

# Chronic Kidney Disease of Unknown Etiology in Sri Lanka: Quest for Understanding and Global Implications

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An important global public health concern is unfolding around chronic kidney disease of unknown etiology (CKDu). CKDu presents as kidney disease in patients who do not exhibit common causative factors such as diabetes or hypertension. There appears to be a link to people working in the soil and as agricultural workers. Symptoms include fatigue, panting, lack of appetite, nausea, and anemia. The disease is said to be “chronic” because it takes many years for symptoms to develop. Renal function decline is gradual and often extremely painful. The impact is traumatic on patients and their families, as the ability to work declines, and families are often unable to pay the high cost of renal dialysis treatments.

Geographic “hot spots” of CKDu have emerged in a number of countries, including El Salvador, Guatemala, Mexico, Nicaragua, Bulgaria, Croatia, Serbia, India, and Sri Lanka, with an estimated more than 50,000 patients diagnosed with late-stage kidney disease. This conservative estimate does not account for early kidney disease, which is often asymptomatic. CKDu affects the social and economic lives of a large number of people and presents significant short- and long-term costs to nations with large numbers of CKDu patients.

## CKDu in Sri Lanka

A large and growing number of Sri Lankans suffer from CKDu. Since the early 1990s, Sri Lanka has seen a rapid increase of CKDu cases, with an observed concentration of cases occurring in selected regions of the country, as highlighted in the map on the following page.

CKDu cases in Sri Lanka are concentrated in the North Central and North Western provinces and are also appearing in the Uva, Eastern, and Northern Provinces. Collectively, these five provinces have a resident population of over 2.5 million people. According to a news report following a December 2013 symposium on CKDu organized by the National Academy of

## CKDu: A Growing Global Concern

- CKDu patients are most often men ages 30 to 60, their most productive working years
- CKDu symptoms appear in the late stages of the disease
- Causes for CKDu are unknown but are multifaceted
- Risk factors include environment, agricultural work and farming practices, diet and nutrition, and genetics

Sciences of Sri Lanka, experts at the symposium estimated that the number of CKDu patients in the endemic areas was 20,336, and that this number was likely to reach over 25,000 by the end of 2013.<sup>1</sup>

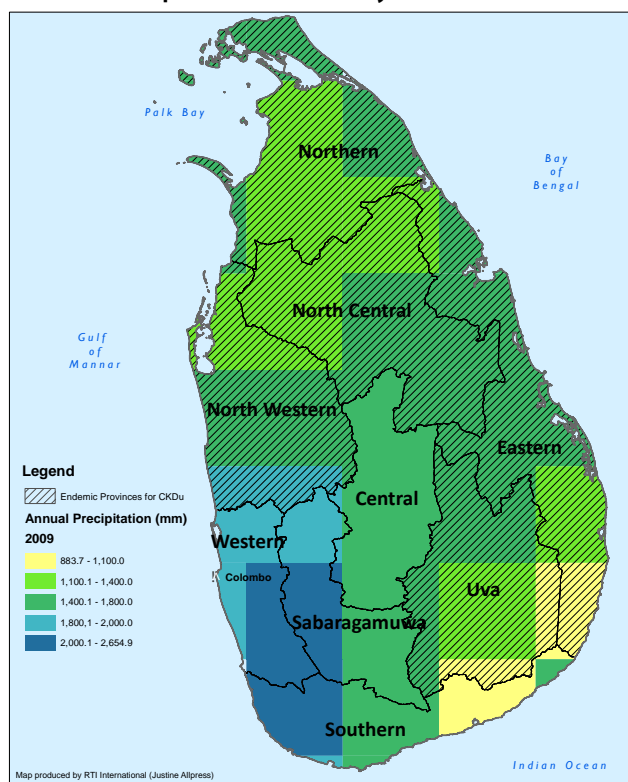
CKDu in Sri Lanka remains concentrated in the dry zone regions of the country.<sup>2</sup> Sri Lankan CKDu patients include both men and women, but a majority of the late-stage patients are men. Additionally, the majority of patients are lower income farm workers. Patients range in age from 17 to 70 but are most commonly men aged 30 to 60.<sup>3</sup>

## Research to Date

In the past two decades, Sri Lanka’s disease pattern has shifted toward non-communicable diseases (NCDs). CKDu is an NCD of great concern that now poses a significant challenge to the health of the nation and its people. Although Sri Lanka is noted for its strong public health system, data on NCDs and CKDu death and disease cases have many gaps. In response, Sri Lanka’s Ministry of Health (MoH) established CKDu disease registries at district hospitals in the dry zone provinces in 2009.

Given its unknown origin, the emerging CKDu crisis has spurred a variety of investigative efforts in recent years, and a number of research studies have been completed in an

### CKDu-affected provinces in the dry zones of Sri Lanka



Data Source: Precipitation data from University of East Anglia Climatic Research Unit (CRU), 2008<sup>4</sup>; endemic provinces from Redmon et al., 2014.<sup>5</sup>

effort to identify CKDu risk factors. Unfortunately, most of these investigations have looked narrowly at one variable or potential risk factor, have had small sample sizes, or have used imprecise methods, and so far, more questions than answers have arisen. A common observation has been that CKDu is caused by multiple factors, likely linked to a combination of environmental factors, diet and nutritional practices, and genetics.

The most comprehensive research program to date is a product of the Sri Lanka National Research Programme for CKDu, a collaborative effort from 2009 to 2012 between the MoH and the World Health Organization (WHO). This case-control research study completed an in-depth look at endemic areas

#### About Sri Lanka

Sri Lanka is a lower middle-income island nation in South Asia with nine provinces and 25 administrative districts in a total land area of approximately 65,000 square kilometers. Among the population of over 20 million, 15% live in urban areas, 80% reside in rural areas, and 5% live on (rural) estates where plantation crops are grown and harvested. The central zones of the country are largely rural and are rich agricultural lands. Life expectancy is now 74 years and rising, and disease patterns have shifted away from infectious and maternal/childhood diseases toward non-communicable diseases (NCDs), which account for approximately 90% of the overall disease burden.<sup>7</sup>

and collected and analyzed environmental and biological samples.

The Sri Lanka MoH and WHO research teams collected and tested blood, urine, hair, and nail biological samples from both CKDu patients and controls and tested a number of environmental samples, including water, soil, rice, fish, tobacco, and selected root crops.<sup>6</sup> Selected data from the population prevalence study were published in late 2013. An article by Jayatilake and colleagues (2013)<sup>6</sup> addresses potential CKDu prevalence, but there are a number of questions and uncertainties associated with the study's case definition, sampling techniques, and statistical analysis. To date, there is still only limited publication of the program's protocols and findings from the other multiyear project studies. Redmon and colleagues (forthcoming)<sup>5</sup> provide a thorough review of this paper and the population prevalence study.

#### Health and Societal Impact

CKDu was first reported in Sri Lanka in the early 1990s, and over the last 10 years its prevalence has progressively increased to epidemic levels.<sup>8</sup> Its population prevalence in the dry zone provinces is now estimated to be over 15% for men.<sup>6</sup>

**Underdiagnosis.** The impact of CKDu is growing, and its prevalence is likely underestimated. Although disease registries promise to help improve data collection, many gaps in diagnosis, data collection, and recordkeeping remain. Sri Lanka has a patient referral system for the government health care services, but it is not functioning well and patients may seek treatment in hospitals outside their local geographic area.

Historically, Sri Lanka has not had reliable registries for chronic kidney disease (CKD) or for CKDu nor regular surveillance systems to identify population distribution patterns and trends. CKDu incidence and prevalence estimates are based on patient records during treatment for end-stage kidney disease or small community research surveys. Yet many rural residents tend to self-treat their ailments or seek ayurvedic treatment, and they do not seek western medical care until symptoms are more severe.

Confounding early diagnosis is the fact that CKDu symptoms usually emerge slowly, often not appearing until stages 3 or 4 of the disease. Although early testing and counseling about CKDu has been limited in most provincial and district hospitals, it has expanded in the last few years in endemic areas. Still, the most common testing methods used to evaluate biomarkers for CKDu in Sri Lanka may not capture early-stage patients, and some endemic areas report a fear or stigma associated with a formal CKDu diagnosis. Combined, these factors add up to a likely significant underdiagnosis of CKDu in Sri Lanka.

**Working Age Patients.** Most patients affected by CKDu are rural residents, and patients include both men and women in their prime adult working years. The most common patient profile is an adult of working age (30 to 60 years old) with more than 10 years of work experience in agriculture.<sup>6</sup> Patients with a family history of CKDu also are more likely to develop the disease. CKDu was initially noted to be most common in men. With more research and better diagnoses, however, more women are being diagnosed with CKDu in the endemic areas. CKDu patients suffer a decline in productivity, reduction in quality of life, monetary loss, decline in earning potential, and an inability to sufficiently provide for their families. For Sri Lanka as a whole, fewer productive workers may correspond to lower agricultural productivity and a negative impact on national income.

**Treatment Costs.** An estimated 8,000 Sri Lankans are now undergoing dialysis treatment for late-stage CKDu.<sup>1</sup> Nationally, an estimated 4% of the public health budget is spent on renal disease, and renal service demands are growing rapidly with the increase of CKD and CKDu cases. Dialysis is very expensive—private dialysis service in Colombo costs approximately \$65 for 4 hours—and its availability is limited in rural Sri Lanka. Rural kidney patients have to travel hours to reach a referral hospital to receive dialysis treatment, placing a time and economic burden on their families. Treating CKDu in agricultural communities requires strategies to reconfigure health service delivery, strengthen human resources capabilities, and manage treatment and dialysis center operations. The cost of care, demand for consumables, and a shortage of health care professionals skilled in treating CKDu present a large and growing challenge for the public health care system in Sri Lanka.

CKDu treatment costs are further confounded by Sri Lanka's rather unique demographic profile among developing countries, that is, its very large elderly population. In 2000, 9.2% of the population was older than age 60, which exceeded the average for most developing countries. Mortality rates among the elderly have not improved in Sri Lanka, primarily because of rising mortality attributed to NCDs. CKDu and its complications only add to the growing mortality and morbidity burden of NCDs and critically strain rural health care systems.

**Health and Diet.** Exposure to sun, heat stress, and dehydration are potential contributing factors to CKDu, and populations at lower elevations may be most at risk.<sup>9,10</sup> Many Sri Lankan CKDu patients work in hot, dry zones and spend hours in the fields with limited water intake. Other risk factors not yet analyzed in detail might include low selenium or other micronutrients in the diet,<sup>6</sup> the use of nonsteroidal anti-

inflammatory drugs, or the use of ayurvedic (traditional) medicines. CKDu patients generally are not overweight and not hypertensive. Links to low birth weight, low body-mass index, low calcium intake, or chronic undernutrition are other areas requiring further study. Furthermore, research to observe potential ethnicity and genetic links has not been completed on a broad scale. Expanded health and diet surveillance and research and genetic biomarker testing will be important to expand knowledge of CKDu.

**Environmental Factors.** Current research efforts are exploring a number of environmental risk factors as potential triggers for CKDu. The leading cause for CKDu hypothesized in the MoH/WHO study is chronic exposure to cadmium and arsenic through the food chain and also from pesticides. However, the study results do not fully support this conclusion, and clear links between biological and environmental samples have not been established.<sup>6</sup> Exposure from pesticides or fertilizers has been a leading theory, as cadmium can enter the environment through repeated agricultural applications. Particular concern is focused on phosphate fertilizers containing traces of cadmium and potentially other heavy metals. In addition, pesticides may be a concern, as well as elevated levels of minerals (hard water), fluoride, or heavy metals (e.g., cadmium, uranium, and lead) in groundwater wells. To date, however, these suspected CKDu environmental risk factors do not consistently show elevated levels throughout the endemic area.<sup>6,11,12</sup> Although the soils in the dry zone regions contain naturally occurring heavy metals, in-depth soils analysis has yet to be completed on a large scale. Phosphate mining in the dry zone regions is also a topic for further investigation.

### Research and Public Policy

The multifaceted nature of this problem and the significant data gaps call for more comprehensive research, data-driven public policy discussion, and a strengthening of the health care system response in Sri Lanka and globally.

#### Key Recommendations

- *Continue to strengthen and standardize disease registries and surveillance reporting systems for cases of CKD and CKDu; share information as a public service and for research purposes.*
- *Strengthen the national environmental toxicology and epidemiological networks by supporting the open, transparent exchange of information; expand and harmonize laboratory equipment, protocols, and training to ensure data quality.*
- *Complete an economic evaluation of CKDu to model the costs and societal impact on Sri Lanka. Evaluating and recognizing the economic impact will help to quantify the costs and impacts and may further mobilize resources.*

Expanded CKDu education access and coverage is desperately needed to address fears and aid in early detection. Programs to reach high-risk and endemic communities are now under-resourced, and far too many patients are unable to access care and treatment. Global health research collaborations are needed to exchange data across countries impacted with CKDu. India and Sri Lanka in South Asia and El Salvador, Guatemala, and Nicaragua in Central America all have growing problems, and more needs to be done to establish commonalities and help mitigate or prevent CKDu.

In Sri Lanka specifically, the MoH/WHO reports estimate that 15% or more of the population in certain endemic areas are at risk of developing CKDu. If so, the national socioeconomic burden on the economy, on the public health system, and on the families in these communities is tremendous. Politics aside, this requires investment now, including a methodical decision-support approach to identify risk factors and encourage improvement in health outcomes in endemic areas by working across health, agriculture, and environmental agencies.

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