/day | 0.040* | 4.215 (1.062-6.219) |
| History of malaria | 0.027* | 4.894 (1.183-6.206) |
| Consumption of black tea | 0.795 | 0.068 (0.281-2.642) |
| Consumption of fresh water fish | 0.062 | 4.146 (2.137-6.438) |
| Consumption of fresh water fish without skin | 0.583 | 0.302 (0.163-0.773) |

*$P$<0.05: Association is significant. CI: Confidence interval, OR: Odds ratio

## Discussion

The climate of the study area "Medawachchiya" is classified as tropical savanna, which is dry and sub-humid around most months of the year. Rain pattern is limited to a few months of the year, peaking around November, with an annual rainfall of approximately 16 inches. The temperature is relatively constant during the year, with August being the warmest (average temperature being 33.4°C at noon) and January being the coolest (average temperature being 20.6°C at night) (Department of Meteorology, 2012, unpublished data). The climatic conditions of the other areas in which CKDu is reported are compatible to these and are located in the dry and intermediate zones of Sri Lanka.

The majority of subjects of both groups were found to be occupied in farming. Farming in the dry zone of a tropical country like Sri Lanka is an occupation, in which the occupants continuously work under the sun and get exposed to considerably high temperatures for long duration of time, owing to paddy extending over several acres of unremitting land without shelter or shade. This exposes the farmers doing rigorous work to direct sunlight.

Irrespective of the fact of majority in each group being farmers, significantly higher percentage of CKDu patients were found to be working >6 h/day under the sun and consumed <3 L of water per day, putting them at higher risk of getting dehydrated. This becomes more evident with these subjects experiencing dysuria subsequent to working for long hours in the sun. As recommended by WHO Guidelines for Drinking-Water Quality (2004), the minimum requirement for fluid replacement for a 70 kg human in a tropical zone equates to 4-6 L/day.[20] High intake of fluids (3.5 L or more per day) is reported to be protective against CKD.[21] Therefore, these protective measures have not been a part of the lifestyle of CKDu affected populations of NCP. In Nicaragua, where a similar nephropathy of unknown cause is reported, dehydration is considered as a predisposing factor for CKD in the settings of rigorous agricultural work and at very high ambient temperatures.[22] Significant dehydration has been observed among agricultural workers exposed to extreme heat in the cotton and sugarcane industries in Nicaragua.[23] The affected farmers in Sri Lanka therefore may have been subjected to chronic dehydration throughout the years, resulting in volume depletion, which potentiates the susceptibility of kidneys to various nephrotoxic agents.

Consuming well water of different areas of NCP has been identified as a risk factor for developing CKDu.[14,24,25] The current study revealed that the source of water for drinking and cooking of the majority of CKDu patients is well water, while the majority of normal subjects consume water from alternate sources. This difference in water source used could have spared the normal subjects from getting the disease, though they live in the same locale as CKDu patients. Consumption of treated water is likely to be protective against CKDu as the majority of normal subjects consumed water subjected to treatment, including boiling, percolating through a filter, etc., A prior study conducted by Thammitiyagodage *et al*., (2009, unpublished data) reported consuming unboiled water to be having a significant association with CKDu. The results of the current study strengthen and enhance this early finding. In the milieu of dietary water source and water consumption patterns, it is more suggestive to say that subjects who consumed untreated water in lesser amounts than recommended levels and only from wells of Medawachchiya were at a higher risk for developing CKDu compared to subjects who consumed more treated water from alternative sources.

Occupational factors associated with the tested populations, including, being a farmer, cultivating wet land only, exposure to pesticides and spraying pesticides without taking precautionary safety measures were not indicated as risk factors associated with CKDu.

Among lifestyle factors, black tea was considered a refreshing drink by both CKDu patients and normal subjects. Tea has been shown to improve kidney functions, owing to the fact that it contains high amounts of antioxidants. In the current study, consuming black tea was not found to be having significant effect with CKDu ($P > 0.05$). Consumption of fresh water fish obtained from the local water reservoirs termed "wewa" is very high among the people of NCP. Bandara *et al*., reported high levels of cadmium in the fresh water fish from local water reservoirs of NCP and suggested this as a possible risk factor for CKDu.[26] The current stuy found that consumption of fresh water fish was almost equal (over 90%) between the CKDu patients and normal subjects, and significant associations between fresh water fish consumption with or without skin and CKDu was not obtained in the analysis.

Malaria, which was highly prevalent in the NCP during the 1980s and gradually became less prevalent since then, had been encountered by subjects of both groups. Some of the individuals had the disease as many as 5-6 times. Renal impairment, including renal ischemia is reported with different species of plasmodium (*Plasmodium falciparum*, *P vivax, P malaria*e and *P ovale*),[27,28] which could get aggravated by low fluid intake, fluid loss due to vomiting, pyrexia, and sweating and dehydration during infections. Histological studies have shown changes suggestive of glomerulonephritis, acute tubular necrosis and interstitial nephritis.[29] Having repeated attacks of malaria might provoke the above-mentioned structural and functional changes in the kidneys and predispose affected individuals to CKD. Antimalarial drugs are also reported to produce nephrotoxic effects [30]. Therefore, drugs used during the 1980s, when malaria reached epidemic proportions in Sri Lanka, along with their recurrent use may have contributed to some extent to the development of CKDu.

The strength of the study is that work was carried out in close collaboration with the Renal Care Unit of the Medawachchiya hospital, a satellite center specially established to diagnose, treat and monitor CKDu patients in the highly prevalent Medawachchiya area. It immensely facilitated the selection of CKDu patients for the current study. The control subjects were selected after careful physical examination, history taking, and biochemical investigations of blood and urine samples. This allowed selection of controls on a scientific basis and enabling exclusion of conditions closely associated with CKD.

The results would have been strengthened further if other measurements associated with hydration status of subjects, including environmental temperature, level of physical activity, hydration efforts during work, awareness regarding the effect of hydration, weight change before and after work, etc., could have been incorporated into the same study, involving larger groups of farmers and maintaining the authentic setup at their work with least interference.

## Conclusion

Chronic dehydration due to working for prolonged hours exposing themselves to sun and inadequate consumption of water is likely to make inhabitants of the affected regions more susceptible to CKDu. Drinking well water only and having a past history of malaria were likely to be contributing toward the development of CKDu. Following a treatment method prior to consumption of water was likely to have a protective effect against CKDu. The low degree of exposure to the risk factors and disparity in lifestyle might have spared the nonaffected from the same locale from CKDu.

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