Review Article

A Review of Chronic Kidney Disease of Unknown Etiology in Sri Lanka, 2001–2015

Abstract

An increase in the prevalence of chronic kidney disease of unknown etiology (CKDu) was observed in several countries of the world since the early 2000s. We reviewed the literature to summarize the existing knowledge regarding epidemiology, clinical features, and risk factors for CKDu in Sri Lanka. We reviewed published literature from PubMed and unpublished literature from literature repository of CKDu published by the World Health Organization. We identified 36 articles based on various inclusion/exclusion criteria and reviewed the full text of all selected articles. The prevalence of CKDu was approximately 5% in endemic areas based on the surveillance data. CKDu accounted for 70% of CKD cases in endemic areas. Clustering of cases was observed in select divisions and districts in the dry region of the country. Low body mass index, normal blood pressure, scanty proteinuria, and tubulointerstitial pathology were characteristics of early stages of a disease. Genetic susceptibility, farmer as occupation, heavy metals (cadmium and arsenic), and drinking well water were identified as risk factors. Data were limited on the association with agrochemical use and heat stress/dehydration. Community- and facility-based surveillance needs to be strengthened to document the burden of disease and trends over time.

Keywords: *Chronic kidney disease, CKDu, Sri Lanka*

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Background

Chronic kidney disease (CKD) is one of the non-communicable diseases of public health importance due to its high burden and high cost of treatment in advanced stages. CKD in adults is predominantly caused by diabetes and hypertension. Autoimmune and systemic conditions also cause CKD, as do inherited conditions. Nephrotoxic drugs, herbal medications, toxins, and infections are other causes of CKD in developing countries.[1] In the 1990s, an increase in the prevalence of CKD was observed in certain areas in several countries of the world, such as El Salvador, Nicaragua, Costa Rica, Egypt, Sri Lanka, and India. The etiology was not clear, and the disease had different epidemiological characteristics. Globally, the cause remains unknown, and therefore the term "chronic kidney disease of unknown etiology" (CKDu) has been used in the literature since the early 2000s. The disease is characterized by an insidious onset and features suggestive of chronic interstitial nephritis. It affects poor, rural, male farmers exposed to the sun and prone to dehydration.[2] There are various potential theories to explain CKDu in Central America, where it is also known as Mesoamerican nephropathy. The hypotheses include heat stress, agrochemicals, heavy metals, aristolochic acid, infections, and genetic susceptibility.[3] The various theories are not mutually exclusive.

CKDu was identified in Sri Lanka around 2000. Initial data emerged from hospital-based studies among patients from the North Central Province of Sri Lanka.[4] Subsequently, community-based studies documented the high burden of CKDu predominantly in the North Central Province.[5,6] Recently, data from screening programs initiated by the Government of Sri Lanka validated the high burden and defined geographical distribution of disease.[7]

We reviewed the literature on CKDu from Sri Lanka to summarize the existing knowledge regarding epidemiology, clinical features, and risk factors based on the work done in the past decade. The objectives of the review were to describe the overall prevalence, time, place, and person distribution of CKDu in Sri Lanka. We also

How to cite this article: Kaur P, Gunawardena N, Kumaresan J. A review of chronic kidney disease of unknown etiology in Sri Lanka, 2001–2015. Indian J Nephrol 2020;30:245-52.

Received: 16-11-2018
Accepted: 07-01-2019
Published: 19-06-2019

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Access this article online

Website: www.indianjnephrol.org

DOI: 10.4103/ijn.IJN_359_18

Quick Response Code:

described the clinical features, progression, biomarkers, histopathological characteristics, various risk factors, and environmental hypotheses for CKDu in Sri Lanka.

Methods

Search strategy and literature sources

We reviewed published and unpublished literature from various sources. The major sources were PubMed, literature repository of CKDu published by the World Health Organization (WHO), and literature and web-based repository maintained by the Coordinating Secretariat for Science, Technology, and Innovation (COSTI), Sri Lanka. In PubMed, we used the search terms "chronic kidney disease," "chronic renal failure," "chronic kidney disease of unknown etiology," "renal failure," "kidney failure" in combination with "Sri Lanka" for the period 1 January 2001 to 30 October 2015. The search retrieved 144 citations. Besides, WHO Country Office, Sri Lanka, has developed a repository of published and unpublished studies on CKDu from 2001 to 2013. We identified the unpublished studies and abstracts not available in PubMed for inclusion in the review as per the inclusion criteria.

Inclusion and exclusion criteria

We reviewed the above sources using well-defined inclusion and exclusion criteria. Inclusion criteria included descriptive studies on epidemiology, clinical features, pathology, and biomarkers; analytical studies on risk factors/environmental exposures; descriptive environmental studies for hypothesis generation; and clinical/epidemiological cohort studies. Exclusion criteria were opinion papers regarding hypothesis, potential risk factors, and interventions; letters to the editor in response to various publications; original articles/abstracts with insufficient data on methods or lack of presented data in the results section; and review papers.

Results

We identified 36 articles/abstracts and reviewed the full text of all selected articles. The results are summarized as given below.

Descriptive epidemiology

Three community-based studies reported on the prevalence of CKDu in endemic and non-endemic areas using diverse sampling methodologies and case definitions [Table 1].[5,6,8] A large community-based collaborative study of the Ministry of Health and WHO surveyed 4777 individuals in the endemic and 250 in the non-endemic districts. The prevalence of CKDu in the endemic districts, namely, Anuradhapura, Polonnaruwa, and Badulla was 15%, 20.6%, and 22.9%, respectively.[6] Athuraliya *et al.* reported an overall prevalence of CKD and CKDu in three study sites. The prevalence of CKDu was 4.2% in endemic Medawachchiya and 0.2% in two non-endemic sites. A more substantial proportion of patients with CKD had an unidentified etiology in Medawachchiya, when compared with the other two sites.[5] The prevalence of microalbuminuria was 7.3% in another community survey in endemic areas[8] [Table 1].

CKDu among patients with CKD was variable in the tertiary care hospitals in various parts of the country. Diabetes was

Table 1: Prevalence of CKDu in three community-based studies, Sri Lanka

	Jayatilake *et al*., 2013	**Athuraliya *et al*., 2011**	**Wanigasuriya *et al*., 2011**
Study design	Community-based cross-sectional analytical survey	Community-based cross-sectional analytical survey	Community-based cross-sectional analytical survey
Study sites	Three districts; endemic: Anuradhapura, Polonnaruwa, and Badulla; nonendemic: Hambantota	Three districts; endemic: Medawachchiya; nonendemic: Yatinuwara and Hambantota	Endemic: Medawachchiya and Padaviya; nonendemic: Rajanganaya; all three divisions from Anuradhapura district
Sample size	The household-based survey; endemic districts, *n*=4777; nonendemic district, *n*=250	The household-based survey; endemic districts, *n*=2600; nonendemic: Yatinuwara, *n*=709, and Hambantota, *n*=2844	The household-based survey, *n*=886 from all divisions
Sampling methodology	Six divisions selected in three districts, 22 Grama Niladhari (village units) randomly from six divisions, 100 households from each sampling unit using the electoral list	Randomly selected 30 Grama Niladhari (village units) from three districts, eligible individuals from sampling units	Three Grama Niladhari (village units) randomly selected in each division, 60 households in each sampling unit from voter register; eligible above 18 years 1110, of which 886 participated
Case definition	ACR ≥30 mg/g twice and exclusion of other causes	Proteinuria ≥30 mg/dL twice and exclusion of other causes	Microalbuminuria positive twice
Age	Age range 15-70 years	Mean age range 39-43 years in three sites	Mean age: 33 years among males and 30 years among females
Prevalence in an endemic area	CKDu: Anuradhapura 15%, Polonnaruwa 20.6%, Badulla 22.9%	Medawachchiya CKD 5.1% and CKDu 4.2%	Microalbuminuria 7.3%
Prevalence in nonendemic areas		Yatinuwara CKD 7.9% and CKDu 0.2%; Hambantota CKD 2.3% and CKDu 0.2%	

CKDu: Chronic kidney disease of unknown etiology; ACR: Albumin-to-creatinine ratio

the leading cause of CKD in two studies from the referral nephrology unit in Colombo that predominantly catered to patients from the western part of the country. The overall prevalence of CKDu was 9.5% (N = 200 outpatients and inpatients), and one-fourth of the inpatients (N = 121) had CKDu.[9,10] In contrast, the prevalence of CKDu based on a review of clinical records (N = 392) of patients with CKD from two renal clinics catering to the endemic North Central Province was 54% and 82% in Kandy and Anuradhapura, respectively.[4]

Jayasekara *et al.,* did geographical information system (GIS) mapping of 11,323 patients attending the community renal clinics in the North Central Region of Sri Lanka. Three areas with a high prevalence were Medawachchiya and Padaviya in North Central Province and Girandurukotte in the Uva Province. Besides, two other clusters were in Medirigiriya and Nikawewa areas. Majority (90%) of the patients were farmers with the mean age was around 54 years. The most common source of drinking water was shallow wells (92%). Only 7% consumed water from tube wells and 1% from water reservoirs. Most of the affected villages were below the level of the reservoirs or canals.[11]

Surveillance for CKDu was set up in the renal clinics catering to highly endemic areas. An analysis of 15,630 patients who were registered between 2004 and 2011 indicated majority were farmers and the main source of drinking water (93%) was shallow dug wells. Among 3996 patients registered between 2009 and 2011 in Medawachchiya, Padaviya, and Kebithigollewa areas, the overall prevalence was 5%. Prevalence was higher among males when compared with females (6% vs. 3%). Among patients with CKD, 70% had CKDu.[7]

Definitions used in the studies were not uniform and therefore prevalence was highly variable across the studies. There was clustering of cases in a few districts and in the defined geographical areas within the district.

Clinical and histopathological features

The clinical features of patients with CKDu (N = 392) treated in two tertiary care facilities in Kandy and Anuradhapura were vague symptoms of backache and dysuria. Mild proteinuria with 24-h urine protein excretion <1 g and small bilateral kidneys on ultrasonography were the key findings. Urine examination did not show any active deposits, and hypertension was seen mostly in later stages of the disease, with no electrocardiography evidence of left ventricular hypertrophy.[4] Similar clinical features were reported from 109 patients with CKDu identified in the community-based survey in the endemic Medawachchiya division. Among 109 patients, 103 patients had no active deposits in urine samples. The mean blood pressure was normal (systolic blood pressure 127 and diastolic blood pressure 81 mmHg). The mean 24-h urine protein was 612 mg, suggesting a higher probability of a tubular lesion.[5]

Nanayakkara *et al.* reported histopathological features based on 57 biopsies at Anuradhapura General Hospital in 2008–2009. Interstitial fibrosis and tubular atrophy were the main features in most of the specimens. Other features, such as nonspecific interstitial mononuclear cell infiltration, were present in varying degrees. Focal segmental glomerular sclerosis (n = 2) and glomerular enlargement (n = 21) were observed in the glomeruli.[12] The prevalence of interstitial renal disease was 87% in a case series of 234 patients who underwent biopsy for confirmation of CKDu between 2004 and 2011 in Kandy and Anuradhapura hospitals.[13] Athuraliya *et al.* conducted community survey for CKDu in Medawachchiya division. Among 109 patients detected in the study, they selected 26 patients for biopsy who did not have a contracted kidney and had no risk factors. The tubulointerstitial disease was the main finding on light microscopy.[5]

In summary, key clinical features were late onset of hypertension, minimal proteinuria and lack of deposits in the urine; pathological features were suggestive of tubulointerstitial disease.

Stages and progression of CKDu

The distribution of the stages of the disease varies, depending on the setting of the study. The estimated glomerular filtration rate (eGFR) based on the Modification of Diet in Renal Disease (MDRD) formula was used to describe the distribution of CKD stages in most studies. A large proportion of patients on treatment in renal clinics in endemic areas had stage 4 and 5 CKD (64.5%).[7] The proportion of patients with early-stage CKD was higher in community-based studies[5,6]

A cohort study from Medawachchiya renal clinic catering to patients with CKDu in the endemic area estimated the progression of disease and risk factors. Patients identified in the screening program (N = 143) in 2003 were followed until 2009 or death, with a total follow-up of 72 months and mean follow-up of 40 months. CKDu was diagnosed after excluding all other causes such as diabetes, malignant hypertension, systemic lupus erythematosus, IgA nephropathy, and urological disease. A large proportion (58%) of patients were males with the mean age of 43 years and 42% had low BMI. Hypertension was prevalent among 24% at the time of diagnosis. The distribution of patients in the various CKD stages using the MDRD formula was 35%, 15%, 22%, 16%, and 11%, in stages 1–5, respectively. Hypertension was the critical predictor of progression [hazard ratio 3.36 (1.31–8.72)] in age-adjusted and sex-stratified multivariate analysis. Loss of follow up and small sample size were two limitations of the study.[14]

Biomarkers

Urinary biomarkers of early renal damage were detected among patients with CKDu in two studies. Biomarker

levels in the urine, namely, alpha 1-microglobulin (A1M) and N-acetyl-beta-D-glucosaminidase (NAG), were compared among 106 patients with CKDu on treatment at Medawachchiya and Girandurukotte renal clinics and 81 controls (first- to third-generation relatives). A1M was elevated in the earlier stages of the disease among cases when compared with unaffected controls. NAG was elevated only among patients with stage 5 CKD.[15] The mean urinary beta-2 microglobulin, another marker of early renal damage, was significantly higher among cases (n = 30) when compared with controls (n = 30) in another study.[16] Biomarkers may facilitate early diagnosis of CKDu, however further research is required to establish the usefulness of biomarkers.

Risk factors

Tobacco and history of snakebite

Smoking was reported as the risk factor in only one study.[8] Nanayakkara *et al.* reported that tobacco chewing was significantly associated with CKDu; however, smoking was not a risk factor.[17] History of snakebite was associated with CKDu in two studies.[17,18]

Source of drinking water

Six analytical studies included the source of drinking water as a potential risk factor; among them, drinking well water was a risk factor in four studies.[8,18-20] One study specified that drinking water was from wells in the field and another referred to recently abandoned wells [Tables 2 and 3]. Jayasekara *et al.* compared the prevalence among communities using different drinking water sources. The prevalence of CKDu was 6.3% among 7604 individuals screened in a community-based screening program in one of the high-prevalence areas, Kebithigollaewa in North Central Province. Prevalence was higher among those who drank water from shallow wells (7.7%) when compared with those who consumed water from natural springs (1.5%).[7] Drinking water emerged as one of the most commonly reported risk factor for CKDu, however the exposure data lacked specific details such as overlapping use of various water sources, duration of use, change in water sources in the past, and user behavior.

Farmer occupation and use of agrochemicals

Use of agrochemicals has been postulated as one of the possible risk factors. Eight case-control and analytical cross-sectional surveys used questions related to farming occupation, spraying pesticides, or use of specific pesticides as surrogate risk factors for exposure to agrochemicals [Tables 2 and 3]. Farmer occupation was a risk factor in four studies among the seven studies where occupation was studied as one of the risk factors [Tables 2 and 3].[20] Only one study reported a history of agrochemical use as a risk factor. However, data regarding confounders and adjusted odds ratios (ORs) were not presented. Another study reported the use of glyphosate as a risk factor.[21] [Table 3].

One study described the presence of glyphosate in the water samples in CKDu-endemic areas, and two studies described the presence of agrochemicals in urinary samples from patients.[6,20,21] The mean glyphosate level in water samples (N = 32 wells) in an endemic area, Padavi Sripura, was 3.5 and 0.7 µg/L in abandoned and serving wells, respectively. All except one abandoned well had >1 µg/L glyphosate and 31% of the serving wells had levels >1 µg/L (number of wells in each category not mentioned in the

Table 2: Risk factors for CKDu in three community-based cross-sectional analytical surveys, Sri Lanka

	Sample size	Demographic characteristics of cases and controls	Water source as risk factor	Farmer/use of agrochemicals as a risk factor	Other risk factors
Jayatilake *et al*., 2013	Cases *n*=733, endemic area controls *n*=4044, and nonendemic area controls *n*=250	Mean age: cases 37.1 years, controls 42.5 years; 37% males among cases and 42% among controls	Drinking water from well OR 0.97 (0.78-1.20); storage in aluminum water container OR 1.0 (0.87-1.22)	Farmer AOR 1.2 (1.01-1.42); paddy cultivation AOR 0.73 (0.54-0.98)	
Athuraliya *et al*., 2011	Cases *n*=130, controls *n*=2470 in Mewachchiya division of Anuradhapura	Mean age: cases 45 years, 60% males among CKDu cases		Farmer AOR 2.1 (1.4-3.3); agrochemical exposure AOR 1.1 (0.7-1.9)	Family history AOR 1.3 (0.9-1.9)
Wanigasuriya *et al*., 2011	Cases *n*=65, controls *n*=821 in Anuradhapura district		Drinking water from well in the field OR 1.79 (1.06-3.01); AOR 1.91 (1.04-3.52)	Farmer OR 1.38 (0.70-2.70); involved in pesticide spraying OR 1.01 (0.59-1.72)	Alcohol use OR 3.08 (1.83-5.20), AOR not presented; smoking OR 3.08 (1.83-5.20) AOR 5.14 (2.56-10.31);hypertension OR 2.16 (1.28-3.65), AOR 4.65 (2.58-8.41); diabetes OR 4.89 (2.46-9.71) AOR 3.83 (1.73-8.46)

Methods as described in Table 1. CKDu: Chronic kidney disease of unknown etiology; OR: Odds ratio; AOR: Adjusted odds ratio

Table 3: Risk factors for CKDu in case-control studies, Sri Lanka

Author	Type of study/study setting	Study population/ sample size/case definition	Demographic characteristics	Water source as risk factor	Farmer/use of agrochemicals as a risk factor
Chandrakumara *et al*., 2013	Case-control study; tertiary care hospital, Anuradhapura	*n*=140 cases, *n*=140 sex-matched controls; cases from CKD registry		Well water drinking in the previous 5 years OR 3.773 (2.112-6.600)	Farmer occupation OR 3.750 (2.160-6.509)
Jayasekara *et al*., 2013	Case-control study; tertiary care hospital, University of Peradeniya	*n*=315 cases, *n*=321 healthy individuals, case definition not mentioned	Male OR 1.947 (1.415-2.927), age >60 years, OR 4.884 (3.04-7.415)		Paddy farming OR 1.945 (1.256-3.010); use of agrochemicals OR 2.034 (1.297-3.190)
Wanigasuriya *et al*., 2007	Case-control study; tertiary care hospital, Nugegoda	*n*=183 cases, *n*=200 controls; case definition not mentioned	Mean age - cases males: 56.73 years, females 54.22 years; controls: males 51.10 years, females 53.67 years	Well water use at home OR 2.29 (1.36-3.87), AOR: NS, pipe water use OR 0.21 (0.09-0.48), AOR: NS	Farmer OR 3.04 (1.88-4.92), AOR: NS; use of pesticides OR 2.24 (1.45-3.45), AOR: NS
Siriwardana *et al*., 2015	Case-control study; Medawachchiya base hospital	Cases *n*=100, control *n*=100; cases had proteinuria, raised serum creatinine, confirmed by USG scan after excluding other causes	Mean age: cases 47.8 years, controls 47.7 years	Drinking well water OR 7.6 (1.7-10.5), drinking treated water OR 5.9 (3.0-7.7), water intake <3 L in a day OR 4.2 (1.1-6.2)	Farmer OR 2.4 (0.4-4.4), cultivating paddy OR 1.0 (0.0-2.5); exposure to pesticides OR 3.0 (0.1-4.2); lack of safety precautions during spraying OR 0.1 (0.3-3.5)
Jayasumana *et al*., 2015	Case-control; hospital based in Padavi Sripura hospital in Trincomalee district	*n*=125 patients with CKDu and *n*=180 controls; MOH case definition	Cases: 71% males, controls: 54% males; among cases 85% farmers	Drinking well water AOR 2.52 (1.12-5.7); from recently abandoned well AOR 5.43 (2.88-10.26)	Ever use of glyphosate AOR 5.12 (2.33-11.26)

CKDu: Chronic kidney disease of unknown etiology; OR: Odds ratio; AOR: Adjusted odds ratio

article).[20] This was a descriptive, cross-sectional survey of water samples and did not examine the association of drinking water from these wells with CKDu.

Comparison of urinary glyphosate levels among CKDu cases and controls showed higher levels among controls; however, creatinine-adjusted levels were higher among cases.[21] The duration between diagnosis of disease and collection of samples for the study was not mentioned and sample size was small. The results were not consistent with an earlier study, where only 3.5% of the patients with CKDu had glyphosate levels above the reference limit in urinary samples.[6]

Jayatilake *et al.* examined the potential role of various pesticides in the context of CKDu. Examination of urine samples showed that 10.5% of patients with CKDu had chlorpyriphos, carbaryl, and naphthalene above the reference limits. The study did not report the levels among controls, although urine samples were also collected from controls.[6]

Farmer was commonly reported risk factor and few studies explored the role of agrochemicals. None of the studies measured exposure regarding frequency, duration, and user behaviors. Conclusions based on generic questions regarding ever use of pesticides/agrochemicals/fertilizers are hard to interpret without examining the dose–response and the role of potential confounders.

Heavy metals

Heavy metals were studied in biological samples and water. The most commonly studied heavy metals in the biological samples were cadmium (Cd) and arsenic (As). The heavy metal Cd has been hypothesized to be one of the potential risk factors for CKDu. High levels of Cd were detected in the water from four reservoirs with independent cascades and one large reservoir linked to the Mahaweli River Diversion scheme in endemic areas. Besides, food items such as rice and lotus rhizomes consumed by the local community were also analyzed. The level of Cd in rice was within permissible limits (0.2 mg/kg). Consumption of lotus was hypothesized as a source of Cd because 100 g lotus storage rhizome has 4.53 mg Cd more than the recommended daily allowance of 0.03 mg/day.[22] Another study based on an analysis of water samples from the same reservoirs did not detect high levels of Cd in the water.[23] Subsequently, five studies published between 2013 and 2015 reported normal Cd levels in the water. All these studies also reported normal levels of As in the drinking water.[6,17,24-26]

Rango *et al.* analyzed the correlation of various heavy metals in urine samples and drinking water from the same population. Concentrations were higher in urine samples when compared with water samples, although both were within the range of reference values available

from various studies. There was a poor correlation, and therefore the authors ruled out the possibility of CKDu due to contamination of water with heavy metals; however, they suggested low doses of exposure from other sources (e.g., Cd due to tobacco use), which needs further investigation.[26]

Initial studies suggested the role of heavy metals As and Cd, however the recent studies did not support the hypothesis. Given the available evidence, heavy metals in water are unlikely to be the risk factor for CKDu in Sri Lanka.

Water quality and fluoride

Chandrajith *et al.* examined the water quality in 142 water samples from endemic and 37 from nonendemic areas. All samples had a neutral to alkaline pH. Ca bicarbonate-type water was predominant in endemic regions, whereas Na–K nondominant anion-type water was present in nonendemic regions. The mean fluoride levels were 0.66–1.21 mg/L in endemic and 1.05–1.42 mg/L in nonendemic regions (all were below the 1.5 mg/L limit recommended by the WHO, although above the recommended level of 0.6 mg/L for tropical countries). The authors concluded that intake of water high in sodium could lead to increased loss of calcium, restricting the formation of calcium fluoride (CaF) in nonendemic areas. In contrast, high Ca activity and high affinity of fluoride for Ca may be the risk factors for CKDu in endemic areas.[27] A higher hardness of water and high fluoride levels were also documented in another study that compared water quality in endemic and nonendemic regions.[25]

The fluoride in water in endemic areas and its interaction with aluminum to form nephrotoxic aluminum fluoride complexes was one of the proposed hypotheses for CKDu.[28] A recent article based on an animal experiment ruled out the possibility of CKDu due to aluminum fluoride complexes.[29] Rango *et al.* measured the fluoride levels in water and urine samples among CKDu cases and controls. The majority of water samples had levels below 2 mg/L; however, there was a higher correlation between drinking water and urinary fluoride concentrations when compared with heavy metals. The authors suggested that water might be the predominant source of fluoride.[26]

Dharma-Wardana *et al.* (2015) hypothesized that prolonged exposure to many ionic species in drinking water, all below maximum allowed limits, could add to high ionicity of the water. The fertilizer run-off into the river system could contribute to increased ionicity (fertilizer ions such as K^+, phosphate, $NH4^+$) of water. A high concentration of phosphorus in the reservoirs in the dry season due to fertilizer run-off in endemic areas was well documented in the data available from the National Water Supply and Drainage Board of Sri Lanka (NWSDB-SL). The Hofmeister series is a ranking of ions in terms of their capacity to denature proteins. Fertilizer ions rank high in their capacity to cause cell membrane protein denaturation that could potentially cause tubulointerstitial disease. The authors also ruled out the role of the hardness of water in enhancing the effect of nephrotoxins, as hard water can precipitate common toxins and may have a protective effect instead. Besides, Ca, Mg, and bicarbonate are less likely to cause protein denaturation as they are at the lower end of Hofmeister series; however, fluoride may contribute through this mechanism.[30]

Role of fluoride and other characteristics of water quality need to be examined further in context of onset of CKDu.

Toxins

Two studies explored the role of toxins in the causation of CKDu. One study examined only food samples, and another included biological samples in addition to environmental samples. Wanigasuriya *et al.* collected 98 food samples from retail outlets in Medawachchiya, Padaviya, and Rajanganaya endemic areas for estimating the levels of ochratoxin (OT). All samples had OT, ranging from 0.3 to 3.2 μg/kg, which was below the recommended statutory limit.[31]

Desalegn *et al.* (2011) compared the urine samples of 31 patients with CKDu, 6 healthy relatives, and 4 healthy Japanese individuals. Patients had higher mean age as compared to and healthy relatives and Japanese controls (41.3 years vs. 20.7 years). The detectable levels of aflatoxins (AFL), OT, and fumonisins were 61%, 93%, and 19%, respectively among patients. Levels of OT and AFL among patients and healthy relatives were comparable; however, they were higher than in Japanese controls.[32]

The presence of cyanotoxins, one of the nephrotoxins, was documented in an endemic area in one study. Cyanotoxin-producing cyanobacteria were isolated from three water reservoirs Kala wewa, Tissawewa, and Nuwarawewa in the Anuradhapura district using molecular and bioassay methods.[33] The presence of cyanobacteria could be due to increased ionicity of the water caused by excess use of phosphate fertilizers.

Based on the studies which examined various toxins, there is lack of evidence to suggest the role of toxins in CKDu in Sri Lanka.

Heat stress and dehydration

Heat stress and dehydration are widely hypothesized to be potential risk factors in the context of Mesoamerican nephropathy. This risk factor was reported only in one recent case–control study from Sri Lanka. Siriwardhana *et al*. reported that water intake <3 L in a day [OR 4.2 (1.1–6.2)] and working >6 h in field [OR 8.5 (2.3–11.4)] were risk factors; however, stratified analysis and adjusted ORs were not presented.[19]

Genetic susceptibility

The genetic association with CKDu was examined in two studies. In the first study, familial clustering was observed in 10 of 106 patients with CKDu on treatment at Medawachchiya and Girandurukotte renal clinics. The pattern of inheritance did not suggest a single-gene disease or autosomal recessive mode of inheritance. The authors suggested the possibility of a susceptible polymorphism with large allele frequencies.[15] In the second study, whole-genome sequencing of eight CKDu cases and controls was done. They identified a specific single-nucleotide polymorphism associated with CKDu. Besides, the authors also suggested the possibility of association of four rare variants in the gene encoding laminin beta-2 (LAMB2).[34]

Given the clustering of disease in the defined geographical areas, role of genetics need to be explored in well designed studies preferably cohort studies.

Conclusion

The prevalence was variable in community-based studies and was higher than the estimates from surveillance data. Lack of a uniform case definition posed a significant challenge in interpreting the prevalence data. Both males and females were affected, though the prevalence was higher in males. Clustering of cases was observed in select divisions and districts in the dry region of the country. The disease had a tubulointerstitial pathology. Low BMI and normal blood pressure were the key clinical features in the early stages of the disease. Proteinuria was scanty, and there were no deposits in the urine. Various risk factors namely heavy metals, drinking water, farmer occupation were hypothesized based on cross- sectional surveys.

Acknowledgment

This article is based on the background paper prepared for the "International Expert Consultation on Chronic Kidney Disease of Unknown Etiology" held in Colombo, Sri Lanka, from 27th to 29th April 2016 by WHO Country Office Sri Lanka.

Financial support and sponsorship

The review was funded by WHO Country Office Sri Lanka.

Conflicts of interest

There are no conflicts of interest.

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