Environ Geochem Health
DOI 10.1007/s10653-010-9339-1

ORIGINAL PAPER

Chronic kidney diseases of uncertain etiology (CKDue) in Sri Lanka: geographic distribution and environmental implications

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Received: 22 January 2010 / Accepted: 1 September 2010

Abstract The increase in the number of chronic kidney disease (CKD) patients from the north central region of Sri Lanka has become a environmental health issue of national concern. Unlike in other countries where long-standing diabetes and hypertension are the leading causes of renal diseases, the majority of CKD patients from this part of Sri Lanka do not show any identifiable cause. As the disease is restricted to a remarkably specific geographical terrain, particularly in the north central dry zone of the country, multidisciplinary in-depth research studies are required to identify possible etiologies and risk factors. During this study, population screening in the prevalent region and outside the region, analysis of geoenvironmental and biochemical samples were carried out. Population screening that was carried out using a multistage sampling technique indicated that the point prevalence of CKD with uncertain etiology is about 2–3% among those above 18 years of age. Drinking water collected from high-prevalent and non-endemic regions was analyzed for their trace and ultratrace element contents, including the nephrotoxic heavy metals Cd and U using ICP-MS. The results indicate that the affected regions contain moderate to high levels of fluoride. The Cd contents in drinking water, rice from affected regions and urine from symptomatic and non-symptomatic patients were much lower indicating that Cd is not a contributing factor for CKD with uncertain etiology in Sri Lanka. Although no single geochemical parameter could be clearly and directly related to the CKD etiology on the basis of the elements determined during this study, it is very likely that the unique hydrogeochemistry of the drinking water is closely associated with the incidence of the disease.

Keywords Chronic kidney disease (CKD) · Fluoride · Cadmium · Groundwater ·

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Published online: 18 September 2010

Hydrogeochemistry · Medical geology · Dry zone · Sri Lanka

Introduction

The prevalence of chronic kidney diseases (CKD) is rising globally and is mainly attributed to an epidemic of diabetes mellitus (Nahas and Belle 2005). The trend in the developing countries appears to be chronic glomerulonephritis and diabetes contributing significantly to the increasing end-stage renal disease (Codreanu et al. 2006). Endemic occurrence of a kidney disease was recognized in the 1990s in geographically discrete areas in the dry zone of Sri Lanka, and this has been increasing over a period of 10–15 years. However, the disease is found to be different and not associated with any known risk factors, i.e., diabetes, hypertension or chronic glomerulonephritis. Studies conducted in several endemic regions from 2001 to until now reveal that the prevalence varies from 2 to 3% of the population and appears to be confined to a certain geographical area of the country (Aturaliya et al. 2006). High prevalence of chronic kidney disease of uncertain etiology (CKDue) is observed in the regions in the north central of Sri Lanka mainly in Medawachchiya, Girandurukotte, Kabithigollawa, Padaviya, Medirigiriya, Dehiattakandiya and Nikawewa regions (Fig. 1). The disease process appears to mainly affect the proximal tubules and the interstitium giving rise to characteristic, recognizable histopathological and clinical features. Clinically, the disease is characterized by tubular proteinuria, usually β2-microglobulinuria, and the absence of hypertension and edema. The histological appearance of the disease is 'tubulo-interstitial' that can commonly be observed in toxic nephropathies. Up to now, there is no unequivocal evidence to recognize the possible environmental causative factors that could lead to a nephrotoxin responsible for the disease.

The etiology of this mysterious chronic kidney disease has been subjected to many studies during the last decade in which most research has focused on the geoenvironmental factors due to its exclusive geographic distribution. Interestingly, the CKDue-prevalent regions in the country overlap with the high groundwater fluoride zone of Sri Lanka suggested by Dissanayake (1996), indicating that at least to some extent, the fluoride content of drinking water may contribute to the CKDue in Sri Lanka.

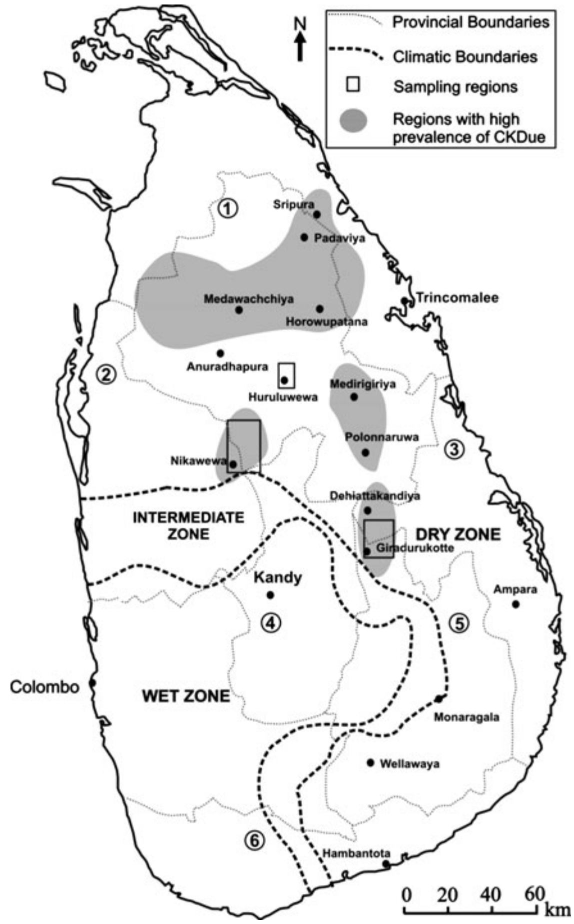

Fig. 1 Map showing the distribution of the endemic chronic kidney disease foci in Sri Lanka with respect to the climatic boundaries. *Shaded regions* show clusters of endemic regions. (1- North Central Province; 2- North Western Province; 3- Eastern Province; 4- Central Province; 5- Uva Province; 6- Southern Province)

As indicated by the medical statistics of the Anuradhapura General Hospital, which is the main hospital in the north central region, there was a 227% increase in live discharge patients with end-stage CKDue, whereas the death rate increased by 354% during the last few years (Fig. 2). The Nephrology Unit of the Teaching Hospital in Kandy, treats 3,000–3,500 patients annually, out of which 50–69% of the treated patients do not have any identifiable cause and interestingly most of them are from the north central region of the country (Abeysekara 2006).

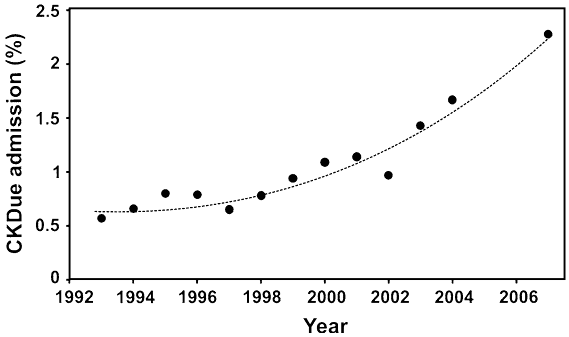

Fig. 2 Number of CKDue admissions as a percentage of total admissions at the Anuradhapura Hospital in the north central region

The disease commonly manifests in male farmers of low socio-economic class. The most affected patients belong to the 30–60 year age group. However, the disease is also observed among women and young children in some parts of the affected region, and more than 9,000 patients are presently followed up at each regional hospital of the high-prevalent areas (Aturaliya et al. 2006). Furthermore, about 2,000 patients are affected with the end stages of the disease each year with 100% mortality unless a kidney is transplanted. This mode of treatment is not affordable for a developing country. Thus, the most cost-effective way of management of the disease is to identify the risk factors/etiology to prevent the disease in vulnerable groups.

Population-based studies and hospital records showed that the disease occurrence is restricted to a remarkably similar geographical terrain. In Sri Lanka, two main eco-climatological divisions are recognized as the wet zone that occupies the south-west quadrant and the dry zone that occupies the north and east. The disease is confined to the north central and adjacent part of the island (Fig. 1). The affected area covers approximately 17,000 km^2 and with a population of about 2.5 million in which more than 95% live in rural areas. The endemic foci are scattered in a mosaic pattern, with endemic CKD regions located within few kilometers from non-endemic villages. Even within an endemic village, certain households may have had the disease, while neighboring households have had no recorded cases. As the disease has a specific geographical distribution, it is very likely that environmental and/or genetic factors are strongly linked to the etiology and progression of the disease.

The CKD with uncertain etiology in the north central dry zone is somewhat similar to that of the Balkan Endemic Nephropathy (BEN) recorded among the population of settlements along the tributaries of the Danube River in Serbia, Bosnia, Croatia, Bulgaria and Rumania (Stefanović 1999; Batuman 2006 and references therein). The Balkan endemic nephropathy is also a slowly progressive chronic tubulointerstitial disease that presents insidiously with signs of uremia during the 50th or 60th decade of life, occurring almost exclusively in farmers, affecting multiple family members in a given household and believed to be associated with a possible environmental nephrotoxin (Batuman 2006).

Trace metals in the environment are considered as a major geoenvironmental factor that could contribute to the etiology of renal damage. Several early studies have shown the potential nephrotoxic effects of heavy metals such as mercury, chromium uranium, lead and cadmium (Doul et al. 1980). Renal damage has also been attributed to the environmental exposure to arsenic, gold, iron, antimony, platinum and thallium (Maher 1976). Saldanha et al. (1975) established a relation between renal damage and silicon. Hence, the exposures to heavy metals have been given more attention in relation to the CKDue in Sri Lanka. Illeperuma et al. (2009) attributed the CKDue in the north central dry zone to the use of poor-quality aluminum utensils for cooking purposes and storing of drinking water that increases the dissolution of aluminum if the water contains high fluoride. They showed that the leaching of Al was 0.43 mg/L from aluminum utensils in the absence of fluoride, while it was about 3.0 mg/L of free Al and 11.9 mg/L of total aluminum in the presence of 1.00 mg/L of fluoride in water. Under acidic conditions that frequently applied during the traditional cooking practices in Sri Lanka, further enhancement of the dissolution of Al in fluoride containing water takes place. At the fluoride level of 1 mg/L, over 98% of all Al species were AlF^+, $AlF_2{}^+$ and AlF_3 in the solution. At the higher fluoride levels, species AlF_3 and the $AlF_4{}^-$ contents were increased (Illeperuma et al. 2009). However, they have not explained the reasons for the existence of non-endemic regions with extremely high drinking water fluoride within the dry zone region such as Ampara, Monaragala and Hambantota among others where similar kinds of utensils are used. Bandara et al. (2008) studied cadmium and some other heavy metals that were found in some environmental media such as reservoir sediment, soils, rice, lotus rhizomes, fresh water fish and urine of CKDue patients from the affected regions. They attributed the CKDue to high Cd levels in such environmental media.

The quality of the drinking water in relation to CKDue is a subject of increasing interest to medical geochemists since shallow and deep wells are the source of potable water in the affected regions. For instance, nearly 87% of the population in the Anuradhapura administrative district in the north central region where most areas are affected by CKDue use either dug well or tube well water (Perera et al. 2008). Water is withdrawn directly from the wells by people in such regions and is consumed directly without any treatment except boiling in most cases. The Working Group of the Research Program on Chronic Kidney Disease of Sri Lanka at the University of Peradeniya and the General Hospital Kandy, Sri Lanka, collaborating with Kyoto University, Japan, has been conducting comprehensive studies on various aspects related to the CKDue in Sri Lanka. Population screening, cohort studies, analysis of geoenvironmental factors, genetic studies are being carried out by the research team. This paper discusses mainly the involvement of possible geoenvironmental factors particularly the content of fluoride and some trace metals in drinking water consumed by the people in affected regions.

Materials and methods

The geographical distribution of chemical parameters in an area is very important for various scientific studies such as human and animal health, agriculture and nutrition, soil fertility. In the dry zone area of Sri Lanka, most of the population consists of farmers who obtain their drinking water from dug wells or deep wells that penetrate the Precambrian metamorphic terrain. Therefore, geochemical composition of drinking water in such regions is very important in dealing with the human health problems associated with natural environmental factors.

During this study, both dug well and deep well water samples were collected from endemic CKD regions of Girandurukotte (n = 46), Nikawewa (n = 52), Medawachchiya (n = 10) and the non-endemic region of Huruluwewa (n = 14) (Fig. 1), and another 135 water samples were collected directly from wells that are used by CKDue patients, currently attending regular renal clinics in district hospitals. All sampling regions are located within the dry zone north central part of the country, and all samples were analyzed for their fluoride content. Another selective set of samples (n = 45) were collected from Giradurukotte, Nikawewa and Huruluwewa regions for trace metal analysis. From two endemic areas, five families were selected with more than two CKDue patients. From Huruluwewa, five families without CKD family history were selected. From each family, water samples were collected directly from the source and after preparation for drinking (at the consumption level). The standard sampling and analytical methodologies were followed throughout the study (APHA 1998). The fluoride content in water samples was measured using the SPADNS method.

In addition to water samples, rice samples and urine samples were collected and analyzed for their Cd content as the Cd considered as the causative agent of CKDue. Urine samples from CKDue patients and their immediate relatives in the Giradurukotte region and control urine samples from asymptomatic individuals from the non-endemic region of Kandy were collected. Analyses of trace metals including Cd and U were preformed by inductively coupled plasma mass spectrometry (ICP-MS) at the Iwate Medical University, Japan.

The data obtained from different regions and different sample sets were statistically compared with independent sample test (*t*-test) using SPSS version 11 at 95% confidence interval. Ethical approval for the collection and use of human subject data was obtained from ethical review committees of the Faculty of Medicine, University of Peradeniya, Sri Lanka.

Results and discussion

The CKDue in the dry zone of Sri Lanka is a chronic tubulo-interstitial disease with insidious onset and very slow progression to end-stage renal failure. Anemia is mild in early-stage patients but severity worsens with the impairment of renal function. Hypertension is found commonly in patients with the advanced disease, and edema is a late feature.

Ultrasonographic imaging studies show bilaterally small kidneys with smooth outline even in early stages, increased echogenicity and loss of cortico-medullary demarcation in late stages. Urothelial malignancies are not seen. Perivascular, periglomerular and focal interstitial hypocellular fibrosis, tubular atrophy and glomerular sclerosis are the common renal histopathological changes that can be observed in CKDue kidneys.

The preliminary studies reveal that the point prevalence of the disease is approximately 2–3% in population over 18 years of age (Table 1). The occurrence of the disease appears to be spatially heterogeneous. As indicated from population screening programs, a young cohort of the population is affected. The absence of CKDue patients in the Ampara District, in the east of the north central region and Hambantota district in the southern part of Sri Lanka, both located in the dry zone with similar socioeconomic background, confirms that the distribution of the disease is restricted to the north central region of Sri Lanka. Medawachchiya in the north central Sri Lanka is one of the areas where a higher incidence of CKDue was reported. A baseline study conducted in the Medawachchiya area revealed that the prevalence of CKD among the adult (>18 years) population is 5% (n = 2,600) and 3.7% (n = 4,107) from the overall population. The female-to-male ratio was 1: 1.3, and the main occupation of the population was rice farming.

Fluoride in drinking water

The link between fluoride geochemistry in water in an area and the incidence of dental and skeletal fluorosis is a well-established relationship in medical geology (Dissanayake and Chandrajith 1999). While the essentiality of fluoride for human health is still being debated, its toxicity has now caused considerable concern in many lands where fluoride is found in excessive quantities in the drinking water. As in the case of some essential trace elements, the optimum range of fluoride varies within a narrow range and this causes fluoride imbalances, very often in large populations, mostly in developing countries of the tropical belt (Dissanayake and Chandrajith 2007). In several regions of the dry zone of Sri Lanka, excessive quantities of fluoride in groundwater have affected the water quality significantly. Apart from the well-known prevalence of dental fluorosis and, up to a certain extent, skeletal fluorosis, CKDue has also heightened interest in the medical geology of fluoride.

Among the studied regions, the Giradurukotte area showed a mean fluoride content of 0.63 mg/L where the maximum fluoride level recorded was 2.14 mg/L (Table 2). Nikawewa area also shows higher fluoride content in groundwater with a mean value of 1.41 mg/L with a maximum of 4.80 mg/L. Fluoride levels in the Medawachchiya area, which is one of the hotspots of CKDue, vary from 0.52 to 4.90 mg/L with an average of 1.02 mg/L. The non-endemic region of Huruluwewa in the north central dry zone also contained higher fluoride with an average of 1.03 mg/L. The mean values of fluoride are not significantly different ($p > 0.005$) among the three studied regions. However, in all studied regions, dental and skeletal fluorosis is widespread. For instance, prevalence of dental fluorosis in the north central part of Sri Lanka is 89.8% with a Community Fluorosis Index of 1.69 (Tennakoon 2004).

Table 1 Prevalence of CKDue in some selected regions in the dry zone based on population-based studies (Proteinuria as an indicator)

Province	North Central	North Central	Uva	Central	Southern	Eastern
Region	Medawachciya	Huruluwewa	Giradurukotte	Yatinuwara	Hambantota	Ampara
Year surveyed	2003	2001, 2005	2006	2004	2008	2008
Sample size	4,107	233	1,345	253	4,023	3,232
CKD prevalence >18 years (%)	3.7	3.2	3.9	3.2	2.53	2.20
Overall population (%)	5	0.2	4.0	3.2	3.49	3.15
CKD with Uncertain etiology (%)	84	0	96	0	1	0.75
Diabetes in >18 years (%)	3.4	–	2.1	16.4	4.88	3.66
Hypertension in >18 years (%)	5.2	–	4.5	9.1	6.11	5.57

Table 2 Fluoride (mg/L) in drinking water in some affected areas

Area	No of samples	Average F	Maximum F
Giradurukotte	38	0.74	2.14
Nikawewa-Siyabalangamuwa	45	1.41	5.30
Medawachchiya	22	1.02	4.90
Padawiya-Sri Pura	14	0.50	1.96
Vaunniya	8	0.63	1.18
Huruluwewa[a]	14	1.03	1.68

[a] control area

The sources with high fluoride water in the north central region could be related to enhanced water–rock interaction. The underlying high-grade metamorphic rocks provide a base of leaching and concentration of fluoride through groundwater and also the main source for the formation of high-fluoride-bearing groundwater. The fluorine-bearing minerals such as hornblende, biotite, mica and apatite are abundant in these high-grade crystalline rocks. As rock and mineral weathering in the tropical climate is intense, fluoride tends to enter the aqueous medium and is therefore leached out from the fluoride-bearing minerals. The geochemical pathways of fluoride in such a physico-chemical environment are strongly influenced by processes involving adsorption–desorption and dissolution–precipitation reactions. Near neutral to alkaline pH and moderate specific conductivity in groundwater are favorable for the dissociation of fluorite in water (Saxena and Ahmed 2001). Such conditions are very common in water in the dry zone of Sri Lanka (Dissanayake and Weerasooriya 1986).

Although the exposure to natural fluorides in the environment and its nephrotoxic effects are not well known, many animal experiments reported that the kidney damage can occur even at lower levels of fluoride exposure over longer periods of time. Liu et al. (2005) reported that over 2.0 mg/L fluoride in drinking water can cause renal damage in children, and the degree of damage increases with the increasing content of fluoride in drinking water.

The fluoride levels in water consumed by known CKDue patients vary from 0.05 to 4.8 mg/L with a mean value of 0.78 mg/L (n = 135). Out of these samples, 19% of the wells had less than 0.3 mg/L F,

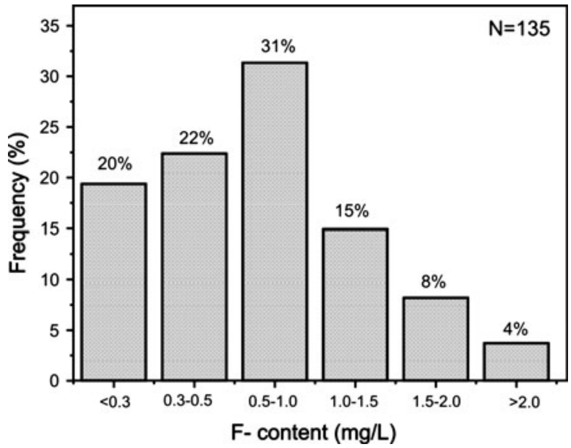

Fig. 3 Distribution of fluorides in drinking water wells used by CKDue patients (n = 135)

22% of the wells had 0.3 to 0.5 mg/L F and 31% of the wells had 0.5–1.0 mg/L F (Fig. 3). In most cases, the content of fluoride in well water in these regions does not exceed the WHO recommended limit of 1.5 mg/L, but in most samples the fluoride contents were above the 0.5 mg/L, the limit recommended for tropical countries by WHO (WHO 1994). Warnakulasuriya et al. (1992) have also been noted that the WHO recommended levels of 1.5 mg/L F in drinking water are not acceptable for hot and dry climates as prevalent in the dry zone of Sri Lanka. The incidence of dental fluorosis is common even in areas with lower levels of fluoride in water. However, the fluoride in groundwater varies remarkably from very low values to extremely high values within a small area. The mean concentration of fluoride increased in the order Nikawewa > Madawachchiya > Giradurukotte > Vavuniya > Padaviya. The mean values of fluoride in five areas are higher than the 0.6 mg/L, which is accepted as the upper level suitable for Sri Lanka (Warnakulasuriya et al. 1992). People in the dry zone regions consume higher volumes of water daily to regulate the water balance.

Although drinking water is traditionally considered to be the main source of fluoride, regular consumption of tea can also increase the fluoride intake. People in the dry zone regions drink 4–6 cups of tea per day, and it is by far the most popular beverage, second only to water. The preference for strong tea without much sugar added to it has been a potent invigorating drink, particularly among the hardworking rural communities of Sri Lanka, most of whom are farmers (Chandrajith et al. 2007), bearing in mind that the range of fluoride tolerance and toxicity is narrow. The traditional Sri Lankan black tea infusion contains up to 1.7 mg/L of fluoride, in which the fluoride may further be enhanced, if the tea was prepared by fluoride-containing water.

Environmental Cd and CKDue

The human health effect of Cd has been studied intensively, particularly after the discovery of the *itai-itai* disease of Japan. The *itai-itai* disease was the first documented case of mass Cd poisoning in the world. Cadmium poisoning can lead to renal tubular dysfunction, bone and pulmonary damages. The main organ for long-term Cd accumulation is the kidney, where the half-life period of Cd is about 10–30 years (Järup and Åkesson 2009). Extensive accumulation of Cd in the kidney results in tubular cell necrosis. Accordingly, the blood concentration of Cd serves as a reliable indicator of recent exposure, while the urinary concentration reflects past exposure body burden and renal accumulation.

Since early studies on CKDue in Sri Lanka are attributed to the environmental exposure of Cd (Bandara et al. 2008), during this study more attention was given to the study of Cd in the environmental materials. Table 3 shows the trace metals in water samples collected directly from households of CKDue patients and non-endemic households in affected regions and control samples from the Huruluwewa region. However, the results obtained in this study show very low level of Cd contents in the drinking water. The mean Cd concentration in water sources in Huruluwewa area is significantly higher ($p < 0.05$) compared to the endemic regions.

The levels are much less than the WHO recommended level of 3 µg/L (WHO 1992). Furthermore, surface water samples from reservoirs (tanks) that were used for the study of Bandara et al. (2008) were also collected and analyzed for their Cd contents. Their study showed 0.03–0.06 mg/L Cd in water, while sediments had 1.78–2.45 mg/kg Cd. Table 4 shows the Cd content in surface water samples collected from the same irrigation reservoirs, but it

Table 3 Summary results of Cd and other trace metals (µg/L) in water from endemic regions of Giradurukotte and Nikawewa and non-endemic region of Huruluwewa measured by ICP-MS

µg/L		Giradurukotte			Nikawewa			Huruluwewa		
		Raw	Drink	Other	Raw	Drink	Other	Raw	Drink	Surface
Cd	Min	<0.0027	<0.0027	<0.0027	<0.0027	<0.0027	<0.0027	<0.0027	<0.0027	<0.0027
	Max	0.006	0.031	<0.0027	0.004	0.004	0.004	0.024	0.033	0.007
Pb	Min	<0.046	<0.046	<0.046	<0.046	<0.046	<0.046	<0.046	<0.046	<0.046
	Max	0.215	0.670	0.191	<0.046	0.091	<0.046	0.016	0.957	0.234
Al	Min	3.25	6.89	2.26	1.53	3.03	1.96	2.54	3.39	3.17
	Max	152.10	191.22	22.70	4.65	113.79	7.39	8.76	6.13	73.29
Ni	Min	0.575	0.477	0.310	0.634	0.450	0.987	0.806	0.726	0.929
	Max	1.262	1.512	3.293	1.580	1.642	3.354	1.458	6.388	1.570
Cu	Min	<0.80	<0.80	<0.80	<0.80	<0.80	<0.80	<0.80	<0.80	<0.80
	Max	<0.80	2.753	6.414	<0.80	<0.80	<0.80	<0.80	1.044	1.003
Zn	Min	0.58	0.66	1.69	0.59	0.45	0.77	0.61	0.39	0.66
	Max	40.71	45.21	50.33	92.81	73.07	49.00	2.78	34.54	2.51
As	Min	<0.15	<0.15	<0.15	<0.15	<0.15	0.221	<0.15	<0.15	0.166
	Max	0.827	0.922	5.393	0.528	0.361	2.694	0.484	0.319	0.358
U	Min	0.003	0.009	0.023	0.121	0.005	0.002	0.084	0.040	0.165
	Max	0.389	0.378	0.172	0.802	0.463	2.328	0.253	0.142	0.336

(*raw* water collected from the source used by patients, *drink* water from drinking vessels, *other* water from the source of non-patient foci, *surface* water from surface water bodies; 5 samples were collected from each category) did not indicate the elevated levels of Cd as observed by Bandara et al. (2008).

Cadmium is considered as an environmentally hazardous trace metals that can be easily be taken up and accumulated by plants and crops through their root systems and is present in all food (Alam et al. 2003). Rice (*Oryza sativa* L.) and its products are the main food in Sri Lanka considered to be a possible source of Cd intake. Table 5 shows the Cd contents in rice samples collected from two endemic CKDue regions, Giradurukotte and Nikawewa. There is no significant difference between the Cd contents in rice grains from both affected regions. The average Cd content in rice samples is 0.011 mg/kg dry weight, which is lower when compared to the Cd values obtained by Bandara et al. (2008). In their study, rice grains collected from CKDue endemic regions of Madawachchiya had the Cd content ranging from 0.001 to 0.093 mg/kg dry weight with a mean value 0.0444 mg/kg and Anuradhapura area had 0.001–0.194 mg/kg Cd, with a mean value of 0.0404 mg/kg. The Cd levels obtained in the present study are lower than those in rice grains collected near a base metal mining area in Macedonia (0.31 mg/kg) (Rogan et al. 2008), raw rice grains from Sri Lanka (0.192 mg/kg) (Jayasekera and Freitas 2005), and rice collected from Lahore, Pakistan (0.23 mg/kg) (Hussain 1991), and the Codex Alimentatius Commission allowable limit (0.2 mg/kg) (Codex 2005).

Table 4 Cd contents in reservoir water, collected from dry zone region, measured with ICP-MS, compared with the data from previous studies

Reservoir (tank)	Cd (μg/L)	Cd (μg/L) after Bandara et al. (2008)
Kumbichchankulama	0.0037	50
Alankulama	0.0029	40
Thuruwila	0.0029	60
Karapikkada	0.0081	60
Ullukkulama	0.0033	30

Table 6 shows the urinary cadmium concentration in CKDue patients, their immediate relatives and asymptomatic persons from Kandy, a non-endemic area in the central Sri Lanka. The results indicate relatively higher values of urinary Cd in CKDue patients compared to asymptomatic groups, but the values are several times lower in magnitude than the data given in Bandara et al. (2008), in which the mean urinary cadmium concentration in CKDue

Table 5 Cd and other trace metals in rice (*Oryza sativa* L.) that collected from CKDue endemic regions

	Sample	Element in mg/kg (dry wt.)							
	cord	Cd	Pb	Al	Mn	Cu	Zn	As	Se
Giradurukotte	S1R1	0.017	0.016	8.07	17.54	6.97	30.82	0.14	0.2
	S1R2	0.016	0.005	2.54	14.51	5.51	26.83	0.09	0.2
	S1R3	0.014	0.028	6.67	12.14	3.10	22.81	0.11	0.1
	S1R4	0.018	0.012	7.22	23.58	6.40	31.61	0.11	0.1
	S1R5	0.009	0.071	7.08	19.58	6.16	29.06	0.10	0.1
Nikawewa	S2R1	0.013	0.005	5.61	12.60	3.47	22.57	0.19	0.1
	S2R2	0.011	0.01	7.53	14.19	3.92	17.81	0.16	0.1
	S2R3	0.003	0.002	3.56	11.38	3.07	13.77	0.12	0.1
	S2R4	0.005	0.004	3.17	10.10	3.79	19.01	0.16	0.1
	S2R5	0.004	0.016	3.67	17.72	5.03	22.13	0.26	0.1
Wild rice1 (Wisconsin, USA)[a]		0.021	0.96	–	–	5.27	43.9	0.11	0.2
Rice from mining area (Macedonia)[b]		0.31	0.5	–	–	5.8	67	0.53	–
Raw rice (Sri Lanka)[c]		0.192	–	5.64	12.4	3.37	22.3	0.034	0.22
Raw rice (Lahor, Pakistan)[d]		0.23	1.31	–	–	0.97	–	–	–

[a] After Bennet et al. (2000)

[b] After Rogan et al. (2008)

[c] Jayasekera and Freitas (2005)

[d] Hussain (1991)

patients of age group 40–60 years was 7.58 µgCd/g creatinine and in asymptomatic persons it was 11.62 µgCd/g creatinine. WHO standards stipulate that a urinary excretion of 2 µgCd/g creatinine is normal, while 10 µgCd/g creatinine would indicate an irreversible situation of chronic exposure and potential renal dysfunction.

The study carried out by Bandara et al. (2008) emphasize that CKDue in the dry zone is due to high Cd in environmental media such as water, fish and lotus rhizome. They attributed high Cd in the environment to the heavy use of Cd-contaminated phosphate fertilizer. Usually significantly high content of metals such as Cd, Hg, Pb, V, U and Cr have been found in phosphate fertilizer (Dissanayake and Chandrajith 2009). Although Bandara et al. (2008) strongly argued that the etiology of CKDue is due to the high intake of Cd, the present study does not support their argument. Furthermore, clinical evidence also does not show any symptoms in CKDue patients that are commonly associated with Cd exposures such as bone disease (*itai-itai*), renal calculi and respiratory effects that manifest before renal effects, among others.

Table 6 Urinary Cd (µg/g creatinine) in patients and asymptomatic individuals from Giradurukotte (GK) and Medawchchiya (MW) compared with the results obtained by Bandara et al. (2008)

	This study	Bandara et al. (2008)
CKDue Patients (GK)	0.788 ± 0.549 (n = 18)	5.65 ± 5.46
Asymptomatic individuals (GK)	0.571 ± 0.289 (n = 18)	13.92 ± 11.40
Asymptomatic individuals (non-endemic)	0.390 ± 0.172 (n = 8)	11.62 ± 8.45
CKDue Patients (MW)	–	10.57 ± 0.85
Asymptomatic individuals (MW)	–	9.52 ± 3.84

Other trace metals in CKDue regions

Table 7 shows some toxic trace metal contents in well water from three study regions, and in general, the contents do not show significant differences among the study regions. The levels are lower compared to the WHO recommended levels and also indicate that the water wells in the area are not contaminated by the toxic metals. The mean contents of B, Se, Zn, Sr and U are higher in Nikawewa compared to those of other two study regions, whereas the average Al and Cu contents are higher

Table 7 Summary statistics of some selected trace metals in drinking water collected from three study regions (in µg/L)

element	Giradurukotte			Nikawewa			Huruluwewa		
	Min	Max	Mean	Min	Max	Mean	Min	Max	Mean
Li	0.01	9.12	3.19	<0.10	13.32	4.27	<0.10	13.52	4.56
B	3.4	11.4	6.9	25.1	183.5	85.1	26.6	101.4	45.5
Al	2.3	152.1	22.3	1.5	7.4	3.5	2.5	73.3	12.2
Mn	0.06	12.42	4.60	<0.05	124.0	13.72	0.15	236.9	35.98
Co	0.019	0.068	0.041	0.027	0.206	0.101	0.053	0.470	0.129
Ni	0.31	3.29	1.14	0.63	3.35	1.44	0.81	1.57	1.13
Cu	<0.80	6.41	1.68	<0.80	<0.80	<0.80	<0.80	1.00	0.53
Zn	0.6	50.3	12.5	0.6	92.8	15.5	0.6	2.8	1.5
As	<0.15	5.39	0.75	<0.15	2.69	0.67	<0.15	0.48	0.25
Se	<0.066	0.123	0.049	<0.066	4.451	1.414	0.182	0.683	0.383
Rb	0.42	3.47	1.84	0.37	8.78	1.81	0.18	9.80	1.97
Sr	30	136	68	147	6,653	1,201	101	660	369
Mo	0.111	4.927	0.855	<0.094	0.880	0.304	0.234	7.770	1.595
Cd	<0.0027	0.0063	0.0022	<0.0027	0.0041	0.0019	<0.0027	0.0240	0.0055
Pb	<0.046	0.215	0.084	<0.046	<0.046	<0.046	<0.046	0.234	0.049
U	0.003	0.389	0.076	0.002	2.328	0.735	0.084	0.336	0.176

in well water from Giradurukotte. Only the Mn content is higher in the control area of Huruluwewa. All the elemental concentrations obtained in well water samples from both study and control regions are lower than the recommended values.

The mean concentrations of uranium in disease-prevalent Giradurukotte and Nikawewa are 0.08 and 0.74 μg/L, respectively, and that of 0.18 μg/L in non-endemic Huruluwewa region. The highest uranium content of 2.33 μg/L was observed in the Nikawewa region. The intake of natural uranium through drinking water has also been identified as a nephrotoxin (WHO 1992; Kurttio et al. 2002), and its nephrotoxic effects are more likely due to its chemical properties rather than its radioactivity. The provisional World Health Organization guideline value for uranium in drinking water is 15 μg/L (WHO 2004), and the tolerable daily intake for soluble uranium is 0.6 μg/kg body wt. per day. Zamora et al. (1998) showed that ingestion of uranium from drinking water (0.004–9 μg/kg body wt) affects kidney function and that the proximal tubule, rather than the glomerulus, is the site for this interference. The injection of uranium in an adult subject with 60 kg body weight, who drinks 3 L of water daily containing 0.5 μg/L U, is 0.025 μg/kg body wt.

Conclusions

Although the endemic chronic kidney disease has been identified in certain geographical regions of Sri Lanka for more than a decade, the etiology still remains unclear. Environmental factors are mostly considered to explain the etiology of the CKD. The drinking water analysis carried out in endemic CKDue areas in Sri Lanka illustrates that most of the drinking water contains medium to high level of fluoride. Even though early studies attributed the etiology of CKDue to the elevated concentration of Cd (Bandara et al. 2008), the results could not be replicated in this study and no such high Cd levels were observed in drinking water, surface water, rice and urine samples. Therefore, the involvement of Cd on the CKDue can be eliminated.

In summary, it can be concluded that no single geochemical or biogeochemical parameter could be clearly and directly related to the etiology of CKD on the basis of the elements determined during this study. It should be stressed, however, that the hypothesis for a waterborne chemical being implicated in the disease is quite strong. As already pointed out, higher temperatures facilitate the ingestion of higher amounts of drinking water, and it is readily filtered by the kidney but not readily secreted by the renal tubules. The high fluoride is not only a possible risk factor but it is possible that there is some relationship with the disease or it could even increase the severity of the disease. For instance, the variability in the Na and Ca in the groundwater and the Ca saturation factor in the presence of fluoride may prove to be an important parameter in the cause of the disease. More work on this hydrogeochemical aspect is clearly needed in view of the fact that a change in salinity can well be caused by the large irrigation scheme that commenced two decades ago.

In order to identify the possible etiology of the unknown kidney diseases in the dry zone of Sri Lanka, further in-depth studies need to be carried out. To demarcate the geographical distribution of CKDue in the country, population screening programmers in high- and low-prevalent regions and location of patients within the region will be extremely important. Systematic mapping of CKDue patients has not yet been carried out, and geographic localization will be the first step in a series of investigations into the potential etiology of CKD, which would facilitate further epidemiological and environmental studies. Analysis of biological fluids (urine and blood) for nephrotoxic heavy metals and disease markers, detailed patho-histopathological studies and histochemical analysis of kidney tissues, liver and renal arteries (biopsies and postmortem specimens) are also needed to be carried out. Study of the fate of environmental contaminants in soil–water–plant systems in the CKDue region should also be considered in depth since the current knowledge on the diseases shows an involvement of an environmental nephrotoxin. As the CKDue is confined to a particular area in the country, it is more likely that the disease occurs in a genetically predisposed group that is exposed to a triggering environmental factor/s. Therefore, genetic epidemiology studies have also to be carried out, and detailed information on familial clustering and clinical phenotypes should be collected.

Acknowledgments Ethical approval has been obtained from the Research and Ethical Clearance committee of the Faculty of Medicine, University of Peradeniya for this study. Japanese team was supported by Japan Society for the Promotion of Science (Grant Nos. 21406018 and 17109007), Special Coordination Funds for Promoting Science and Technology (No. 1300001), Japan Science and Technology Agency and Ministry of Health, Labor and Welfare of Japan (No. H21-food-003) and a grant from the Ministry of Education, Science, Sports and Culture of Japan (No. 18018022). The funding agents had no roles in the study design, data collection and analysis, decision to publish or preparation of the manuscript.

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