Open Journal of
Clinical & Medical
Case Reports

Volume 9 (2023)
Issue 07

Research Article ISSN: 2379-1039

Unraveling mystery: Role of fluoride in Sri Lanka CKDu epidemic

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Abstract

Purpose: A mysterious form of chronic kidney disease prevails in epidemic proportions in certain geographical regions of Sri Lanka and globally. A section of a larger study is presented as a case series in this article. Clinical histories of cases from a leading General Hospital in Sri Lanka are matched with prioritized biochemical parameters and exposure assessments.

Methods: The clinical history and progression of twenty-four Chronic Kidney Disease (CKDu) of unknown aetiology patients from endemic region in Sri Lanka were obtained posthumously by medical records and interviewing next of kins. Bone samples of deceased were analyzed for lead cadmium and fluoride which were considered as prioritized potential nephrotoxins. The water consumed by the patents were also analysed for same elements.

Results: Analysis reveals significantly higher skeletal deposits of fluoride in the tissues. Fluoride in the drinking water consumed by most of them were higher. Progression of the disease to terminal stage seems to be rapid in patients consuming water with higher fluoride.

Conclusion: Higher fluoride exposure seems to be a negatively modifying factor in the progression of the CKDu. The patients with already compromised kidneys with low Glomerular Filtration Rate (GFR) due to other aetiologies when exposed to higher fluoride levels through potable water rapidly deteriorate. At a certain point of low GFR, fluoride excretion is impaired to the extent that retention of fluoride set in, which in turn further deteriorate the failing kidney which seems to be the most plausible explanation for the observed phenomenon. As pointed out in previous work chronic exposure to lead seems to be the primary nephrotoxic compound lowering the GFR.

Keywords

Chronic Kidney Disease; CKDu; Nephropathy; lead; Fluoride; Nephrotoxins.

Abbreviations

CKDu: Chronic Kidney Disease of uncertain aetiology; EFSA: European Food Safety Agency; GFR: Glomerular Filtration Rate; RRT: Renal Replacement Therapy

Introduction

The exact aetiological factors for the Chronic Kidney Disease (CKDu) found in Sri Lanka are still unresolved. The disease is reported in epidemic proportion in certain geographical areas and considered to be a public health concern as it is associated with low life expectancy, catastrophic health expenditure and serious social consequences. A similar clinical entity is reported world-wide [1].

In Sri Lanka, apparently heathy individuals including a substantial proportion of younger people in their twenties living in rural communities become ill with non-specific symptoms. Following clinical investigation patients are diagnosed with compromised renal function without evidence of common conventional causes such as hypertension and diabetes as well as immunological nephropathies. Without appropriate supportive renal replacement therapy these patients deteriorate rapidly and succumb to death. Renal replacement therapy (RRT) is carried out extensively in these patients but prognosis is unfavorable. In spite of number of research studies during the last three decades, the pathophysiology of the disease is not yet clearly understood. Therefore, optimum patient management is hampered whilst meaningful public health interventions to curb the disease are hindered.

Jayalal [2] showed evidence of long-term exposure to moderately increased dietary lead levels in the affected population compared to other nephrotoxic heavy metals such as cadmium, mercury and arsenic. Further, Jayalal [3] has demonstrated excessive skeletal bioaccumulation of lead and fluoride in Chronic Kidney Disease of uncertain aetiology (CKDu) patients in post mortem studies. The described exposures amount to produce 20 - 36% reduction in Glomerular Filtration Rate (GFR), 1.5% annual increase of population- based systolic blood pressure and 4.3% reduction in full-scale intelligent Quotient (IQ).

Health risks of chronic low dose lead exposure include, inter alia, a decrease in glomerular filtration rate [4-10].

Consuming excessive fluoride contaminated water has been reported as an association with CKDu in number of studies [11-16]. In addition, cadmium exposure has also been associated with the disease [17]. Vervaet [18] suggests patients undergo a tubulotoxic mechanism similar to calcineurin inhibitor nephrotoxicity and lists exposure to herbicides and pesticides as a potential etiological factor in CKDu cases reported in countries of Sri Lanka, El Salvador, India and France.

A component of larger research project of which CKDu patients subjected to autopsy examination is presented in this article. The clinical history, analysis of water consumed by them and post mortem analysis of bone fluoride are investigated and analyzed in this component of the study.

Methods

Diagnosed CKD patients whose death occurred in Anuradhapura Teaching Hospital during the period of December 2016 till July 2018 and subjected to autopsy examinations were included in the study. The Medical history and other relevant information were collected by a forensic pathologist at the time of autopsy. Patients kidneys and bones were sampled and chemical analysis was done in another component of the research project and presented as Jayalal [3].

The patients' homes were visited and samples of water which was regularly consumed by the deceased were collected. At the same time the available information was reconfirmed and additional relevant medical history was collected by the principal investigator. Pertinent information on the life of the deceased such as childhood diseases, onset and course of CKDu including its treatment, timing of start of haemodialysis, occupational history, details of residence change, dietary habits, source of drinking water and other relevant medical and social history were obtained. The start of renal replacement therapy (RRT) or death in cases who did not undergo RRT was considered as the study endpoint. The patients' survival time from onset of the disease up to the study endpoint was recorded. The water samples were collected into to clean plastic bottles which were transported and stored in refrigeraters. Later samples were airfreighted on dry ice to the Laboratory of Pathophysiology, University of Antwerp, Belgium. Samples were coded so that patients' details could not be disclosed to the laboratory.

A novel method using High-Resolution Sector Field ICP-MS (ELEMENT XR, Thermofisher, Bremen, Germany) with medium (4000 m/Δm) mass resolution mode was developed for fluoride measurement in water. Water samples which were previously frozen for storage, were defrosted at room temperature. Since frozen water samples tend to form suspended flocks when thawed, the samples were subjected to ultrasonic homogenization. No further pretreatment for water samples prior to analysis was required. Fluoride was measured in the medium 4000 m/Δm mass resolution mode in order to overcome the spectral interferences caused by polyatomic molecules inherently present in the plasma such as carrier gas, water, acid, or other elements present in the sample. When the instrument was optimized for best performance, the quantification limit for fluoride in solution was estimated at 0.01 mg/L. Taking into account sample dilutions prior to analysis, the limit of quantification for water samples was estimated at 0.05 mg/L. Reference material consisting of simulated rainwater (ERM-CA408; EU Joint Research Centre – IRMM, Geel, Belgium) was used as an external quality control standard. The measured values for fluoride concentrations in the reference standard was 0.18 ($\pm$0.01) mg/L, which is about 93% recovery of the certified value.

Results

Twenty-four patients with chronic kidney disease of uncertain aetiology were studied. Twenty-two of them were males. Age at onset of disease ranged from 27 to 72 and age at death ranged from 30 to 75 years. The age at disease onset was anlysed to see two peaks, one at 25-34 age group and second peak at fifties. Age at the time of diagnosis distribution is shown in Figure 1.

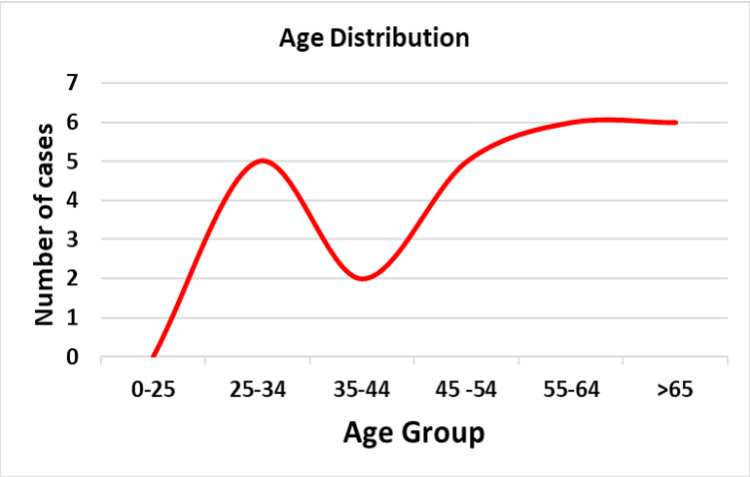

Figure 1: Age groups and their numbers at the time of diagnosis.

Table 1: The principal occupation, Gender, age at death, exposure history to pesticides and/or herbicides, duration of Renal Replacement Therapy (RRT).

	Principal occupation	Gender	Age at death (years)	History of chronic exposure to pesticide / herbicide	If subjected to RRT, the duration
Case 1	Farmer	M	75	Yes	No
Case 2	Farmar	M	53	Yes	Last six years
Case 3	Watcher	M	73	No	No
Case 4	Farmer	M	55	Yes	No
Case 5	Painter	M	30	No	Last one month
Case 6	Farmer	M	70	Yes	No
Case 7	Farmer	M	34	Yes	Last four years
Case 8	Farmer	M	59	Yes	No
Case 9	Farmer	M	70	Yes	No
Case 10	Labourer	M	72	Yes	No
Case 11	Farmer	M	65	Yes	Last six years
Case 12	Labourer	M	53	No	No
Case 13	Farmer	M	58	Yes	No
Case 14	Labourer	M	48	No	Last week
Case 15	Security Guard	M	37	No	Last Six years
Case 16	Farmer	M	62	Yes	No
Case 17	Farmer	F	64	Yes	No
Case 18	Labourer	M	68	No	No
Case 19	Housewife	F	35	No	Last three years
Case 20	Farmer	M	36	Yes	No
Case 21	Insecticide Sprayer	M	60	Yes	No
Case 22	Farmer	M	73	Yes	Last six years
Case 23	Farmer	M	55	Yes	Last week
Case 24	Farmer	M	61	Yes	Last week

Table 2: Patients' age at onset of the disease, survival years to the study endpoint (i.e., start of RRT or patients' death), time period lived after diagnosis of CKD, and corresponding concentration of fluoride, lead and cadmium in their drinking water. (<DL: below detection limit).

	Gender	Age at diagnosis of CKD (years)	Survival years up to study endpoint after diagnosis of CKD	Total years lived after detection of CKD	Fluoride level in water (mg/L)	Lead level in water (µg/L)	Cadmium level in water (µg/L)	Bone fluoride (µg/g)
Case 1	M	72	3	3	28.08	0.17	<DL	911.2
Case 2	M	43	4	10	18.59	8.64	<DL	NA
Case 3	M	72	1	1	16.33	0.46	<DL	65.2
Case 4	M	52	1	3	12.96	<DL	<DL	494.3
Case 5	M	27	3	3	11.91	0.99	<DL	NA
Case 6	M	69	1.5	1.5	11.62	0.99	<DL	NA
Case 7	M	28	2	6	10.93	<DL	<DL	381.9
Case 8	M	57	2	2	10.48	0.59	<DL	NA
Case 9	M	65	5	5	10.2	<DL	<DL	NA
Case 10	M	67	5	5	9.87	3.85	<DL	226.8
Case 11	M	59	4	6	7.89	0.67	<DL	1318
Case 12	M	50	3	3	7.59	0.28	<DL	588.6
Case 13	M	53	5	5	6.82	0.83	<DL	NA
Case 14	M	47	0.7	0.7	6.64	<DL	<DL	440.3
Case 15	M	27	3	10	6.18	0.1	<DL	290
Case 16	M	59	3	3	4.81	<DL	<DL	593.6
Case 17	F	58	6	6	4.35	<DL	<DL	NA
Case 18	M	68	Diagnosed immediately before death		4.05	<DL	<DL	975.1
Case 19	F	30	2	5	3.56	0.14	<DL	919.2
Case 20	M	31	5	5	2.5	<DL	<DL	NA
Case 21	M	56	4	4	2.43	<DL	0.02	NA
Case 22	M	61	6	12	2.08	<DL	<DL	443.9
Case 23	M	37	18	18	0.42	1.08	<DL	NA
Case 24	M	**51**	10	10	0.31	<DL	<DL	NA

All the patients studied were reliant on ground water from shallow wells or tube wells for their regular consumption. Their regularly consumed water were analyzed for fluoride, lead and cadmium content. The principal occupation, gender, age at death, exposure history to pesticides and/ or herbicides, duration of Renal Replacement Therapy (RRT) of those who underwent RRT are shown in the table 1.

The age at onset of the disease, survival time to study endpoint and the concentration of fluoride, lead and cadmium concentrations in water they consumed during life are shown in table 2.

Fluoride levels ranging from 0.31 to 28.08 mg/L were detected in the water consumed by the patients under study.

Seven out of the 24 patients were non farmers and did not give any history of exposure to herbicides or pesticides.

Six out of the 24 patients underwent regular hemodialysis for at least two years and another four were subjected to haemodialysis immediately before death. The remaining 14 patients were either managed conservatively or did not consent or did not have the opportunity to undergo any form of RRT. The six cases who underwent regular haemodialysis deteriorated to a level of haemodialysis dependency within 2 to 6 years of the diagnosis. Kidney transplant had been planned for one case but could not be performed before the patient succumbed to his illness. The years of survival up to one of the two study endpoints i.e., survival time between making the diagnosis of CKD and (i) start of RRT (haemodialysis) or (ii) death in cases not subjected to RRT, was calculated and matched with the fluoride levels of the water they consumed (Figure 1). Results show that the survival time to the study endpoint of patients consuming water with higher fluoride content is shorter indicating that patients who consume water with higher fluoride content seem to progress more rapidly to end-stage renal disease. The odd ratio was calculated to see the statistical significance of the observation. The fluoride concentration of 2.5 mg/L was assumed as the cutoff value for calculation of the odds ratio (Table 3). The average number of years of survival to endpoint is 2.8 years in patients consuming water with a fluoride content > 2.5 mg/L whereas in patients who consumed water with a fluoride level below this value the average survival to end-point was 8.6 years ($p = 0.004$, Kruskal Wallis test). This was further substantiated by calculating the odds ratio of exposure and survival up to the study endpoint. Odds of five-year survival up to the study endpoint in patients consuming water with low fluoride content (<2.5 mg/L) versus those consuming high (>2.5 mg/L) fluoride water is 15 (95 % CI: 1.29 - 174.39, p=0.0305).

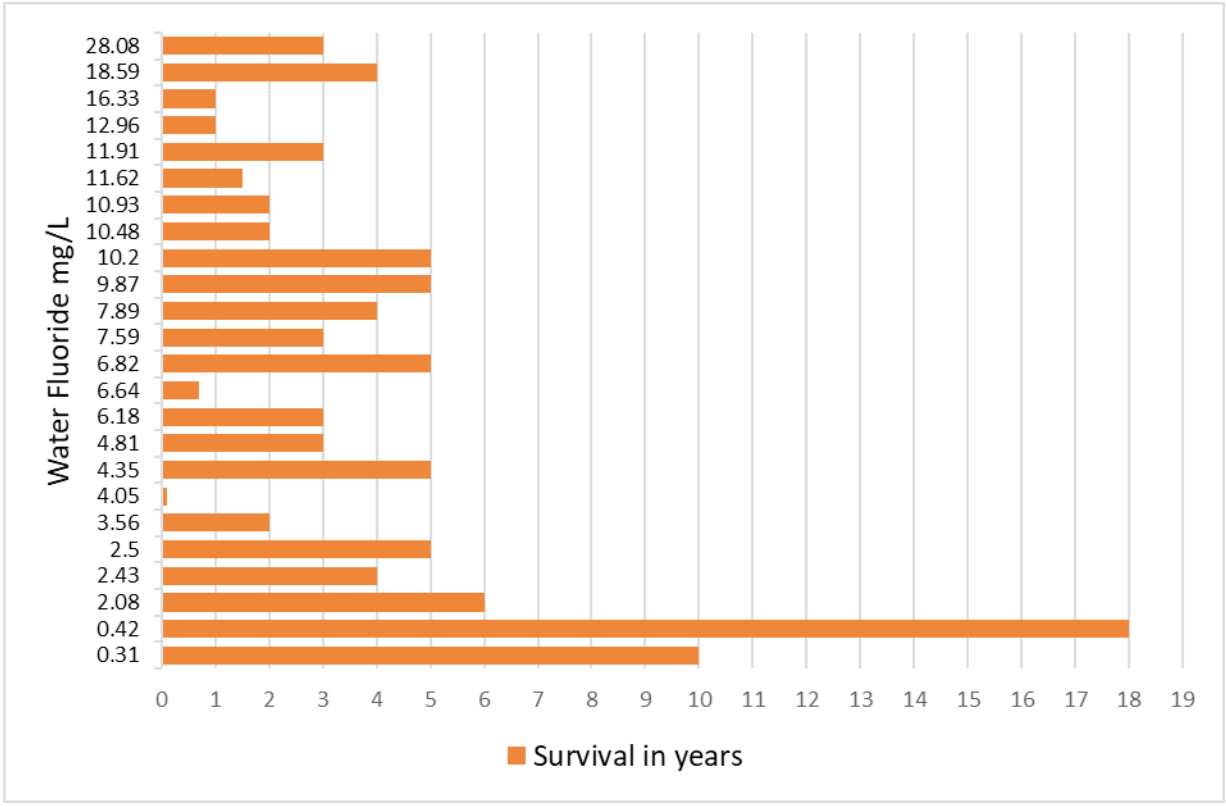

Figure 2: Drinking water fluoride and years of survival up to the study endpoint after diagnosis of renal failure.

Table 3: Two by two frequency table of number survived up to the study endpoint for less than five years and more than five years following detection of CKD.

Water fluoride exposure status	Number of patients that survived up to the study endpoint for < 5 years following diagnosis of CKD	Number of patients that survived up to the study endpoint > 5 years following diagnosis of CKD	
>2.5 mg/l	15	4	**19**
<2.5 mg/l	1	4	**5**
			24

Odd ratio = 15. 95% Confidence Interval 1.29 - 174.39. p = 0.0305

In the study cohort, cases showed bone fluoride deposits of 65.2 to 1318 µg/g (mean ± SD: 588 ± 351.5; median = 494.3 µg/g). However, water fluoride levels do not show any correlation with bone fluoride deposition.

Thirteen samples of water out of 24 contained detectable lead levels varying between 0.1 up to 8.64 µg/L. However, none of the samples exceeded the maximum allowable guideline value of 10 µg/L recommended by the WHO and Sri Lanka standards.

Only one water sample had the detectable cadmium levels (0.02 µg/L).

Discussion and Conclusions

In the study series seventeen patients were found to be occupationally involved in agrochemicals including pesticide, herbicide spraying, fertilizer applications. Fifteen farmers, a labourer and an insecticide sprayer were among them. Seven cases were non farmers with no exposure history to pesticides or herbicides, thereby indicating the disease is occurring not only in agricultural workers but other individuals who have not been involved in agriculture and occupationally not exposed to agrochemicals. Therefore, the term agricultural nephropathy is not an appropriate term to be used in this cohort of cases. The disease is found in geographical areas where agriculture is the main livelihood of the people in the area. However, the factor "agriculture related occupation" may not be an associated factor with the disease as thought earlier [19] and agriculture may be a confounding factor. In addition, this finding opposes the view of toxin induced nephropathy due to agricultural communities by Vervaet [18].

Age at diagnosis of the CKD shows two peaks of younger 25 to 34 and 50 and older group. If this disease is due to chronic exposure of bioaccumulating contaminant such as lead or cadmium the exposure may have begun possibly 25 years ago in both age groups. Interestingly, this disease was first described 25 years ago in 1990's (Annual health Statistics of Sri lanka 2007) [20]. This age distribution also supports the fact that an environmental change occurred approximately 25 to 35 years ago leading to chronic environmental toxicant exposure. The continuous exposure has shown its effects 25 to 35 years after the onset. This type of lead time period is compatible with chronic exposures such as lead and cadmium.

According to Kafle [21] almost all the households with CKDu patients were dependent on ground water from shallow wells for their drinking and cooking. Similarly, our study population is also totally dependent on ground water obtained from shallow wells or tube wells. Following the hydrogeochemical atlas

for fluoride [22] in Sri Lanka a distinct overlap is seen between the ground water fluoride content and the prevalence of CKDu. Herath and Chandrajith [12,23] supports this view. It had been reported in Sri Lanka, that severely fluoride contaminated ground water wells (>4.0 mg/L) exist among low fluoride ground water wells (<1.5 mg/L) [24]. Not all wells are equally contaminated with fluoride explain the sporadic distribution of cases. The latter study and as well as a substantial number of other studies support the view that intensive exposure to fluoride may be a causative or aggravating factor in the development of CKDu [12,13,21,24].

Further, Fernando [11] have shown higher serum fluoride levels in CKDu patients compared to healthy people living in the same area. However as drinking water sources were not traced and analyzed in the study it is not clear whether higher serum fluoride is due to higher exposure or retention due to poor excretion or both factors coexist. Further, Fernando [11] have shown similar pattern in urinary levels of fluoride also and thus may reflect increased exposure to fluoride which suggest higher exposure. Jayalal [3] previously reported mean ± SD concentration of bone fluoride of 22.49 ± SD 43.9 µg/g in a study cohort consisting of persons with normal kidney functions living in a non CKDu endemic area of Sri Lanka. Higher exposure to fluoride from water and food and/or poor excretion from the compromised kidney function may explain the observation of higher fluoride in the serum.

Nephrotoxicity of fluoride in animals and humans has been reported at higher exposure settings [14,15]. Dental fluorosis and skeletal fluorosis have been reported in humans exposed to fluoride levels similar to those of found in the present study [24,25]. Bone and the pineal gland are the major sites of fluoride accumulation in humans [16]. Therefore, measuring the bone fluoride concentrations is considered a reliable biomarker of chronic fluoride exposure. Individuals with normal excretory functions should be able to excrete the low to moderate chronic doses of fluoride load that enter the body. Therefore, it is unlikely that fluoride in chronic moderate doses as mostly found in ground water plays a direct causative role in CKDu. Further, in our cohort there were cases diagnosed with CKDu consuming low fluoride water, it also supports the view that fluoride is not the causative factor in those patients. If fluoride in water is the sole cause, and as there are large number of people consuming high fluoride water, the expected number of CKDu cases need to be higher. Besides this study has shown longevity or non- progression to terminal renal failure is higher in CKDu patients who are consuming low fluoride water which supports the view that fluoride act as a negative modifying factor of the disease.

This study allows to suggest that progression towards a severe stage of CKD is faster in patients consuming water with higher fluoride content. Those who consume low fluoride water apparently survive three times longer than those who consume high fluoride contaminated water. The odds ratio to die or become dependent on RRT within a shorter period; i.e., less than five years after diagnosis, is 15 (95% CI: 1.29 - 174.39, p=0.0305) in patients with exposure to high fluoride water (>2.5 mg/L). As patients diagnosed with CKDu but consuming high fluoride water survive for shorter period than low in takers, it is apparent that fluoride negatively modifies the progression of the course of the disease.

Jayalal and Levine [2,3,26] had reported that exposure to lead is higher in people living in the CKDu

endemic area. Jayalal [3] have shown the bioaccumulation of lead in bones of CKDu patients is higher in the CKDu affected individuals.

Jayalal [2], have reported that the estimated lead exposure in the studied population contributes to 20 to 36% reduction of GFR in the inhabitants of this area based on the European Food Safety Agency (EFSA) [4] estimation. Considering these facts lead and fluoride exposure may be the root cause of the clinical syndrome detected as CKDu in this population. Lead may be the initiating factor of the renal damage. Due to chronic lead toxicity a gradual decline of GFR may be induced. In the context of higher fluoride exposure skeletal retention followed by increased mobilization from the bone during the resorption phase may occur. Such increased accumulation of fluoride in blood may contribute to the rapid progression of the renal failure.

The lead concentrations in water were within the threshold levels recommended by the WHO and did not correlate with corresponding bone lead levels. This indicates that the primary source of lead is not the drinking water. In this scenario the most probable source is food as pointed out by Jayalal [2]. An industrial or occupational exposure is highly unlikely in these cases according to their occupational history and the environment where they lived.

In conclusion, continuous chronic excessive exposure to lead may be the primary toxin which progressively lower the GFR and at a certain point of low GFR fluoride excretion is impaired to the extent that retention of fluoride set in and further deteriorating the failing kidney seems to be the most plausible explanation in the observed phenomenon. The observed clinical syndrome where patients more rapidly evolve to terminal stage of renal failure as compared to renal diseases with conventional underlying etiologies is also clarified by the above explanation.

Limitation of the study: For obvious reasons, sample size is limited as the cases were deaths reported from CKDu in a leading hospital. The sample represent the patients admitted and died in the hospital. The CKDu deaths that occurred outside the hospital were not available for analysis. Water samples were collected after the death of the patient and seasonal variations of water quality may not have been captured.

Statements & Declarations

Funding: The study was partly funded by the Second Health Sector Development Project of World Bank component II.

Conflicts of interest/Competing interests: All authors declare no conflicts of interest and no competing interests.

Authors' contributions: Conceptualization: Jayalal Thalarabe Bulathge Ananda, Methodology: Jayalal Thalarabe Bulathge Ananda, Material collection; Jayalal Thalarabe Bulathge Ananda, Senannayake Mudiyanselage Harshana Kumara Senanayake, Dasanayaka Prasanna Bandara, Material preparation and analysis and investigation: Jayalal Thalarabe Bulathge Ananda, Patrick D'Haese, Kayawe Valentine Mubiana, Ludwig Lamberts, Gayan Surendra Writing - original draft preparation: Jayalal Thalarabe Bulathge Ananda; Writing

- review and editing: Patrick D'Haese, Kayawe Valentine Mubiana, Funding acquisition: Jayalal Thalarabe Bulathge Ananda. All authors commented on previous versions of the manuscript and all authors read and approved the final manuscript

Data availability: The datasets generated and analyzed during the current study are presented in the manuscript safeguarding the privacy of the individuals. If further information required data are available from the corresponding author on reasonable request.

Ethics approval: The study protocol was approved by the Ethics Committee of the Sri Lanka Medical Association (ERC 17/014).

Consent to participate (include appropriate statements): Informed prior written consent was obtained from next of the kin of each subject on whom sample collection was done.

Consent for publication (include appropriate statements): Informed prior written consent was obtained from next of the kin of each subject.

Acknowledgement: N.G.T.Indika and S.N.Disanayaka Public health Inspectors of CKD unit RDHS office Anuradhapura for tracing the patients residence and assisting in interviewing and water sample collection.

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Manuscript Information: Received: February 02, 2023; Accepted: March 01, 2023; Published: March 10, 2023

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Citation: Jayalal TBA, D'Haese P, SMHMK S, Dasanayaka PB, Mubiana KV, et al. Unraveling Mystery: Role of Fluoride in Sri Lanka CKDu Epidemic. Open J Clin Med Case Rep. 2023; 1990.

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